

# **2014 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE**



## **PART V: ACTIVITIES OF MEMBER STATES AND OTHER EUROPEAN COUNTRIES IN THE FIELD OF RARE DISEASES**

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The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

More information on the activities of the former European Union Committee of Experts on Rare Diseases and the EUCERD Joint Action can be found at [www.eucerd.eu](http://www.eucerd.eu).

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## ACRONYMS

CAT - Committee for Advanced Therapies at EMA  
CHMP - Committee for Medicinal Products for Human Use at EMA  
COMP - Committee on Orphan Medicinal Products at EMA  
DG - Directorate General  
DG Enterprise - European Commission Directorate General Enterprise and Industry  
DG Research - European Commission Directorate General Research  
DG Sanco - European Commission Directorate General Health and Consumers  
EC - European Commission  
ECEGRD – EC Expert Group on Rare Diseases  
ECD - European Conference on Rare Diseases  
EEA - European Economic Area  
EMA - European Medicines Agency  
ERN - European reference network  
EU - European Union  
EUCERD - European Union Committee of Experts on Rare Diseases  
EUROCAT - European surveillance of congenital anomalies  
EUROPLAN - European Project for Rare Diseases National Plans Development  
EURORDIS - European Organisation for Rare Diseases  
FDA - US Food and Drug Administration  
HLG - High Level Group for Health Services and Medical Care  
HTA - Health Technology Assessment  
IRDiRC – International Rare Diseases Research Consortium  
JA - Joint Action  
MA - Market Authorisation  
MoH - Ministry of Health  
MS - Member State  
NBS - New born screening  
NCA - National Competent Authorities  
NHS - National Health System  
PDCO - Paediatric Committee at EMA  
RDTF - EC Rare Disease Task Force  
WG - Working Group  
WHO - World Health Organization

## GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD) Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2013. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the Commission Expert Group on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2013

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Parts I – V also include a description of the methodology, sources and validation process of the entire report, and a selected bibliography and list of persons having contributed to the report.

Each year, there are around 15 000 downloads of the different sections of the report combined.



# 1. EUROPEAN UNION MEMBER STATES

## 1.1. AUSTRIA

### Definition of a rare disease

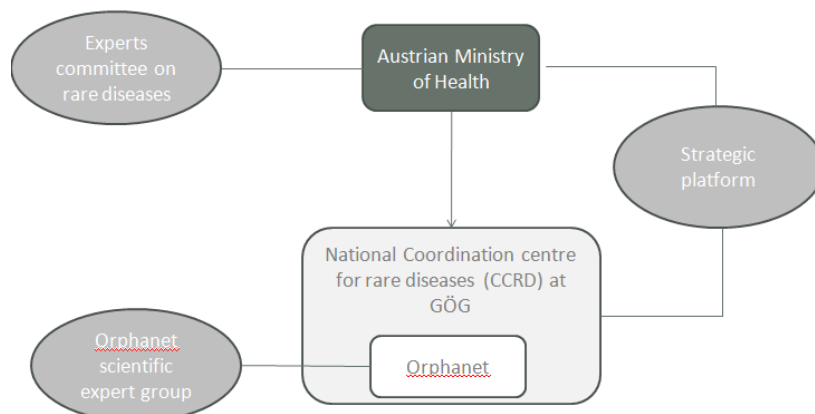
In 2013 an official definition of rare diseases in Austria had not yet been established; on an informal basis, stakeholders in Austria accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 persons. In the national plan of action (still under development in 2013; see below) it is foreseen to officially adopt the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

In response to a petition by health professionals and patient organisations for a national action plan on rare diseases in Feb 2008 and considering the recommendations of the European Council of 8 June 2009 to implement a national action plan on rare diseases by 2013 the Highest Austrian Health Advisory Board (“Oberster Sanitätsrat”) of the Austrian Ministry of Health (BMG) established a subcommittee for rare diseases in May 2009, consisting of 17 members from 13 different organisations or institutions (covering the main stakeholders in the field). This working group was managed by the Austrian Orphanet team and laid the foundation for a national plan of action for rare diseases. It was the first time in Austria that an expert committee of this size, covering a broad spectrum of viewpoints, was working on rare diseases in a comprehensive manner, with topics ranging from the description of the situation of rare diseases in general to legal and ethical aspects, equality in legal and practical terms, the identification of concrete problems, bottlenecks and restrictions that patients, relatives, physicians and scientists are confronted with, and, finally, the identification of possible measures and strategies aiming to improve the situation, to combat (structural) deficits, to optimise health care pathways, and to minimise disease burden wherever possible.

To further support the development of the national plan and in particular to involve further key stakeholders in the elaboration process, the Austrian Ministry of Health established, on January 1, 2011, the National Coordination Centre for Rare Diseases (CCRD, Nationale Kontaktstelle für Seltene Erkrankungen, NKSE) at the Austrian Health Institute (Gesundheit Österreich GmbH, GÖG). As of 2013, the CCRD has a team of 1.4 full time equivalents. It also integrates part of the Austrian Orphanet team. Most members of the subcommittee for rare diseases (including patient representatives, physicians and representatives of social health insurance and industry) are still involved in the topic as they were appointed to the Expert committee on rare diseases that was established in mid 2011 by the Ministry of Health (see Figure 1 below). In addition a strategic platform with delegates of the Ministry of Health, representatives of the regions and payers (Austrian provinces and the Main association of the Austrian social security institutions) was set up. In 2013 these two platforms continued their active participation in the development of the national plan for rare diseases.

Figure 1: Organisational Chart of the Austrian CCRD





The establishment of the CCRD was one of the first steps in the development of a national plan for rare diseases as proposed by the subcommittee for rare diseases in November 2010. The founding of the CCRD included and includes a sustained funding until the end of 2014 of Orphanet as the national information system for rare diseases and the involvement of both, the Medical University of Vienna and the GÖG as partners in the Joint Action Orphanet Europe.

In December 2013 the national plan for rare diseases including several annexes was in its final phase of development. The draft will be completed in the first months of 2014 and will then be revised by the Ministry of Health, the Ministry of Social Affairs and the Ministry of Science, Research and Economy, as well as other relevant stakeholders and authorities including the health sectors of the counties of Austria. This last revision process will probably be finalised in the second half of 2014. In its current draft format, the plan covers nine priority areas. No general budget will be allocated to the plan in advance. Instead, it is intended that the budget for each measure in each priority will be defined as soon as this measure will be implemented.

The main activities of the CCRD in 2013 were the following:

- Acting as the main driving force in drawing the national plan for rare diseases until the end of 2013 through a participative process of discussing the nine priorities of the national plan with all representatives of the expert group as well as of the strategic platform;
- Continuous awareness raising among professionals / experts / doctors / patients on the topic of rare diseases through presentations and dissemination of information;
- Acting as the focal point for European activities in the field of rare diseases through active participation in EU-funded projects and initiatives such as Orphanet and EUCERD and the Cross Border Health Care Directive as well as other European initiatives in the area of Orphan Medical Products;
- Continuation of Orphanet activities:
  - Continuous updating of Austrian services in the Orphanet database;
  - Dissemination of information on Orphanet in Austria ;
- Acting as the communication hub between actors in the field, focusing on health care professionals and other stakeholders.

### **Centres of expertise**

Currently, there are no officially designated centres of expertise in Austria; informally, however, there are a few well-recognised centres with outstanding expertise in their field, which have not yet undergone a national designation process.

The eligibility criteria for centres of expertise, which take into account the recommended EUCERD criteria, the criteria developed in the context of the elaboration of the delegated decision accompanying article 12 of the cross-border healthcare directive, and national healthcare regulations, will be included in the national plan for rare diseases. The development of a national designation process for centres of expertise is expected to start in the second half of 2014. It is intended that the developed criteria will be embedded in the Austrian health care structure plan, which might also specify the designation of future centres of expertise.

### **Registries**

Currently, no nationwide, general, comprehensive registry for rare disease patients exists in Austria. Also, there is no national committee or designation process for rare disease registries in Austria at the moment. Approximately 25 registries or bio-banks for individual rare diseases or groups of rare diseases are run by specialised clinics or networks of experts from different clinics. These registries are primarily maintained on a private/institutional basis, in many instances "in kind" by the expert teams; some registries are additionally supported by corresponding patient support groups. Some of the European registries Austrian teams participate in are EURO CARE CF, AIR, RARE CARE, EIMD, EMSA-SG, EURO CAT, SCNIR and ENRAH. Actions in this area will be included in the National Plan for Rare Diseases.

Apart from registries, Austria aims to fully integrate rare diseases into its diagnosis and activity documentation system (Diagnosen- und Leistungsdokumentation; DLD). To address this objective, a collaboration with Germany to introduce Orpha Codes into the health information system (for use in centres of expertise) is foreseen in the National Plan for Rare Diseases.

### **Neonatal screening policy**

Since the late 1960s, Austria has a well-established, nationwide newborn screening (NBS) program that is carried out for practically all newborns in one screening centre, operated by the University Children's Hospital of the Medical University of Vienna. The Austrian NBS program is one of the most comprehensive programs worldwide and screens for the following 31 diseases and conditions: adrenogenital syndrome, biotinidase

deficiency, carnitine-acylcarnitine translocase deficiency, carnitine palmitoyl transferase IA deficiency, carnitine palmitoyl transferase II deficiency, carnitine uptake deficiency, citrullinemia, argininosuccinic aciduria, congenital hypothyroidism, cystic fibrosis, galactosemia, glutaric acidemia type I, glutaric acidemia type II / multiple acyl-CoA dehydrogenase deficiency, homocystinuria and hypermethionemia, isobutyryl CoA dehydrogenase deficiency, isovaleric acidemia,  $\beta$ -ketothiolase deficiency, long-chain acyl-CoA dehydrogenase deficiency, mitochondrial trifunctional protein deficiency, maple syrup urine disease, methylmalonic aciduria, propionic acidemia, holocarboxylase synthetase deficiency, phenylketonuria and hyperphenylalaninemia, short-chain acyl-CoA dehydrogenase deficiency, tyrosinemia type I, very long-chain acyl-CoA dehydrogenase deficiency, 2-Methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency, 3-Hydroxy-3-methylglutaric aciduria, 3-Methylcrotonyl-CoA carboxylase deficiency, and 3-Methylglutaconic aciduria type I. The screening for medium-chain acyl-CoA dehydrogenase deficiency was removed from the screening panel in 2013.

In addition, the project to establish the screening for six different lysosomal storage disorders (e.g. Mucopolysaccharidosis (MPS) type 1, Gaucher, Fabry, Pompe, and Nieman-Pick Type A/B) concluded during 2013.

Detailed information regarding the Austrian NBS is provided online<sup>1</sup> in three languages (German, English, and Turkish). As an additional service, nearly all diseases listed and explained on the NBS homepage are directly linked to the relevant disease entity in the Orphanet database.

As a next step, the establishment of an independent national scientific committee for the NBS is planned.

### Genetic Testing

Molecular genetic testing in Austria is regulated by the so-called “Gentechnikgesetz” (GTG), first established in 1994<sup>2</sup> and last revised in 2005<sup>3</sup>. The GTG covers all legal, ethical and (bio-) safety aspects regarding diagnostics and research in the field of molecular genetics (including generation and handling of genetically modified organisms). In the chapter on human molecular genetic testing, genetic tests are subdivided into the following four types:

- (a) Type 1 comprises tests to identify either concrete somatic changes in the number, structure, or sequence of chromosomes, genes or DNA fragments or concrete chemical modifications in chromosomes, genes or DNA fragments in patients suffering from a clinically manifested and diagnosed disease (for instance, the search for a somatic mutation or altered methylation status in a tumour tissue sample);
- (b) Type 2 covers tests searching for germline mutations in patients suffering from a clinically manifested and diagnosed disease;
- (c) Type 3 comprises tests to establish the genetic risk/predisposition of a healthy individual to potentially develop a genetic disease in the future, or to establish the carrier status of a healthy individual for a certain genetic disease, in disorders where prophylaxis or treatment are available;
- (d) Type 4 covers tests to establish the genetic risk/predisposition of a healthy individual to potentially develop a genetic disease in the future, or to establish the carrier status of a healthy individual for a certain genetic disease, in disorders where prophylaxis or treatment do not exist.

While for genetic tests of categories 1 and 2 no authorisation is necessary, tests of categories 3 and 4 can only be performed in laboratories officially authorised by the Austrian Ministry of Health. Institutions seeking authorisation have to register their activity and apply with a detailed description of their laboratories, equipment, technical procedures, quality schemes, and experience in genetic testing. The formal authorisation for the respective genetic test is granted after an evaluation process, which includes consultation of the scientific board of the Committee on Gene Technology (“Gentechnikkommission”).

Laboratories performing genetic testing in Austria are listed in a special registry (“Genanalyseregister”) administrated by the Ministry of Health. Of note, the designation “reference laboratory” as an official term does (currently) not exist in Austria.

In Austria, reimbursement is primarily a responsibility of the individual states (“Bundesländer”) and not centrally regulated (of note, some exceptions exist). This responsibility is further split between two different types of institutions, depending on whether the patient had been treated (a) in the hospital sector (as inpatient or outpatient) or (b) in the private sector (i.e. by a general practitioner or consultant of a specific

<sup>1</sup> <http://www.meduniwien.ac.at/hp/neugeborenen-screening/>

<sup>2</sup> [http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/510\\_1994.pdf](http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/510_1994.pdf)

<sup>3</sup> <http://www.bmg.gv.at/cms/home/attachments/7/8/8/CH1060/CMS1226929588865/gtg-nov.11-05.pdf>

medical discipline that has his own practice and a service contract with the relevant health insurance fund). In the first case, the costs of any type of diagnostic test or treatment have to be paid from the budget of the hospital. The hospital, in turn, is indirectly reimbursed by the health fund of the respective state (“Landesgesundheitsfonds”) on DRG basis. However, hospitals have to make efforts to not exceed the budgets allotted to them for each calendar year. In the second case (private practice), reimbursement is the responsibility of the sickness fund of the patient. In this instance, specific tariffs are calculated by the sickness fund for each type of service and services are reimbursed according to the tariff catalogue. Basically, mainly services that have been successfully negotiated with the sickness fund and integrated into their individual tariff catalogue are eligible for reimbursement. Still, patients/their doctors always have the possibility to apply for individual reimbursement.

Taking into account this dual reimbursement system with all its regulations, the reimbursement of genetic testing is as follows:

- (a) As an obligatory prerequisite, all tests have to be officially accepted/approved by the (local) sickness fund of the patient and integrated into their tariff catalogue (either as a specific single test, or on the basis of average calculations for long versus short genes, number of exons, complexity of the analysis, or other criteria);
- (b) For in- and outpatients, the hospital covers the costs according to the tariffs of the laboratory performing the test;
- (c) For patients in the private practice, the respective insurer carries the costs; however, it is possible that certain analyses (depending on the internal regulations of the sickness fund) require an ex-ante approval by the head physician (“Chefarzt”) of the health insurance, even if the analysis is requested/recommended by a specialist for human genetics.

Genetic testing abroad is possible as soon as the test is strongly indicated for an individual patient and cannot or not easily be performed within the country (again, the same rules apply as above and the determination has obligatorily to be approved ex-ante either by the respective insurance fund or – for inpatients - by the medical director of the hospital).

Diagnostic tests are registered as available in Austria for 665 genes and an estimated 767 diseases in the Orphanet database<sup>4</sup>.

### **National alliances of patient organisations and patient representation**

Pro Rare Austria was established in December 2011. This national “Allianz für seltene Erkrankungen” was founded by Dr. Riedl, chairman of DEBRA Austria, the Epidermolysis bullosa patient support group.

In 2013 Pro Rare Austria achieved inter alia the following milestones:

- Publications in different media; development of a social media platform;
- Fundraising for the organisation of the Rare Disease Day 2013 with around 400 participants;
- Further development and maintenance of the website: [www.prorare-austria.org](http://www.prorare-austria.org);
- Out of around 60 rare disease patient organisation, 20 organisations are members of Pro Rare Austria;
- Member of EURORDIS;
- Active participation at the meetings of the expert committee on rare diseases under the lead of the national coordination centre for rare diseases;
- Establishment of a medical expert committee.

Apart from Pro Rare, general alliances of patient organisations (both for rare and non-rare diseases) do exist on the state level (ARGE Selbsthilfe Carinthia, Upper Austria, Lower Austria, Salzburg, Styria, Tyrol, Vorarlberg, and Vienna). They are united under the supra-umbrella *Arbeitsgemeinschaft (ARGE) Selbsthilfe*, which is located in Vienna. The *ARGE Selbsthilfe* can provide limited funding for a period of 6 months (with repeat applications possible) for all patient organisations (including those in the rare diseases field), however, funding is confined to support the formation of a new patient organisation or to provide interim aid for an existing one bridging a limited time gap. The Austrian Health Institute supports Pro Rare by providing meeting rooms and optional funding for further education in the field.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Austria***

With the establishment of the National Coordination Centre for Rare Diseases (CCRD) the dedicated Austrian team that was in charge for Orphanet for almost ten years expanded to include GÖG staff members. Part of the

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<sup>4</sup> Information extracted from the Orphanet database in January 2014.

staff is still hosted by the Institute of Neurology at the Medical University of Vienna. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, bio-banks, clinical trials and patient organisations) in Austria for entry into the Orphanet database. The reason for including two institutions in the Orphanet work is to guarantee long-term sustainability of the Orphanet activities in the Austrian health care system. Therefore, the teams work closely together.

Since 2011, the Orphanet-Austria<sup>5</sup> national website provides an entry point to the Orphanet database. The objectives are to provide basic information on the Orphanet database and the local Orphanet team, as well as to raise public awareness on rare diseases in general. The team reports about major events and activities organised either by Orphanet Austria itself or by other stakeholders.

As of 2013, the plan is to integrate sustained funding for Orphanet Austria into the rare disease national plan.

### **Official information centre for rare diseases**

Until 2010, Orphanet was the only official source of information specific to rare diseases in Austria. With the establishment of the National Coordination Centre for Rare Diseases (Nationale Koordinationsstelle für Seltene Erkrankungen, NKSE) at the Austrian Health Institute (Gesundheit Österreich GmbH, GÖG<sup>6</sup>) in January 2011 an official information platform for all stakeholders was established. The CCRD is funded by the Austrian Ministry of Health (Bundesministerium für Gesundheit) and shall act as information provider along with its other functions. Orphanet Austria was integrated into this coordination centre to enable maximum synergy between the two structures. In the first phase the CCRD launched the Austrian orphanet website<sup>7</sup> and provided information to health professionals, e.g. by presenting rare disease specific congresses and events.

### **Help line**

Currently, there is no official nation-wide national helpline for rare diseases in Austria. In the last couple of years individual regional activities developed such as the helpline in Salzburg, focusing primarily on rare genetic skin disorders (genodermatoses) and metabolic disorders.

### **Other sources of information**

Further sources of information on rare diseases include:

- Disease-specific websites of patient organisations. A number of patient organisations for specific rare diseases – or groups of rare diseases – exist in Austria that host excellent websites providing extensive and very detailed information on “their” rare disease/group of rare diseases (including information on the medical background, symptoms, diagnostics and treatment/care of patients)<sup>8</sup>.
- A number of medical departments or patient registries also host websites with comprehensive and useful information on those rare diseases they are focusing on<sup>9</sup>.
- The Austrian Ministry of Health<sup>10</sup> as well as the website of the National Coordination Centre for Rare Diseases (CCRD)<sup>11</sup> provide general information on rare diseases in Austria.
- Rare disease-specific information is also published on the official governmental health platform of Austria. Provided information include: a link to the report on rare diseases, as well as information regarding the establishment of the CCRD<sup>12</sup>.

### **Guidelines**

In several medical disciplines good practice guidelines exist or are worked on for individual rare diseases. The development of good practice guidelines will be part of the designation criteria for centres of expertise, as suggested by the EUCERD.

There are currently no centralised efforts to translate/transpose emergency guidelines for rare diseases. The development and implementation of emergency cards for rare disease patients is part of the

<sup>5</sup> <http://www.orpha.net/national/AT-DE/index/startseite/>

<sup>6</sup> <http://www.goeg.at/de/Bereich/Koordinationsstelle-NKSE.html>

<sup>7</sup> [www.orpha.net/national/AT-DE/index/startseite](http://www.orpha.net/national/AT-DE/index/startseite)

<sup>8</sup> Some examples (non-exhaustive) are <http://www.mps-austria.at>, <http://www.klinefelter.at>, <http://www.rett-syndrom.at/index.html>, <http://www.debra-austria.org>, <http://www.pah-info.at>

<sup>9</sup> Some (non-exhaustive) examples are: [www.genodermatosen.at](http://www.genodermatosen.at), <http://www.akromegalie-register.at/wDeutsch/akromegalie/index.php?navanchor=1110006>, <https://www.studienregister.at/web/guest/home> (select info folder for haemophilia).

<sup>10</sup> [http://bmg.gv.at/home/Schwerpunkte/Krankheiten/Bericht\\_Seltene\\_Erkrankungen\\_in\\_Oesterreich](http://bmg.gv.at/home/Schwerpunkte/Krankheiten/Bericht_Seltene_Erkrankungen_in_Oesterreich)

<sup>11</sup> <http://www.goeg.at/en/Area/National-Coordination-Centre-for-Rare-Diseases-CCRD.html>

<sup>12</sup> <https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/aktuelles/aktuelles-seltene-erkrankungen-in-oesterreich.html>

draft of the rare disease national plan. This will include information on emergency guidelines as provided by Orphanet.

#### **Training and education initiatives**

The Academy of the Epidermolysis Bullosa House AUSTRIA hosts training workshops for epidermolysis bullosa on a regular basis. In addition, the Department of Dermatology of the Paracelsus Medical University Salzburg organised the "Fostering Courses for Genodermatoses" under the auspices of the European Academy of Dermatology and Venerology in 2009, 2010 and 2012 with another course being scheduled for January 2014.

#### **National rare disease events in 2013**

A number of events were held to mark the Rare Disease Day 2013, including the march for rare diseases in Vienna on March 2, 2013.

On 27 and 28 September 2013, the 4th Austrian National Conference on Rare Diseases was organised in Innsbruck.

#### **Hosted rare disease events in 2013**

The 2nd Conference of 'EB-CLINET - Clinical Network of EB Centres and Experts' was held on 17-18 September 2013 in Salzburg.

#### **Research activities and E-Rare partnership**

##### ***National research activities***

Currently, there is no specific and explicit funding policy for rare diseases in Austria. Funding for all fields of research is available through grant applications at different funding bodies (for instance, the *Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund; FWF)*, the *Österreichische Forschungsförderungsgesellschaft mbH (Austrian Research Promotion Agency; FFG)*, or the *Anniversary Fund of the Austrian Nationalbank*), mostly following a bottom-up approach.

In 2013, the FFG published a specific programme for rare diseases for SME, amounting to €5 million in total.

##### ***Participation in European research projects***

Teams in Austria participate (or have participated) in 36 FP7 rare disease related projects and have coordinated 6 projects.

##### ***E-Rare***

Austria was not an official partner in the E-Rare consortium before 2009 and did not participate in the first E-Rare Joint Transnational Call in 2007. The *Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund)*<sup>13</sup> joined the second E-Rare Joint Transnational Call in 2009, and around € 580,000 of funding was granted for Austrian teams participating in 3 projects. Austria participated in the 3<sup>rd</sup> Joint Transnational Call in 2010/11 and Austrian teams participate in all together seven of the funded projects. Austria joined the 4<sup>th</sup> Joint Transnational Call on Rare Diseases Driven by Young Investigators in 2012 and 2 of the 11 projects selected included a team from Austria. Austria joined the 5<sup>h</sup> Joint Transnational Call in 2013; however no Austrian teams participate in the 12 funded projects.

##### ***IRDIRC***

The *Fonds zur Förderung der wissenschaftlichen Forschung* as part of the E-Rare group of funders joined the IRDiRC in 2012.

#### **Orphan medicinal products**

##### ***Orphan medicinal product committee***

There is currently no committee for orphan drugs in Austria.

##### ***Orphan medicinal product incentives***

The Austrian Medicines Law (2001) provides for "the waiving of fees (e.g. for marketing authorisation or variations) for orphan drugs authorised through the national procedure (applicable until 20 November 2005,

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<sup>13</sup> <http://www.fwf.ac.at/>

date from which the centralised route of marketing authorisation of designated orphan medicinal product became mandatory)<sup>14</sup>”.

### **Orphan medicinal product market availability situation**

As soon as marketing authorisation is provided, orphan medicinal products are available quite quickly in Austria. Actions are foreseen by the National Plan for Rare Diseases in this area (“Recognition of the specificity of rare diseases” and “Improving equal access to established therapies”) to further improve availability.

At the end of 2012/beginning of 2013, 72 orphan medicinal products with an EU market authorisation were available. The majority of the orphan medicinal products were included in the out-patient reimbursement code (either in the no box or in any of the other categories); only 13 orphan medicinal products were not included in the out-patient reimbursement code. But it is possible that they were used in-patient, i.e. during hospital stay. Only Plenadren is definitely not marketed in Austria.

Table 1. Availability of authorised orphan medicinal products in the Austrian reimbursement code in 2012/2013

<b>Available in out-patient reimbursement code (no box or other categories)</b>		
<b>Active Ingredient</b>	<b>Brand name</b>	<b>Company</b>
Pegvisomant	Somavert	Pfizer
Clofarabin	Evoltra	Genzyme
Imatinib Mesilat	Glivec	Novartis Europharm
Mercaptopurin	Mercaptopurin Nova Labo	Nova Laboratories
Histamin Dihydrochlorid	Ceplene	EpiCept GmbH
Arsentrioxid	Trisenox	Cell Therapeutics (UK)
Tafamidis	Vyndaqel	Pfizer
Aztreonamlysin	Cayston	Gilead
Tobramycin	TOBI Podhaler	Novartis Europharm
Ofatumumab	Arzerra	GlaxoSmithKline
Nilotinib	Tasigna	Novartis
Dasatinib	Sprycel	Bristol-Myers Squibb
Rilonacept	Rilonacept Regeneron	Regeneron
Ibuprofen	Pedea	Orphan Europe
Trabectedin	Yondelis	Pharma Mar S.A.
Deferasirox	Exjade	Novartis Europharm
Dexrazoxan	Savene	SpePharm
Icatibant	Firazyr	Jerini AG
Betain	Cystadane	Orphan Europe
Carglumsäure	Carbaglu	Orphan Europe
Pirfenidon	Esbriet	InterMune
Romiplostim	Nplate	Amgen
Eltrombopag	Revolade	GlaxoSmithKline
Busulfan	Busilvex	Pierre Fabre
Thiotepa	Tepadina	Adienne S.r.l.
Amifampridin	Firdapse	Eusa Pharma SAS
Sorafenib	Nexavar	Bayer HealthCare
Rufinamid	Inovelon	Eisai
Bosentan	Tracleer (Ftbl)	Actelion Registration

<sup>14</sup> Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005 (p7).

<b>Available in out-patient reimbursement code (no box or other categories)</b>		
<b>Active Ingredient</b>	<b>Brand name</b>	<b>Company</b>
Iloprost	Ventavis	Schering AG
Sildenafil	Revatio (Ftbl)	Pfizer
Ambrisentan	Volibris	GlaxoSmithKline
Nelarabin	Atriance	GlaxoSmithKline
5-Aminolaevulinsäure	Gliolan	Medac
Plerixafor	Mozobil	Genzyme
Miglustat	Zavesca	Actelion Registration
Velaglucerase alfa	VPRIV (1 ST)	Shire
Alglucosidase alfa	Myozyme	Genzyme Europe
Zinkacetat Dihydrat	Wilzin	Orphan Europe
Laronidase	Aldurazyme	Genzyme Europe
Idursulfase	Elaprase	Shire
Lenalidomid	Revlimid	Celgene Corporation
Thalidomid	Thalidomide	Celgene Corporation
Azacitidin	Vidaza	Celgene Corporation
Mitotan	Lysodren	Laboratoire HRA
Temsirolimus	Torisel	Wyeth
Cladribin	Litak	Lipomed
Mifamurtid	Mepact	IDM Pharma
Levodopa/Carbidopa	Duodopa Gel	Abbot Products GmbH
Eculizumab	Soliris	Alexion Europe
Sapropterin	Kuvan	Merck Serono
Coffeincitrat	Peyona	Chiesi Farmaceutici
Mecasermin	Increlex	Tercica
Ziconotid	Prialt	Eisai Limited
Everolimus	Votubia	Novartis Europharm
Ruxolitinib	Jakavi (new in 2012)	Novartis Europharm Limited
Decitabine	Dacogen (new in 2012)	Janssen-Cilag
Mannitol	Bronchitol (new in 2012)	Pharmaxis Pharmaceuticals Limited
Pasireotide	Signifor (new in 2012)	Novartis
<b>Not available in the out-patient reimbursement code</b>		
<b>Active Ingredient</b>	<b>Brand name</b>	<b>Company</b>
Anagrelid-Hydrochlorid	Xagrid	Shire
Nitisonon	Orfadin	Swedish Orphan
Hydroxycarbamid	Siklos	Addmedica
Porfimer Natrium	Photobarr	Axcan Pharma
Hydrocortison	Plenadren	Duocort Pharma
Galsulfase	Naglayzme	BioMarin
Stiripentol	Diacomit	Laboratoires Biocodex
Alipogene tiparvovec	Glybera (new in 2012)	uniQure biopharma B.V.
Teduglutide	Revestive (new in 2012)	Nycomed
Mercaptopurine	Xaluprine (new in 2012)	Nova Laboratories Limited

<i>Available in out-patient reimbursement code (no box or other categories)</i>		
<i>Active Ingredient</i>	<i>Brand name</i>	<i>Company</i>
Brentuximab vedotin	Adcetris (new in 2012)	Seattle Genetics UK Limited
Ivacaftor	Kalydeco (new in 2012)	Vertex Pharmaceuticals (U.K.) Limited
Concentrate of proteolytic enzymes enriched in bromelain	NexoBrid (new in 2012)	Teva Pharma GmbH

Source: Austrian PPI service 2013

### **Orphan medicinal product pricing policy**

In case a marketing authorisation holder applies for reimbursement at the Austrian Social Insurance in case of out-patient treatment, i.e. inclusion in the positive list / Austrian Reimbursement Code (Erstattungskodex, EKO), the product falls under statutory price regulations. Thus, its maximum ex-factory price may not exceed the EU-24 average price. The final decision on the reimbursement price is made by the Association of Austrian Social Security Institutions after negotiations with the company. The way of the application and the decision process is regulated according to specific principles called VO-EKO in German. In case the orphan medicinal product is not reimbursed, its price may be determined by the manufacturer alone.

The Austrian Social Insurance Fund reported to have received 14 submissions for orphan drugs between 2006 and 2011, whereby:

- 2 submissions included 1 clinical trial
- 7 submissions included 2 clinical trials
- 5 submissions included 3 clinical trials (maximum allowed)
- All but one submissions included at least 1 Randomised Clinical Trial
- In half of the submissions placebo was used as the only comparator, although therapeutic options were available

Unauthorised orphan medicinal products may be imported on case-by-case decisions, but in general compassionate use of orphan medicinal products is not allowed. The vast majority of orphan drugs are dispensed in hospitals.

### **Orphan medicinal product reimbursement policy**

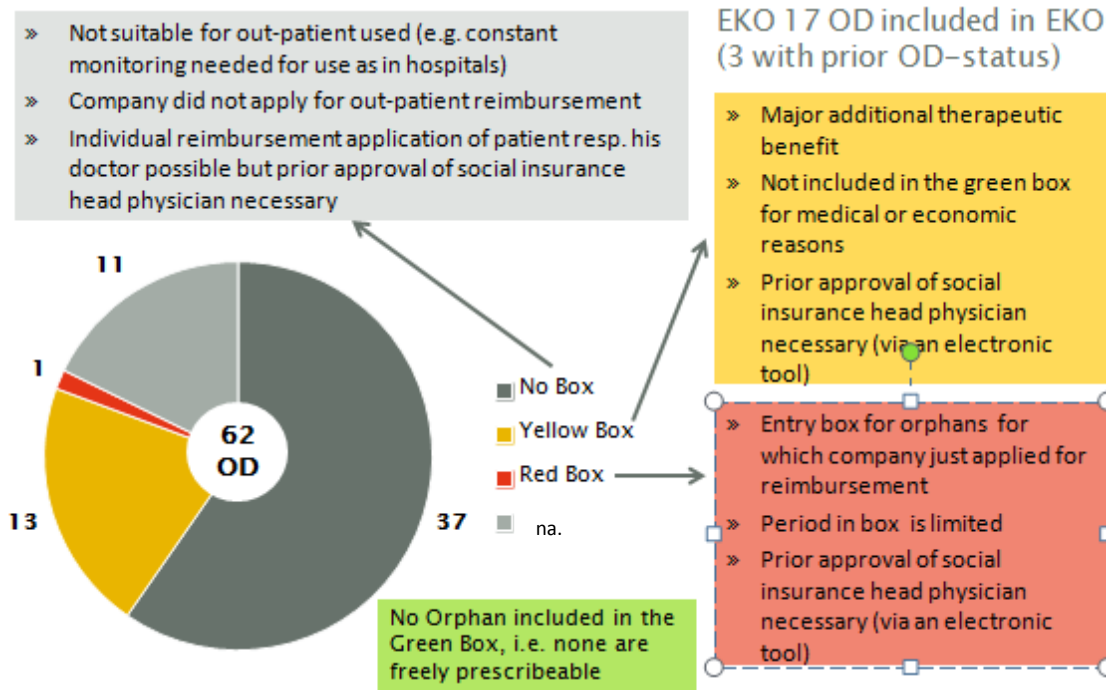
According to the Austrian Social Insurance Law (ASVG) insured patients must be granted all necessary forms of medical treatment in a sufficient and appropriate way as long as adequacy of resources used is reasonable<sup>15</sup>. Contract physicians are entitled to prescribe all medicines included in the Austrian Reimbursement Code (EKO)<sup>16</sup> - considering specific rules (e.g. second-line therapy) - on behalf of the sickness funds (general reimbursement). Specific medicines require ex-ante or ex-post approval of a head physician ("Chefarzt") of the contracting sickness fund. The same is true for exceptional cases where a pharmaceutical is not listed in the Reimbursement Code. To obtain the approval the prescribing physician needs to send a written request to the sickness fund via an electronic online tool. Decisions of the sickness fund's head physicians depend on medicinal and pharmacological necessities as well as economic criteria. In practice, orphan medicines usually belong to a group requiring prior approval, see Figure 2 below.

<sup>15</sup> Art. 133 ASVG 1955, regulating the extent of medical treatment [Art. 133 ASVG 1995; BGBl. No. 189/1955]

<sup>16</sup> Art. 31.3(12) ASVG, on the publication of the Reimbursement Code EKO (Art. 31.3(12) )



Figure 2: Out-patient reimbursement status of all authorised orphan medicinal products with an active orphan designation in Austria, 2012<sup>17</sup>



If it is determined that a medicine is best applied in a hospital setting, e.g. because of the complexities of administration (as it is for instance the case for “Elapraxe”, a drug for an enzyme replacement therapy), then there is no need for reimbursement in the outpatient setting. In exceptional cases, reimbursement may be still approved, however, if the administration is done on an outpatient basis and this is medically justified. For orphan medicinal products not included in the reimbursement code (EKO), the attending physician may still seek approval from the sickness fund (e.g. requesting administration of the orphan drug as out-patient treatment).

In case a patient is seeking to obtain approval for treatment outside of Austria, the same procedure as described above applies (i.e. ex-ante approval by the head physician). In the last four years no treatment with orphan drugs taking place outside of Austria has been approved, however, several patients underwent diagnostic testing in other countries, e.g. in Germany.

Interviewed national experts explained to the CCRD team that patients could experience delays in the reimbursement of orphan medicinal products due to fragmented funding responsibilities. The public payer of medicines in Austria depends on the place of treatment, i.e. the owners of hospitals having to pay for intramural care whereas the regional sickness funds cover medicines prescribed in out-patient care. Sickness funds pay a lump-sum for the provision of in-patient care for their insured to the regional hospital funds.

In 2012, for instance, public expenditure per prescription for orphan drugs amounted to around €2,700. Altogether the Austrian Social Insurance spent €106.5 million on orphan drugs in 2012, and €93.2 million in 2011<sup>18</sup>. In 2011 3.5% of all pharmaceutical expenditure was caused by orphan medicinal products where as expressed by number of prescriptions the share was only 0.03%.

<sup>17</sup> CCRD 2013 based on EKO 1/2013 and Warenverzeichnis 1/2013.

<sup>18</sup> See table 2.

Table 2: Expenditure of Austrian Social Insurance for medicines and orphan drugs used out-patient, 2011 and 2012<sup>19</sup>

Indicators	2011	2012
<b>Expenditure</b>		
Total PE by Social Insurance	€ 2 654 205 566	-
Social Insurance Expenditure for Orphan Drugs*	€ 93 173 418	€ 106 471 427
OD share on Total PE	3.5%	-
<b>Medicines Prescriptions</b>		
Total number of prescriptions	120 348 529	-
No. Of OD-prescriptions *	34 522	39 322
OD share on total number of prescriptions	0.03%	-
<b>Ø Cost per prescription</b>		
All medicines	€ 22.05	
Orphan Drugs *	€2,700	

PE = Pharmaceutical Expenditure, OD = Orphan Drug

### **Other initiatives to improve access to orphan medicinal products**

Any kind of off-label use is not well accepted by public authorities in Austria.

### **Other therapies for rare diseases**

No specific information reported.

### **Orphan devices**

No specific information reported.

### **Specialised social services**

No specific activity reported.

## **RARE DISEASE ACTIVITIES IN 2013 IN AUSTRIA**

### **National plan/strategy for rare diseases and related actions**

In December 2013 the national plan for rare diseases including several annexes was in its final phase of development. The draft will be completed in the first months of 2014 and will then be revised by the Ministry of Health, the Ministry of Social Affairs and the Ministry of Science, Research and Economy, as well as other relevant stakeholders and authorities including the health sectors of the counties of Austria. This last revision process will probably be finalised in the second half of 2014. In its current draft format, the plan covers nine priority areas. No general budget will be allocated to the plan in advance. Instead, it is intended that the budget for each measure in each priority will be defined as soon as this measure will be implemented.

The main activities of the Coordination Centre for Rare Diseases (CCRD) in 2013 were the following:

- Acting as the main driving force in drawing the national plan for rare diseases until the end of 2013 through a participative process of discussing the nine priorities of the national plan with all representatives of the expert group as well as of the strategic platform;
- Continuous awareness raising among professionals / experts / doctors / patients on the topic of rare diseases through presentations and dissemination of information;
- Acting as the focal point for European activities in the field of rare diseases through active participation in EU-funded projects and initiatives such as Orphanet and EUCERD and the Cross Border Health Care Directive as well as other European initiatives in the area of Orphan Medical Products;
- Continuation of Orphanet activities:
  - Continuous updating of Austrian services in the Orphanet database;
  - Dissemination of information on Orphanet in Austria ;
- Acting as the communication hub between actors in the field, focusing on health care professionals and other stakeholders.

<sup>19</sup> Note: All medicines expenses below the prescription fee (around € 5,-) are not included in these figures. Source: Austrian Social Insurance 2013 (Maschinelle Heilmittelabrechnung).

### **Centres of expertise**

The development of a national designation process for centres of expertise is expected to start in the second half of 2014. It is intended that the developed criteria will be embedded in the Austrian health care structure plan, which might also specify the designation of future centres of expertise.

### **Registries**

Apart from registries, Austria aims to fully integrate rare diseases into its diagnosis and activity documentation system (Diagnosen- und Leistungsdokumentation; DLD). To address this objective, a collaboration with Germany to introduce Orpha Codes into the health information system (for use in centres of expertise) is foreseen in the National Plan for Rare Diseases.

### **Neonatal screening policy**

The screening for medium-chain acyl-CoA dehydrogenase deficiency was removed from the screening panel in 2013. In addition, the project to establish the screening for six different lysosomal storage disorders (e.g. Mucopolysaccharidosis (MPS) type 1, Gaucher, Fabry, Pompe, and Nieman-Pick Type A/B) concluded during 2013.

### **National alliances of patient organisations and patient representation**

Pro Rare Austria, the national "Allianz für seltene Erkrankungen" was achieved the following milestones in 2013:

- Publications in different media; development of a social media platform;
- Fundraising for the organisation of the Rare Disease Day 2013 with around 400 participants;
- Further development and maintenance of the website: [www.prorare-austria.org](http://www.prorare-austria.org);
- Out of around 60 rare disease patient organisation, 20 organisations are members of Pro Rare Austria;
- Member of EURORDIS;
- Active participation at the meetings of the expert committee on rare diseases under the lead of the national coordination centre for rare diseases;
- Establishment of a medical expert committee.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Austria***

As of 2013, the plan is to integrate sustained funding for Orphanet Austria into the rare disease national plan.

### **Guidelines**

The development and implementation of emergency cards for rare disease patients is part of the draft of the rare disease national plan. This will include information on emergency guidelines as provided by Orphanet.

### **National rare disease events in 2013**

A number of events were held to mark the Rare Disease Day 2013, including the march for rare diseases in Vienna on March 2, 2013.

On 27 and 28 September 2013, the 4th Austrian National Conference on Rare Diseases was organised in Innsbruck.

### **Hosted rare disease events in 2013**

The 2nd Conference of 'EB-CLINET - Clinical Network of EB Centres and Experts' was held on 17-18 September 2013 in Salzburg.

### **Research activities and E-Rare partnership**

#### ***National research activities***

In 2013, the FFG published a specific programme for rare diseases for SME, amounting to €5 million in total.

#### ***E-Rare***

Austria joined the 5<sup>th</sup> Joint Transnational Call in 2013; however no Austrian teams participate in the 12 funded projects.

## 1.2. BELGIUM

### Definition of a rare disease

Stakeholders in Belgium define rare diseases as life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. As a guide, low prevalence is taken as prevalence of less than 5 per 10 000 individuals in the European Community.

### National plan/strategy for rare diseases and related actions

In addition to the Belgian Cancer Plan (since 2008), the Minister of Social Affairs and Public Health has developed a National Plan for Chronic Illness with five priorities: (1) the recognition of a statute for persons with a chronic disease; (2) the creation of an observatory for chronic illness; (3) to increase the quality of life of persons with a chronic illness by simplification of the healthcare and social security administration; (4) the social inclusion of persons with a chronic illness both in the work situation as in the society in general and finally (5) to ensure the access and the financial affordability to adequate health care in the broad sense of the word for persons with a chronic illness.

During the development of this plan, the awareness of the specificities of the needs of patients with rare diseases grew and as a consequence the need to develop specific measures for Rare Diseases became apparent.

A request was made by the Fund for Rare Diseases and Orphan Drugs to the Belgian Minister of Health and Social Affairs, on 12 December 2008 for political and financial support to the Fund so as to advance the development of a proposition for a Belgian Plan for Rare Diseases. In February 2009, the Belgian House of Representatives adopted a resolution for a plan of action for rare diseases and orphan medicinal products. The Fund for Rare Diseases and Orphan Drugs, managed by the King Baudouin Foundation, was financially supported for two years (2009-2011) within the framework of the Belgian Plan for Chronic Diseases to develop a proposition of a Belgian Plan for Rare Diseases. An additional request was made for financial support for the umbrella patient association "Rare Diseases Organisation Belgium" (RaDiOrg).

Patient representatives, physicians and other specialists, paramedical staff, insurance organisms, social service representatives, members of industry, the Orphanet Belgium team and administration participated in the working groups of the Fund for Rare Diseases and Orphan Drugs which developed a set of recommendations grouping specific measures into different domains. The development of these recommendations was elaborated in two phases:

- Phase 1 concerned recommendations elaborated in 2010 for the following four central topics: (1) diagnostics and treatment; (2) codification and registration; (3) information, awareness and patient empowerment; and (4) access and cost.
- Phase 2 concerned recommendations elaborated in 2011 for the following topics: non-medical costs of rare diseases; international networking, research, adherence; advanced therapy medicinal products, ethical issues, teaching and education, including therapeutic education and finally clinical trials.

The final set of proposals consisting of the updated recommendations of phase 1<sup>20</sup> integrated with the recommendations of phase 2 was sent to the minister of Social Affairs and Public Health at the end of the first semester of 2011. This report is available online on the website of the King Baudouin Foundation in English, French, German and Dutch languages<sup>21</sup>. The proposed plan consisted of 42 recommendations and measures that can be grouped into five central themes: Expertise and multidisciplinary; Collaboration and networking; Knowledge, information and awareness; Equity in access; and Governance and sustainability."

A steering committee appointed by the Minister of Public Health was put in place which analysed the proposals in terms of financing and the existing plans for cancer and chronic diseases. At the end 2013, a Plan<sup>22</sup> was developed based on the analysis of this steering committee and adopted by the Minister of Public Health. Twenty actions are identified in 4 main categories with specific tasks, budget and leading authorities defined for each point. The four main categories included: the improvement of access to diagnostics and information for patients, the optimisation of health care, the improvement of knowledge generation and the governance and sustainability of the plan.

<sup>20</sup> <http://www.kbs-frb.be/publication.aspx?id=271066&LangType=2060>

<sup>21</sup> <http://www.kbs-frb.be/publication.aspx?id=288128&LangType=1033>

<sup>22</sup> [http://www.laurette-onkelinx.be/articles\\_docs/Plan\\_Belge\\_pour\\_les\\_maladies\\_rares.pdf](http://www.laurette-onkelinx.be/articles_docs/Plan_Belge_pour_les_maladies_rares.pdf)

A budget of €15 million per year is foreseen for the Plan: this budget does not include treatment costs. A unit dedicated to the monitoring and evaluation of the plan will be created to oversee the implementation and define any additional required measures. In addition a working group has been established at the Chronic Disease Observatory to monitor and define unmet needs of patients with rare diseases in Belgium.

Besides the funding for the plan, most of the expenditures for rare diseases are covered by the general health system budget. A Special Solidarity Fund is also in place which can be used for patients whose costs are not covered by the health care system (for example some Orphan medicinal product costs). In addition a small specific budget is allocated specially for rare diseases.

### **Centres of expertise**

In Belgium there are several centres specialised in one rare disease or a group of rare diseases. Some of these centres are recognised by the National Institute for Health and Disability (NIHDI) and work under a convention. These centres include: cystic fibrosis centres, and the centres for metabolic diseases and neuromuscular diseases. A new convention with centres of expertise in haemophilia will start in 2014. New centres will be created on basis of an evaluation of needs in multidisciplinary specific care. A group of experts have developed a tool for prioritisation and the working modalities of the centres of expertise in order to implement this action.

A budget of €2 million is allocated for the development and the strengthening of centres of expertise in the multidisciplinary diagnosis of rare diseases, and expertise laboratories in several specific non-genetic tests used for the diagnosis and the follow-up of rare diseases.

On the other hand, genetic counselling, carried out by a multidisciplinary team, will be financed through a new convention with the 8 Belgian genetics centres. The convention also includes guarantees for the adequate quality control and registration of clinical activities. The Belgian Centres for Human Genetics have a full service offering different types of tests and technologies, and patient and family counseling.

An elaborate mapping of expertise in the Belgian hospitals will be carried out in 2014 by the WIV-ISP. The mapping takes into account the EUCERD recommendations concerning criteria for designation.

### **Registries**

Nationally funded patient registries exist for cystic fibrosis and a set of neuromuscular diseases, and collect extensive data. Belgian clinicians also contribute to the following European registries: EUROCAT, AIR, ECFS, RBDD, ESID, EIMD, ENRAH, EUROGLYCANET, EUNEFRON and EURECHINOREG. At the moment there are no designation procedures in place for rare disease-specific registries.

As epidemiological data on the complete Belgian rare disease population are scarce and fragmented and as this information is essential for health care planning and monitoring, the development of a Central Registry for Rare Diseases is needed, aiming to collect basic information on all rare disease patients. A conceptual note was written concerning the creation of a Central Registry of Rare Diseases able to collect a small set of basic variables. The conceptual note, approved by a group of stakeholders was accepted in December 2011 and a budget was allocated for 2012-2013 to the Scientific Institute of Public Health through a convention with the NIHDI for the creation of the registry. Objectives were defining the common data set and developing a business plan and privacy plan for a central registry, the further mapping and characterisation of existing rare disease patient databases, defining criteria for prioritisation in elaborating new disease-specific registries, participation in national rare disease activities as well as in EPIRARE and other European initiatives. In 2013, an authorisation was granted by the Privacy Commission to start up a first edition of a Central Registry for Rare Diseases. This first edition entails the prospective data-collection on rare disease patients that consult the genetic centres. In the future, a new authorisation request will be filed to allow for data-collection in treatment centres. Work is also underway to include Orpha codes in the health information system in Belgium. The convention has been prolonged for the time period 2014-2016 as one of the actions of the Belgian plan on rare diseases.

### **Neonatal screening policy**

Neonatal screening in Belgium is a regional competency and is organised by the Vlaams Agentschap Zorg en Gezondheid (Flemish Community) and La Direction générale de la santé du Ministère de la Communauté française (French Community). The program in Flanders encompasses screening for following 11 metabolic diseases: phenylketonuria/hyperphenylalaninemia, congenital hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency, medium-chain acyl-CoA dehydrogenase deficiency (MCAD), multiple acyl-CoA dehydrogenase deficiency (MADD), glutaric acidemia type I, isovaleric acidemia, maple syrup urine disease (leucinosis), propionic acidemia and methylmalonic acidemia. In the French community neonatal screening is

provided for 6 metabolic diseases: phenylketonuria, congenital hypothyroidism, maple syrup urine disease (leucinosis), galactosaemia, tyrosinemia and homocystinuria. In addition, a specific screening for the risk group for thalassemia is organised by the Brussels Capital Region.

### **Genetic testing**

Genetic testing is carried out exclusively by 8 Centres for Human Genetics, whose operational standards are established by Royal Decree and reimbursed by the NIHDI.

All genetic centres have obtained an accreditation of their diagnostic activities. An accreditation of the laboratories will be obligatory as of January 2014. There are no officially recognised reference laboratories for specific diseases or tests, however the genetic centres cooperate intensively and exchange patient samples for genetic testing based on the expertise of the different laboratories on an informal basis. National guidelines for genetic testing, genetic counselling and clinical management are available for some diseases and are being developed within the College of Human Genetics in cooperation with the scientific organisation of the geneticists, the Belgian Society for Human Genetics.

The reimbursement conditions of genetic tests have been revised. The new nomenclature offers a stratified reimbursement system and includes a comprehensive list of diagnoses and genes for which testing is available in Belgium.

Genetic testing abroad is possible, when referred by the Belgian genetic centres: the genetic centres send the samples to a foreign reference laboratory. The genetic tests carried out abroad will be reimbursed by convention with the 8 Belgian genetic centres. This is one of the actions of the plan. A list of authorised tests and the foreign reference laboratories is available: this initiative is part of a decree for the creation of a convention between the NIHDI and the genetic centres that is in force since 1 January 2013.

Diagnostic tests are registered as available in Belgium for 401 genes and an estimated 561 diseases in the Orphanet database<sup>23</sup>.

### **National alliances of patient organisations and patient representation**

Rare Disease Organisation Belgium (RaDiOrg.be) is a non-profit organisation established in January 2008. RaDiOrg.be regroups around 49 patient organisations for rare diseases in Belgium and is affiliated with EURORDIS. All these organisations are members of the general council of RaDiOrg.be. RaDiOrg.be activities include the organisation of the Rare Disease Day, information and training for patient organisations as well as defending their needs towards public authorities. RaDiOrg.be is funded by the Federal Government and the Belgian pharmaceutical industry umbrella group Pharma.be and will receive regular structural funding from the former from 2013 onwards.

Patients are well represented in meetings concerning the rare disease situation in Belgium: RaDiOrg.be and two other patient organisation platforms (VPP and LUSS) are recognised representatives of patients in the Fund for Rare Diseases as well as in the working group of rare diseases of the NIHDI. In addition, it was decided by law (11 February 2010) that an observatory on chronic diseases will be created including patient organisation representatives and health insurance representatives in order to advise the NIHDI on all issues concerning accessibility of care for chronically ill people, including rare disease patients. The mission of the observatory on chronic diseases is to create awareness of the existing everyday problems of people with a chronic illness and to formulate recommendations and solutions in order to address these needs. This observatory consists of two taskforces: a scientific taskforce and a consultative taskforce.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Belgium***

From 2001 onwards there is a dedicated Orphanet team in Belgium. In the past the team was hosted by the Centre of Human Genetics at the Catholic University of Leuven. As of April 2011, the start of the Orphanet Joint Action, a team for Belgium has been designated at the Scientific Institute for Public Health (IPH) by the Federal Public Service for Public Health, Food Chain Safety and Environment. The Federal Public Service of Public Health itself also participates in the Orphanet project from April 2011 onwards. The team published the Orphanet Belgium national web page in 2012. The team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The NIHDI provides further support for the Orphanet team at the institute as to carry out the Dutch translation of Orphanet content in order to increase the linguistic accessibility for Belgium's population. Scientific board meetings for the Belgian Orphanet site started in 2008 to

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<sup>23</sup> Information extracted from the Orphanet database in January 2014.

validate the data already gathered on the existing rare disease services and research activities in Belgium. Currently the validation procedure is being revised. For most activities the validation procedure has been revised by the coordinating board. Inclusion criteria and the registration procedure are published on the country Orphanet site. The Belgian Scientific Institute of Public Health received funding for the period 2012-2013 from the National Institute for Health and Disability Insurance for the translation of the Orphanet portal into the Dutch language. This includes the translation of the structure of the site, the lists of diseases with medical terms and the scientific abstracts. This was one of the measures recommended by the Belgian Fund of Rare Diseases and Orphan Drugs. The Dutch Orphanet team is collaborating with the Belgian collaborating team on this project.

#### **Official information centre for rare diseases**

There is no official information centre or website on rare diseases other than Orphanet, but the centres of expertise for rare diseases will have the obligation to give information to patients and family members

#### **Help line**

There is currently no rare diseases help line in Belgium.

#### **Other sources of information**

RaDiOrg.be maintains an informative website ([www.radiorg.be](http://www.radiorg.be)) which publishes information on rare diseases and patient groups in Belgium: RaDiOrg is also since 2012 present on Facebook. The websites [www.weesziekten.be](http://www.weesziekten.be) and [www.maladiesrares.be](http://www.maladiesrares.be) provide additional information on the actions of the Fund for Rare Diseases and Orphan Drugs, in both French and Dutch.

The FAMHP (Federal Agency for Medicines and Health Products) contributes to the European database on clinical trials, which became available to the general public in 2011 in line with the transparency position with relation to clinical trials.

#### **Guidelines**

Proposals for the development of good practice guidelines or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

#### **Emergency cards and guidelines**

The possibility of introducing and adapting the Orphanet emergency guidelines will be considered in 2014.

#### **Training and education initiatives**

Proposals for their development or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

#### **National rare disease events in 2013**

To mark of Rare Disease Day 2013 RaDiOrg carried out an awareness campaign using social media<sup>24</sup>.

#### **Hosted rare disease events in 2013**

A number of European events were held in Brussels to mark Rare Disease Day. Eurordis co-hosted with Members of the European Parliament a Policy Discussion Meeting entitled "*Faster Access to Medicines for Rare Disease Patients*", designed to move forward the process of improving access to treatment in the context of the revision of the EU Transparency Directive. The event was attended by 100 participants, and watched simultaneously by over 200 viewers from 10 countries through a live feed.

#### **Research activities and E-Rare partnership**

##### **National research activities**

There are no specific research programmes for rare diseases in Belgium. The FRS-FNRS (Fund for Scientific Research, French-speaking community of Belgium)<sup>25</sup> and its associated FRSM (Fund for Scientific Medical Research)<sup>5</sup> provides funding for basic research on rare diseases including rare cancers. Rare disease research also benefits from initiatives such as programmes to stimulate translational R&D. Some fundraising patient organisations also finance rare disease research.

<sup>24</sup> <http://radiorg.be/activiteiten/Zeldzame%20ziektendag/RDD%202013>

<sup>25</sup> [www.frs-fnrs.be](http://www.frs-fnrs.be)

### **Participation in European research projects**

Belgium teams are participating partners in 7 FP7 related to rare diseases and coordinated 12 projects.

#### **E-Rare**

The F.R.S.-FNRS (Fund for Scientific Research) is a full contracting member of the E-Rare and the E-Rare 2 consortium, participating in the decision and implementation process of the network, while the FWO (Research Foundation Flanders) joined the E-RARE 2 network as an associate member. Although none of the Belgian funding agencies participated in E-Rare's first two Joint Transnational Calls, the FWO and F.R.S.-FNRS did participate in the E-RARE 2 3rd Joint Transnational Call in 2011 and the 5th Joint Transnational Calls in 2013. Furthermore, the FWO also participated in the 4th Joint Transnational Call in 2012. During these calls, several Belgian research teams were selected for funding. Finally, both the FWO and the F.R.S.-FNRS have the intention to participate in the next Joint Transnational Call of 2014.

#### **IRDiRC**

The FNRS and FWO as a member of the E-Rare group of funders joined the IRDiRC in 2012.

### **Orphan medicinal products<sup>26</sup>**

#### **Orphan medicinal product incentives**

Since 2006, at the initiative of the NIHDI, the revenues of orphan medicinal products are no longer subject to so called 'pharmaceutical taxes' (i.e. taxes, earmarked for social security), on sales of reimbursable drugs. But since 2013, given the expenditures for these products, the government has decided to engage the firms with the creation of a tax, but lower than those in charge of firms with non-orphan drugs

#### **Orphan medicinal product market availability situation**

Since 2001, orphan medicinal products obtain Marketing Authorisation (MA) through the centralised procedure at the EMA. In addition orphan status can also be attributed by AFMPS (National Procedure) ex: Flolan, Duodopa. As for the list of the reimbursed orphan medicinal products, please see the section "Orphan medicinal product reimbursement policy". The products that are not reimbursed can be nonetheless available on the market and this is the case for Wilzin and Pedeia, which are included in the list of CBIP.

#### **Other initiatives to improve access to orphan medicinal products**

The Law of 1 May 2006 provides for Compassionate Use programs (in case of a medicinal product without a MA in Belgium), or Medical Need programs (in case of a medicinal product with a MA in Belgium but for another indication)<sup>27</sup>. A last possibility for non-reimbursed pharmaceutical products is reimbursement by the Special Solidarity Fund (SSF), which is regulated by the Law of 14 July 1994, Articles 24 and 25. Conditions for compassionate use or reimbursement through the SSF are defined by law. In 2007, orphan medicinal products accounted for about 35% of the SSF's total budget<sup>28</sup>. With the "law and accessibility" [February 2014] legal basis was established for a structural answer to unmet medical needs. For identified needs, based upon a list of priorities set up by the General Council at NIHDI, financial intervention will be made possible ins case of early access to promising drug therapies ins unmet medical need (including orphan drugs)

#### **Orphan medicinal product pricing policy**

The Minister for Economic Affairs determines the maximum manufacturer selling price of reimbursed prescription medicines, taking advice from the Ministry's Medicines Pricing Commission. The agreed price is forwarded to the NIHDI for a recommendation to the Minister of Social Affairs and Public Health on reimbursement. The actual purchase price of medicines used in hospitals is based on negotiations between manufacturers and the hospitals<sup>29</sup>.

#### **Orphan medicinal product reimbursement policy**

According to information collected for the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products, "in Belgium, one of the most important measures has been the adoption of the Royal Decree of 8 July 2004 on the reimbursement

<sup>26</sup> This section has been written with information from the section on Belgium in the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins* – 2009 (pp35-45).

<sup>27</sup> *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins* – 2009 (p40).

<sup>28</sup> *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins* – 2009 (pp35-45).

<sup>29</sup> *Orphan Drugs in Europe : Pricing, reimbursement, Funding and Market Access Issues (2011 Edition)*, Donald Macarthur, (p 99).



of orphan medicinal products. This Decree, which entered into force on 20 July 2004, created a 'Committee of Doctors for Orphan Medicinal Products' within the Healthcare service of the NIHDI, the body responsible for issuing opinions on orphan medicinal products when an opinion is required, including with regard to evaluating individual rights to reimbursement. It also evaluates the existing reimbursement conditions for these products and draws up an annual activity report"<sup>30</sup>.

Drug reimbursement decisions are taken by the Minister of Social Affairs, after advice from the Drug Reimbursement Committee (DRC) as well as the Minister of Finances and the agreement of the Minister of the Budget. Orphan medicinal products follow the same procedure as Class I pharmaceutical products, i.e. products for which the company claims a therapeutic added value. However, unlike for Class I pharmaceutical products, no pharmaco-economic evaluation has to be submitted for orphan medicinal products. A decision on the reimbursement is taken within 180 days following the submission of the reimbursement request.

At the end of December 2013, 63 orphan medicinal products were eligible for reimbursement in Belgium (including two products that do not have EMA orphan medicinal product status, but that are reimbursed for an orphan indication) for a total of around 80 orphan indications. Orphan medicinal products are most of the time fully reimbursed (except Tracleer in the prevention of digital ulcers in sclerodermia); although for some of them reimbursement depends on prescription by specialists belonging to a recognised centre that provides treatment.

The list of medicinal products, including those which have in the past the label of orphan drugs, reimbursed by the NIHDI<sup>31</sup> includes: Afinitor, Aldurazyme, Atriance, Benefix, Busilvex, Carbaglu, Casyston, Cerezyme, Cystadane, Cystagon, Dacogen, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyr, Flolan, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kogenate, Kuvan, Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Normosang, Nplate, Orfadin, Refacto AF, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Sutent, Tassigna, Thalidomide, Thelin, Tobi (Podhaler), Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Vpriv, Xagrid, Xyrem, Yondelis, Zavesca<sup>32</sup>.

In normal circumstances, the specialist first obtains the approval of a Medical Advisor of the patient's sickness fund to prescribe the medicine. The Medical Advisor is able, but is not obliged to, request the advice of a "College of Medical Doctors for Orphan Drugs" (CMDOD). In practice, all sickness funds have agreed to refer all requests to the CMDOD if one exists. Separate Colleges exist for separate products and the DRC decides whether or not a College is established. At the end of 2013, there were 32 colleges for 63 orphan medicinal products. Individual reimbursement decisions are made on a case by case by the Medical Advisor based on the advice of the CMDOD. They are valid for periods going from 6 to 12 months<sup>33</sup> and can be renewed.

A study entitled "Policies for Orphan Diseases and Orphan Drugs"<sup>34</sup>, compiled by the Belgian Health Care Knowledge Centre, was published in June 2009. This is a comprehensive English-language report that compares the Belgian orphan medicinal product reimbursement policy with other countries, estimates the current budget impact of orphan medicinal products, forecasts the expected future budget impact, and offers recommendations for policy makers concerning orphan medicinal products.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Orphan devices**

No specific information reported.

#### **Specialised social services**

Facilities for respite care and therapeutic recreational programmes are under investigation but do not currently exist in a structured fashion exclusively for rare diseases. A budget is foreseen in the framework of the Chronic Disease Programme for the financing of respite care structures for children with chronic diseases, including rare diseases patients. Three projects started in 2011. Governmental measures for the integration of handicapped persons already exist in Belgium by means of social and financial support. The NIHDI reimburse for the transport cost for the children who are in treatment in a centre of expertise.

<sup>30</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p8).

<sup>31</sup> [http://www.inami.fgov.be/inami\\_prd/ssp/cns2/pages/OrphanCns.asp](http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/OrphanCns.asp) (updated 01/04/2010)

<sup>32</sup> Please note that for Afinitor, Sutent and Xyrem, the orphan designation was withdrawn.

<sup>33</sup> *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp43-44).

<sup>34</sup> Link to the report: <https://kce.fgov.be/publication/report/policies-for-rare-diseases-and-orphan-drugs>

## RARE DISEASE ACTIVITIES IN 2013 IN BELGIUM

### National plan/strategy for rare diseases and related actions

At the end 2013, a Plan for rare diseases<sup>35</sup> was developed based on the analysis of this steering committee and adopted by the Minister of Public Health. Twenty actions are identified in 4 main categories with specific tasks, budget and leading authorities defined for each point. The four main categories included: the improvement of access to diagnostics and information for patients, the optimisation of health care, the improvement of knowledge generation and the governance and sustainability of the plan.

A budget of € 15 million per year is foreseen for the Plan: this budget does not include treatment costs. A unit dedicated to the monitoring and evaluation of the plan will be created to oversee the implementation and define any additional required measures. In addition a working group has been established at the Chronic Disease Observatory to monitor and define unmet needs of patients with rare diseases in Belgium.

Besides the funding for the plan, most of the expenditures for rare diseases are covered by the general health system budget. A Special Solidarity Fund is also in place which can be used for patients whose costs are not covered by the health care system (for example some Orphan medicinal product costs). In addition a small specific budget is allocated specially for rare diseases.

### Centres of expertise

In Belgium there are several centres specialised in one rare disease or a group of rare diseases. Some of these centres are recognised by the National Institute for Health and Disability (NIHDI) and work under a convention. These centres include: cystic fibrosis centres, and the centres for metabolic diseases and neuromuscular diseases. A new convention with centres of expertise in haemophilia will start in 2014. New centres will be created on basis of an evaluation of needs in multidisciplinary specific care. A group of experts have developed a tool for prioritisation and the working modalities of the centres of expertise in order to implement this action.

A budget of €2 million is allocated for the development and the strengthening of centres of expertise in the multidisciplinary diagnosis of rare diseases, and expertise laboratories in several specific non –genetic tests used for the diagnosis and the follow-up of rare diseases.

On the other hand, genetic counselling, carried out by a multidisciplinary team, will be financed through a new convention with the 8 Belgian genetics centres. The convention also includes guarantees for the adequate quality control and registration of clinical activities. The Belgian Centres for Human Genetics have a full service offering different types of tests and technologies, and patient and family counseling.

An elaborate mapping of expertise in the Belgian hospitals will be carried out in 2014 by the WIV-ISP. The mapping takes into account the EUCERD recommendations concerning criteria for designation.

### Registries

In 2013, an authorisation was granted by the Privacy Commission to start up a first edition of a Central Registry for Rare Diseases. This first edition entails the prospective data-collection on rare disease patients that consult the genetic centres. In the future, a new authorisation request will be filed to allow for data-collection in treatment centres. Work is also underway to include Orpha codes in the health information system in Belgium. The convention has been prolonged for the time period 2014-2016 as one of the actions of the Belgian plan on rare diseases.

### Genetic testing

All genetic centres have obtained an accreditation of their diagnostic activities. An accreditation of the laboratories will be obligatory as of January 2014. The reimbursement conditions of genetic tests have been revised. The new nomenclature offers a stratified reimbursement system and includes a comprehensive list of diagnoses and genes for which testing is available in Belgium.

Genetic testing abroad is possible, when referred by the Belgian genetic centres: the genetic centres send the samples to a foreign reference laboratory. The genetic tests carried out abroad will be reimbursed by convention with the 8 Belgian genetic centres. This is one of the actions of the plan. A list of authorised tests and the foreign reference laboratories is available: this initiative is part of a decree for the creation of a convention between the NIHDI and the genetic centres that is in force since 1 January 2013.

<sup>35</sup> [http://www.laurette-onkelinx.be/articles\\_docs/Plan\\_Belge\\_pour\\_les\\_maladies\\_rares.pdf](http://www.laurette-onkelinx.be/articles_docs/Plan_Belge_pour_les_maladies_rares.pdf)

### **National alliances of patient organisations and patient representation**

Rare Disease Organisation Belgium (RaDiOrg.be) is a non-profit organisation established in January 2008. RaDiOrg.be is funded by the Federal Government and the Belgian pharmaceutical industry umbrella group Pharma.be and will receive regular structural funding from the former from 2013 onwards.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Belgium***

The Belgian Scientific Institute of Public Health received funding for the period 2012-2013 from the National Institute for Health and Disability Insurance for the translation of the Orphanet portal into the Dutch language. This includes the translation of the structure of the site, the lists of diseases with medical terms and the scientific abstracts. This was one of the measures recommended by the Belgian Fund of Rare Diseases and Orphan Drugs. The Dutch Orphanet team is collaborating with the Belgian collaborating team on this project.

#### **Guidelines**

Proposals for the development of good practice guidelines or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

#### **Emergency cards and guidelines**

The possibility of introducing and adapting the Orphanet emergency guidelines will be considered in 2014.

#### **Training and education initiatives**

Proposals for their development or implementation of existing guidelines have been formulated in the proposals for a Belgian plan.

#### **National rare disease events in 2013**

To mark of Rare Disease Day 2013 RaDiOrg carried out an awareness campaign using social media<sup>36</sup>.

#### **Hosted rare disease events in 2013**

A number of European events were held in Brussels to mark Rare Disease Day. Eurordis co-hosted with Members of the European Parliament a Policy Discussion Meeting entitled "*Faster Access to Medicines for Rare Disease Patients*", designed to move forward the process of improving access to treatment in the context of the revision of the EU Transparency Directive. The event was attended by 100 participants, and watched simultaneously by over 200 viewers from 10 countries through a live feed.

#### **Orphan medicinal products<sup>37</sup>**

##### ***Orphan medicinal product incentives***

Since 2006, at the initiative of the NIHDI, the revenues of orphan medicinal products are no longer subject to so called 'pharmaceutical taxes' (i.e. taxes, earmarked for social security), on sales of reimbursable drugs. But since 2013, given the expenditures for these products, the government has decided to engage the firms with the creation of a tax, lower than those in charge of firms with non-orphan drugs.

## **1.3. BULGARIA**

### **Definition of a rare disease**

Stakeholders in Bulgaria accept the definition of a prevalence of no more than 5 in 10 000 individuals. This definition is officially stated in the Bulgarian National Plan for Rare Diseases, and it is also included in the provisions of the Health Act.

<sup>36</sup> <http://radiorg.be/activiteiten/Zeldzame%20ziektendag/RDD%202013>

<sup>37</sup> This section has been written with information from the section on Belgium in the *KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* (pp35-45).

### **National plan/strategy for rare diseases and related actions**

On 27 November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009 – 2013). The Bulgarian National Plan for Rare Diseases started on 1 January 2009 and lasted for 5 years. The Plan consists of nine priorities targeting all rare diseases:

- Collection of epidemiological data for rare diseases in Bulgaria by creation of a national register;
- Improvement of the prevention of genetic rare diseases by enlarging the current screening programmes;
- Improvement of the prevention and diagnostics of genetic rare diseases by introducing new genetic tests, decentralisation of the laboratory activities and easier access to medico-genetic counselling;
- Integrative approach to the prevention, diagnostics, medical treatment and social integration of patients and their families;
- Promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases;
- Feasibility study on the necessity, possibility and criteria for the creation of a reference centre for rare diseases of functional type;
- Organisation of a national campaign to inform society about rare diseases and their prevention;
- Support and collaboration with NGOs and patient associations for rare diseases;
- Collaboration with the other EU members.

A National Consulting Council on Rare Diseases (NCCRD) was established by the Ministry of Health, to supervise the progress and implementation of the plan. NCCRD includes medical professionals, Ministerial representatives and a representative of the National Alliance of People with Rare Diseases. Although the initial budget of the Plan was €11.3 million, subsequent funds assigned were much less and were mostly directed to genetic testing and screening activities. The National Health Insurance Fund (NHIF) reimburses rare disease treatments, while the Ministry of Health is funding some services like prenatal and neonatal screening for rare diseases. The Ministry of Health is also providing funds for treatment abroad and transplantations through subordinated national agencies, although these are not rare disease-specific bodies.

The Plan officially ended on 31 December 2013. Before that, the Ministry of Health had established a working group to prepare a draft for a Second National Plan. The Plan is expected to work closely with the National Rare Disease Registry and the centres of expertise for rare diseases, both of which are supposed to be officialised by the end of 2014. However, no schedule for the adoption and the implementation of the Second Plan was available by the end of 2013.

Starting in 2010, the year in which a EUROPLAN National Conference was held<sup>38, 39</sup>, annual rare diseases conferences are organised by the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD), gathering all national rare diseases stakeholders to discuss topics of common interests. The event in 2011 focused on registries for rare diseases, while 2012 and 2013 events covered centres of expertise for rare diseases.

### **Centres of expertise**

Significant progress was achieved in 2013 regarding the centres of expertise for rare diseases in Bulgaria. The National Assembly voted amendments in the Health Act (Article 144a), requiring the Minister of Health to adopt a regulation, which will establish a National Registry for Rare Diseases, as well as will determine the criteria for designation of centres of expertise for rare diseases. The Ministry of Health established a working group, which prepared a draft regulation, containing criteria for designation of centres of expertise and reference networks for rare diseases, as well as rules and procedures for their implementation, monitoring and evaluation. The draft regulation also envisages the establishment of a permanent National Rare Diseases Council to the Ministry of Health, as well as an official list of rare diseases. The draft was discussed at several meetings, including the National Conference for Rare Diseases in September 2013. The final draft was submitted to the Ministry of Health early in 2014. This legislation is expected to be approved by the Ministry of Health and to come into force by the end of 2014.

Despite the lack of official designation for the moment there are several academic centres that are specialised as centres of research, treatment and management for rare diseases, i.e. cystic fibrosis,

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<sup>38</sup> <http://www.conf2010.raredis.org/>

<sup>39</sup> [http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/FINAL%20Report\\_Bulgarian%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Bulgarian%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf)

mucopolysaccharidosis, thalassemia major, Gaucher disease, neuromuscular diseases, Wilson disease, porphyrias, primary immunodeficiency. Treatment with orphan medicinal products is currently reimbursed in these centres, which also manage the provision of very expensive orphan medicinal products. Medical experts from these centres also participate in developing protocols for the National Health Insurance Fund, which serve the treatment of rare disease patients.

In addition, since May 2009, the Bulgarian Association for Promotion of Education and Science (BAPES) runs highly specialised medical centre for rehabilitation and education of people with rare diseases "RareDis". Since September 2013, RareDis and ICRDOD were merged into the Institute for Rare Diseases (IRD), together with the newly-established Centre for Health Technology Assessment and Analyses (CAHTA).

### Registries

The first priority in the National Plan was to provide epidemiological data on rare diseases in Bulgaria through the establishment of a National Registry. The Registry's tasks included:

- Collecting, summarising, and providing epidemiologic information on the incidence and prevalence of rare diseases in Bulgaria;
- Assisting the preparation of diagnostic and therapeutic protocols and standards for treatment of rare diseases;
- Assisting the Ministry of Health, the Ministry of Labour and Social Policy, and the National Health Insurance Fund in the planning and delivery of expensive treatment and medical care to patients with rare diseases;
- Improving the interaction between health services and patient organisations;
- Providing and publishing data needed for planning and comparison on a regional and national level.

However, during the National Plan (2009 – 2013), no National Registry was established.

The idea to implement a National Registry for Rare Diseases re-emerged in 2013. This was motivated by the upcoming implementation of the centres of expertise for rare diseases in the country. Initial plans suggest that the Registry will collect data from these centres and prepare annual reports on rare disease epidemiology. Thus, the Registry will contain only data for rare diseases, for which there are officially designated centres of expertise. However, by the end of 2013 it is not yet decided which institution will coordinate and manage the Registry.

Despite the lack of an official National Registry, Bulgaria has recently gained a considerable amount of experience and knowledge on rare disease epidemiology. ICRDOD released a report<sup>40</sup> in 2012 listing the epidemiological registries for rare diseases in Bulgaria: the report aimed to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country. Eight nation-wide epidemiological registries concerning rare diseases were identified: the National registry of Patients with Phenylketonuria, the National Registry of Patients with Primary Immunodeficiencies (PID), the National Registry of Patients with Thalassemia Major, the National Registry of Chronic Myeloid Leukaemia Patients, the National Registry of Crohn Disease Patients, the National Registry of Wilson Disease Patients, the National Registry of Gaucher Disease Patients, the National Registry of Mucopolysaccharidosis type 2 Patients. In 2013 ICRDOD established two new registries – for primary myelofibrosis and neuroendocrine tumours.

### Neonatal screening policies

One of the national plan's priorities was to improve the availability and accessibility of the current screening programs. In 1979 mass neonatal screening was introduced in Bulgaria for phenylketonuria, galactosaemia (discontinued in 1993), congenital hypothyroidism and congenital adrenal hyperplasia. Some selective metabolic screening programmes are coordinated by the University Maternity Hospital National Genetic Laboratory in Sofia for the metabolic screening programmes (phenylketonuria), and the University Paediatric Hospital in Sofia for the endocrine screening programmes (congenital hypothyroidism and congenital adrenal hyperplasia). There is coverage of the entire country with more than 130 neonatal structures carrying out blood sampling 3-5 days after birth. Over 90% of neonates are included in existing measures. Ordinance 26 2007 of the Ministry of Health provides equal access to the neonatal screening programmes. However, there exist certain problems, such as postponed mailing of screening cards to centralised labs, and the need for technological upgrades.

It is expected that with the implementation of the Ministry of Health regulation on centres of expertise for rare diseases, the neonatal screening laboratories will be designated as centres of expertise as well, and they will be organised into a reference network.

<sup>40</sup> [http://raredis.org/pub/Epi\\_Reg\\_Report\\_2012\\_EN.pdf](http://raredis.org/pub/Epi_Reg_Report_2012_EN.pdf)

### **Genetic testing**

National guidelines for performance of genetic testing in Bulgaria are regulated by the Health Act and the National Medical Genetics Standard. Genetic tests for the diagnosis of rare diseases are provided mainly by the National Genetic Laboratory (NGL). NGL is a national reference laboratory that provides methodological guidance and control over the activities of the genetic laboratories and performs centralised some specialised tests. It was established more than 35 years ago, by initiating of biochemical analysis for some rare disorders and mass neonatal screening for PKU. At the moment NGL provides routine diagnosis with DNA analysis (including prenatal and evaluation of carrier status) for many disorders: cystic fibrosis, phenylketonuria, Wilson disease, neuromuscular disorders, Niemann–Pick (in target population), beta thalassemia, galactokinase deficiency (in target population), microdeletions and microduplications syndromes, inborn hypothyroidism and other. The NGL also has the capacity to perform routine enzymatic analysis and GS/MS analysis for diagnosis of many rare disorders (Krabe, Pompe, MPS). In 2010 the laboratory introduced MS/MS analysis for metabolic study of inherited disorders.

The government organises support of testing by financing diagnostic kits and consumables. Genetic testing abroad is possible for diseases for which genetic tests are not available in Bulgaria, after commission approval. Furthermore, clinical centres, as well as separate research teams have the opportunity through research funded projects by relevant universities and the Ministry of Education's Research Fund to apply for routine implementation of molecular genetic diagnosis for certain rare diseases. In these cases, patients' diagnosis is provided free of charge.

Diagnostic tests are registered as available in Bulgaria for 34 genes and an estimated 84 diseases in the Orphanet database<sup>41</sup>.

### **National alliances of patient organisations and patient representation**

The National Alliance of People with Rare Diseases (NAPRD) in Bulgaria is an umbrella organisation of more than 30 rare disease patient associations and groups. It aims to create a link between the people with rare diseases and the representatives of the social and healthcare system. NAPRD advocates for the right to timely and equal medical care, as well as for the creation of adequate laws in the field of the protection of the rights of people with rare diseases. A NAPRD representative is also a member of National Consulting Council on Rare Diseases at The Ministry of Health.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Bulgaria***

Since 2004 there is a dedicated Orphanet team in Bulgaria, currently hosted by the Information Centre for Rare Diseases and Orphan Drugs (ICRDOD). This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database.

#### ***Official information centre for rare diseases***

ICRDOD<sup>42</sup> is a project and activity of the Bulgarian Association for Promotion of Education and Science (BAPES<sup>43</sup>) – a non-government non-profit organisation, registered under the Bulgarian law on non-profit legal in 2003. ICRDOD is a free educational and informative service in Bulgarian and English, providing personalised replies to requests from patients, families and medical professionals. It operates a multilingual website ([www.raredis.org](http://www.raredis.org)) and a rare disease help line - (+359) 32 57 57 97. The ICRDOD also provides a bi-monthly newsletter<sup>44</sup> ("Rare Diseases & Orphan Drugs"): every issue contains a cover story with an interview, news and announcements and a rare diseases reading list. It is electronic and distributed free of charge. The newsletter is published in two versions – Bulgarian (ISSN 1314-3581) and English (ISSN 1314-359X). The ICRDOD also provides an online registry of rare diseases patients, and a Rare Diseases Library in Bulgarian.

In 2010 ICRDOD started publishing reviews on rare diseases topics. These papers' objective is to summarise important information on particular topics in the field and to present it in a reader-friendly format.

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria<sup>45</sup>. The report contains 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive drug list and reimbursement; mechanisms for accelerated access to innovative

<sup>41</sup> Information extracted from the Orphanet database in February 2014.

<sup>42</sup> <http://www.raredis.org/>

<sup>43</sup> [http://www.raredis.org/?page\\_id=2147&mel=8&smel=81&lang=en](http://www.raredis.org/?page_id=2147&mel=8&smel=81&lang=en)

<sup>44</sup> [http://www.raredis.org/?page\\_id=2311&mel=7&smel=71&lang=en](http://www.raredis.org/?page_id=2311&mel=7&smel=71&lang=en)

<sup>45</sup> *Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria:* [http://raredis.org/pub/OD\\_Report\\_2013\\_EN.pdf](http://raredis.org/pub/OD_Report_2013_EN.pdf)

medicines; conclusions. There are 2 annexes, attached to the review: list of orphan medicinal products in EU and Bulgaria, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorisation holder and date of marketing authorisation for each item (additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds); and a list of references.

The Bulgarian Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) released a report in 2012<sup>46</sup> listing the epidemiological registries for rare diseases in Bulgaria: the report aimed to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country.

### **Help line**

ICRDOD provides a rare disease help line - (+359) 32 57 57 97 providing personalised replies to requests from patients, families and medical professionals. ICRDOD is a member of EURORDIS-led European Network of Rare Diseases Help Lines and took part in the Network's Caller Profile Analysis 2011, 2012 and 2013.

### **Other sources of information**

Departments of Medical Genetics at all University Hospitals and the National Genetic Laboratory also provide information.

### **Guidelines**

Currently, there are no official good practices guidelines for rare diseases in Bulgaria. The Ministry of Health's medical specialty standards and NHIF's clinical pathway protocols are considered as official best practice guidelines. Nevertheless, they are general ones and do not focus on rare diseases as whole.

Medical societies tend to prepare and adopt guidelines for specific diseases, including rare diseases. These guidelines take into account leading European and international best practices guidelines, thus increasing the quality of health care for rare diseases provided in Bulgaria.

Currently, there are no specific emergency guidelines for rare diseases in Bulgaria.

### **Training and education initiatives**

Bulgarian rare diseases stakeholders are active in promoting EU rare policy at local and regional level. The country hosted the First Rare Diseases Summer School for Health Authorities and Legislators<sup>47</sup>, an event designed to raise awareness of rare diseases among Eastern European health authorities and legislators. The event was successfully organised again in 2012 and 2013 in Greece and Turkey respectively. This initiative is a joint initiative of BAPES, the National Association of Rare Diseases Patient Organisations "Genetics" (Russia) and the Italian National Centre for Rare Diseases (CNMR). School participants come from a wide range of public fields – legislative bodies and health authorities, medical institutions, academia. The week-long event covers a variety of topics.

BAPES also traditionally organises an annual two-day rare disease training seminar for medical students. Medical students have the chance to get acknowledged with the main rare diseases concepts, such definition, major problems, important initiatives, etc. Similar events have been initiated by various patient organisations in 2013, as patients try to raise the awareness of and improve knowledge on particular rare diseases among students. Healthcare institutions and academia largely support these initiatives, holding frequent workshops for rare diseases.

### **National rare disease events in 2013**

Rare Disease Day was marked on 28 February 2013 with events organised by the National Alliance of People with Rare Diseases<sup>48</sup>. A series of information, education and charity events took place with a balloon launch in front of the Ministry of Health in Sofia, followed by an official press conference. The Second Balkan Conference of Patients with Rare Diseases, entitled "Communication and Support to Patients, Based on Modern Technologies" was held in April in Sofia. Outside of Sofia, a series of rare diseases events were organised in the towns of Plovdiv, Varna, Burgas, Stara Zagora, Pleven and Sandanski.

The 4<sup>th</sup> Annual Conference on Rare Diseases and Orphan Drugs was organised on 13-14 September 2013 in Plovdiv<sup>49</sup>. The First National Conference on Rare Diseases for Medical Students was held in parallel,

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<sup>46</sup> [http://raredis.org/pub/Epi\\_Reg\\_Report\\_2012\\_EN.pdf](http://raredis.org/pub/Epi_Reg_Report_2012_EN.pdf)

<sup>47</sup> [http://raredis.org/pub/Newsletter/Rare\\_Diseases\\_Summer\\_School\\_2011.pdf](http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf)

<sup>48</sup> <http://rare-bg.com/>

<sup>49</sup> [www.conf2013.raredis.org](http://www.conf2013.raredis.org)

bringing together more than 130 students from medical universities across Bulgaria and neighbouring countries..

### **Hosted rare disease events in 2013**

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### **Research activities and E-Rare partnership**

#### ***National research activities***

In Bulgaria, there is no specific call for rare diseases at the national fund for research, although rare disease related projects can apply. The National Plan does not envisage any official policies to stimulate research on rare diseases; it only envisages encouraging partnerships.

#### ***Participation in European research projects***

A team in Bulgaria participates in 1 of the FP7 rare disease related projects.

#### ***E-Rare***

Bulgaria is not currently a partner of E-Rare.

#### ***IRDiRC***

Bulgarian funding agencies have not yet committed national funding to the IRDiRC.

### **Orphan medicinal products**

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria<sup>51</sup>. The report contains information on important orphan medicinal products activities and explained how they are set up in Bulgaria in 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive Drug List (PDL) and reimbursement; mechanisms for accelerated access to innovative medicines; and conclusions.

#### ***Orphan medicinal product committee***

There is currently no orphan medicinal products specialised committee in Bulgaria. Orphan medicinal products are subject as are all other medicinal products to the Commissions on the pricing of medicines and on the Positive drug list. In order to optimise these procedures, in 2011 the two commissions were merged into a single one under the Ministry of Health. Subsequently, the Parliament adopted in 2012 new legislation, by which a National Council for Pricing and Reimbursement of Medicinal Products replaced the Commission at the beginning of 2013. The new body has a status of a State agency and is responsible for both pricing and reimbursement of all medicinal products. Medicinal products' safety is monitored by the Bulgarian Drugs Agency.

#### ***Orphan medicinal product incentives***

No specific activity reported.

#### ***Orphan medicinal product market availability situation***

While the decision of market authorisation for orphan drugs is taken at European level by EMA, national authorities regulate access to these medicinal products at national level. The reimbursement decision-making

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<sup>51</sup> Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: [http://raredis.org/pub/OD\\_Report\\_2013\\_EN.pdf](http://raredis.org/pub/OD_Report_2013_EN.pdf)

<sup>51</sup> Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: [http://raredis.org/pub/OD\\_Report\\_2013\\_EN.pdf](http://raredis.org/pub/OD_Report_2013_EN.pdf)



procedure includes pricing and inclusion in the Positive Drug List (PDL). Medicinal products, listed in PDL's Appendix 1 (Medicinal products for treatment of conditions which is paid under the Health Insurance Act) are covered by the National Health Insurance Fund (NHIF) and those, listed in PDL's Annex 2 – by the hospitals' budget under Articles 5, 9 and 10 of the Medical Establishments Act.

There were no significant changes in medicinal product reimbursement legislation in 2013. By 2013, PDL of Bulgaria includes one (1) orphan drug in Appendix 1, seven (7) in Appendix 2, and ten (10) in both Appendices. These include: Elaprase, Evoltra, Exjade, Litak, Lysodren, Mozobil, Myozyme, Nexavar, Nplate, Revatio, Sprycel, Tasigna, Tobi Podhaler, Torisel, Ventavis, Volibris, Vyndaqel, and Yondelis.

Despite the recent increase of these figures, institutions dealing with planning and funding for treatment and rehabilitation of patients with rare diseases still do not have actual and reliable data on the number and distribution of patients in the country and information on the compliance and effectiveness of this expensive treatment. A recent cross-sectional observational study<sup>52</sup> appearing in the journal *Health Policy* evaluated the conditions that impact orphan drug availability in Bulgaria and other Eastern European countries. The authors observe that in Bulgaria: *"All the other orphan drugs, being not reimbursed, are practically inaccessible for the individual patients because of their high price. Despite the increasing number of orphan drugs, which are being reimbursed in Bulgaria, in reality there is no significant improvement of the accessibility of treatment for rare diseases. Neither a national epidemiological registry nor expert centres for rare diseases exist. Regulation of alternative access to orphan drugs (e.g., compassionate use, off-label use) is also missing. In these conditions many patients are left without correct diagnosis, adequate treatment, follow-up and rehabilitation."* The system for determining pricing is proving detrimental to orphan drug availability. Bulgaria uses a history-based budget through which funds for orphan drug treatments are allocated annually based on the previous year's calculated needs. Thus if the population of newly diagnosed patients grows, medicinal treatment shortages and access limitations also increase. The inclusion of new drugs in the country's reimbursement scheme results from improved awareness for rare diseases among physicians and patient associations, as well as the intentions of pharmaceutical manufacturers to market their products in Bulgaria. The authors outline the flaws with the current EU pricing system: *"In Bulgaria, the mechanism of smallest value from a set of international reference prices reduces the opportunities for flexible solutions. The inclusion of reference countries with floating euro exchange rate makes the pricing of orphan drugs dependent on the macroeconomic indicators in these countries and thereby allowing serious fluctuations of the price. This is a specific reason for the reluctance of some companies to register prices of their orphan drugs in the small Eastern European non-Eurozone countries. Financial difficulties in one country may lead to lower prices in all referring ones. It should be also underlined that Member State authorities have little negotiating leverage since these medicines have no therapeutic alternative"*. Another important element that negatively impacts small countries is a lack of clinical data around the cost-effectiveness of rare disease medicinal products. Epidemiological rare disease registries are needed to improve knowledge in this area. Thus the authors call for a reformed orphan drug policy-making process that is transparent, and based on a convergence of medical, economic, ethical and social elements.

A new study published in 2013 further concluded that the current reimbursement decision-making framework in Bulgaria is too generalised and not sufficiently transparent. It is unable to precisely assess innovative health technologies. Authors gave as an example the official criteria for inclusion into PDL (which is a must for reimbursement). These were reorganised into an assessment scoring system with decision-making criteria (presence of therapeutic alternative, clinical effectiveness, safety, pharmacoeconomics and societal value) divided into weighted indicators. A medicinal product must score 60 points at least to be included in PDL. Under the currently defined reimbursement decision-making criteria a hypothetical middle- of-the-road scenario planning shows that an orphan drug would score 20 points for therapeutic alternative, 28 for clinical effectiveness and 12 for safety. It would take no points for pharmacoeconomics and societal value. This leaves the orphan drugs with a total score of 60 points, making the final outcome of real-life assessment and decision-making heavily dependent on small fluctuations, thus, endangering patients' access to timely treatment.<sup>53</sup>

### **Orphan medicinal product pricing policy**

There is no specific orphan medicinal product pricing policy and orphan medicinal products are subject to the general conditions as any other medicaments. The negotiation of price and level of reimbursement of orphan medicinal products in Bulgaria is determined by the Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers), and it is based on

<sup>52</sup> <http://www.ncbi.nlm.nih.gov/pubmed/22939047>

<sup>53</sup> <http://www.ncbi.nlm.nih.gov/pubmed/24712287>

reference pricing, using data from Romania, France, Estonia, Greece, Slovakia, Lithuania, Portugal, Italy, Finland, Denmark, Slovenia, Spain, Belgium, Czech Republic, Poland, Latvia and Hungary.

#### **Orphan medicinal product reimbursement policy**

There is no specific orphan medicinal product reimbursement policy and orphan medicinal products are subject to the general conditions as any other medicaments. Medicinal products' reimbursement is regulated on national level by two legal acts – Ordinance on the pricing and inclusion of medicinal products in the Positive Drug List (PDL) (adopted by Decree 340 of the Council of Ministers) and Ordinance 38 of the Minister of Health (on the list of diseases, whose outpatient treatment is covered by the National Health Insurance Fund, NHIF). To be accessible, orphan drugs have to be priced and included in PDL, as well as their indicated medical condition has to be in the NHIF list of diseases according to Ordinance 38.

#### **Other initiatives to improve access to orphan medicinal products**

The Centre for Health Technology Assessment and Analyses (CAHTA) officially started activities in September 2013. CAHTA currently operates as an independent unit within the Institute of Rare Diseases in Plovdiv, Bulgaria.

The idea behind the establishment of CAHTA is to complement the current activities of the Institute by covering the increasingly dynamic field of health technology assessment (HTA). Introducing and applying the HTA concept in Bulgaria will allow for more transparency, objectivity and efficiency in the health system. HTA is greatly important in the field of rare diseases and orphan drugs. The extended life expectancy and improved quality of life for patients with rare diseases are the most important outcomes of all rare disease policies. These two directly depend on the timely access to advanced diagnostic and therapeutic health technologies. Proper and reliable assessment of innovative health technologies is not only important for rare diseases – it is crucial for the overall effectiveness of the entire health care system in Bulgaria.

In October 2013 CAHTA co-organised a public lecture and discussion on HTA prospects for Bulgaria at the Medical University of Plovdiv. Professor Ken Stein (University of Exeter Medical School, UK), Dr Edmund Jessop (National Health System England, UK) and Dr. Domenica Taruscio (Istituto Superiore di Sanità, Italy) were guest speakers and moderators. The discussion was followed by a training workshop on HTA on 5 October for all interested stakeholders.

#### **Other therapies for rare diseases**

No information reported.

#### **Orphan devices**

No information reported.

#### **Specialised social services**

Respite care services and therapeutic recreational programmes are provided in certain medical centres in Bulgaria and are partially reimbursed by the National Health Insurance Fund.

In Bulgaria, there are currently no specialised programmes for people for rare diseases: these patients are forced to seek alternatives in the existing general schemes for the rehabilitation and integration of people with disabilities which do not often meet European standards and recommendations in the area. They are unevenly distributed across the country and public awareness of these services is low. In addition, rare disease patients may be denied access as the Territorial Expert Medical Commission's legislation is not adapted to the specificities of rare disease. As such, one of the priorities of the National Plan is to work on an integrative approach and specialised programmes for physical and social rehabilitation of rare disease patients, however no progress has been made to date, and patients feel that specialised services for rare diseases should not be separated or be in opposition to current programmes for people with disabilities.

## RARE DISEASE ACTIVITIES IN 2013 IN BULGARIA

### National plan/strategy for rare diseases and related actions

On 27 November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and nonhereditary diseases (2009 – 2013).

The Plan officially ended on 31 December 31. Before that, the Ministry of Health had established a working group to prepare a draft for a Second National Plan. The Plan is expected to work closely with the National Rare Disease Registry and the centres of expertise for rare diseases, both of which are supposed to be officialised by the end of 2014. However, no schedule for the adoption and the implementation of the Second Plan was available by the end of 2013.

### Centres of expertise

Significant progress was achieved in 2013 regarding the centres of expertise for rare diseases in Bulgaria. The National Assembly voted amendments in the Health Act (Article 144a), requiring the Minister of Health to adopt a regulation, which will establish a National Registry for Rare Diseases, as well as will determine the criteria for designation of centres of expertise for rare diseases. The Ministry of Health established a working group, which prepared a draft regulation, containing criteria for designation of centres of expertise and reference networks for rare diseases, as well as rules and procedures for their implementation, monitoring and evaluation. The draft regulation also envisages the establishment of a permanent National Rare Diseases Council to the Ministry of Health, as well as an official list of rare diseases. The draft was discussed at several meetings, including the National Conference for Rare Diseases in September 2013. The final draft was submitted to the Ministry of Health early in 2014. This legislation is expected to be approved by the Ministry of Health and to come into force by the end of 2014.

Since September 2013, RareDis and ICRDOD were merged into the Institute for Rare Diseases (IRD), together with the newly-established Centre for Health Technology Assessment and Analyses (CAHTA).

### Registries

The idea to implement a National Registry for Rare Diseases re-emerged in 2013. This was motivated by the upcoming implementation of the centres of expertise for rare diseases in the country. Initial plans suggest that the Registry will collect data from these centres and prepare annual reports on rare disease epidemiology. Thus, the Registry will contain only data for rare diseases, for which there are officially designated centres of expertise. However, by the end of 2013 it is not yet decided which institution will coordinate and manage the Registry.

In 2013 ICRDOD established two new registries – for primary myelofibrosis and neuroendocrine tumours.

### Sources of information on rare diseases and national help lines

#### **Official information centre for rare diseases**

ICRDOD issued a report in July 2013 reviewing access to medicines for rare diseases in Bulgaria<sup>54</sup>. The report contains 4 sections: orphan medicinal product designation and marketing authorisation; pricing, inclusion in the Positive drug list and reimbursement; mechanisms for accelerated access to innovative medicines; conclusions. There are 2 annexes, attached to the review: list of orphan medicinal products in EU and Bulgaria, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorisation holder and date of marketing authorisation for each item (additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds); and a list of references.

### Training and education initiatives

Bulgarian rare diseases stakeholders are active in promoting EU rare policy at local and regional level. The country hosted the First Rare Diseases Summer School for Health Authorities and Legislators<sup>55</sup>, an event designed to raise awareness of rare diseases among Eastern European health authorities and legislators. The event was successfully organised again in 2012 and 2013 in Greece and Turkey respectively. This initiative is a joint initiative of BAPES, the National Association of Rare Diseases Patient Organisations “Genetics” (Russia)

<sup>54</sup> Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria: [http://raredis.org/pub/OD\\_Report\\_2013\\_EN.pdf](http://raredis.org/pub/OD_Report_2013_EN.pdf)

<sup>55</sup> [http://raredis.org/pub/Newsletter/Rare\\_Diseases\\_Summer\\_School\\_2011.pdf](http://raredis.org/pub/Newsletter/Rare_Diseases_Summer_School_2011.pdf)

and the Italian National Centre for Rare Diseases (CNMR). School participants come from a wide range of public fields – legislative bodies and health authorities, medical institutions, academia. The week-long event covers a variety of topics.

### **National rare disease events in 2013**

Rare Disease Day was marked on 28 February 2013 with events organised by the National Alliance of People with Rare Diseases<sup>56</sup>. A series of information, education and charity events took place with a balloon launch in front of the Ministry of Health in Sofia, followed by an official press conference. The Second Balkan Conference of Patients with Rare Diseases, entitled “Communication and Support to Patients, Based on Modern Technologies” was held in April in Sofia. Outside of Sofia, a series of rare diseases events were organised in the towns of Plovdiv, Varna, Burgas, Stara Zagora, Pleven and Sandanski.

The 4<sup>th</sup> Annual Conference on Rare Diseases and Orphan Drugs was organised on 13-14 September 2013 in Plovdiv<sup>57</sup>. The First National Conference on Rare Diseases for Medical Students was held in parallel, bringing together more than 130 students from medical universities across Bulgaria and neighbouring countries.

### **Hosted rare disease events in 2013**

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<sup>56</sup> <http://rare-bg.com/>

<sup>57</sup> [www.conf2013.raredis.org](http://www.conf2013.raredis.org)

<sup>59</sup> *Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria:* [http://raredis.org/pub/OD\\_Report\\_2013\\_EN.pdf](http://raredis.org/pub/OD_Report_2013_EN.pdf)

<sup>59</sup> *Orphan drugs in Bulgaria: Periodic review of the access to orphan drugs in Bulgaria:* [http://raredis.org/pub/OD\\_Report\\_2013\\_EN.pdf](http://raredis.org/pub/OD_Report_2013_EN.pdf)

two directly depend on the timely access to advanced diagnostic and therapeutic health technologies. Proper and reliable assessment of innovative health technologies is not only important for rare diseases – it is crucial for the overall effectiveness of the entire health care system in Bulgaria.

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## 1.4. CROATIA

### Definition of a rare disease

Stakeholders in Croatia accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

There is currently no officially adopted strategy or plan in Croatia regarding rare diseases. In 2008, the Croatian Society for Rare Diseases<sup>60</sup> was established as part of Croatian Medical Association, with the aim of preparing a proposal to be presented to governmental authorities (including the parliament and the Ministry of Health and Social Welfare of Republic of Croatia) for the development of a national plan for rare diseases. Since this initiative, the Ministry of Health and Social Care established the National Commission for Rare Diseases in May 2010 in order to elaborate a National Plan for Rare Diseases. This Committee includes three representatives of civil organisations for rare diseases. During 2011, 2012 and 2013 the Committee met on the regular basis which resulted in creating the national plan for rare diseases.

The Croatian national plan for rare diseases has been developed around of the following nine priority areas:

1. Promotion of the knowledge and the availability of information on rare diseases;
2. Support of rare disease registries and securing of their sustainability;
3. Facilitation of referral centres and centres of expertise activities;
4. Improvement of the availability and quality of health services for rare disease patients (prevention, diagnosis, treatment);
5. Improvement of access to treatment with orphan medicinal products;
6. Securing the availability of special social services for rare diseases patients.
7. Empowerment of patient's organisations;
8. Encouraging research activities in the field of rare diseases;
9. International networking in the field of rare diseases.

The draft was presented to the Croatian Society of Patients with Rare Diseases in December 2012 and further amended in 2013 after public consultation. The Croatian national plan is currently awaiting the final acceptance by the MoH. The presentation to the Parliament was scheduled for 2014.

The First National Conference on Rare Diseases (17-19 September 2010)<sup>61</sup>, organised by the Croatian Association for Rare Disorders, under the auspices of the President of the Republic in the scope of the Europlan conference, allowed stakeholders to meet and discuss priorities for the plan. General proposals and guidelines for actions at national level were agreed on by the participants: to improve access to health care and social services, including the protection of patients' social rights and their right to multidisciplinary approach to care; to ensure the introduction of the category of rare diseases in the legal acts of health and social care; to establish a registry for RD and ensure its long term sustainability by providing ongoing funding; to establish a network of Centres of Expertise or a network of physicians working with RD patients; to aid the empowerment

<sup>60</sup> <http://www.rijetke-bolesti.org>

<sup>61</sup> [http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/FINAL%20Report\\_Croatia\\_n\\_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Croatia_n_%20EUROPLAN%20NC%202010%20-%20Report%20Package.pdf)

and support for patient organisations: to support international networking and cooperation in the field of rare diseases. The Second National Conference on Rare Diseases was held on 8 October 2011. Like the previous conference, it was again the meeting of all national stakeholders. Numerous problems were discussed. The need to strengthen efforts and accelerate the activities to fulfill the goals outlined during the previous conference was emphasised.

There is currently no earmarked budget for rare diseases in the national health care budget, but special funding is available for orphan medicinal products that are on the "List of Especially Expensive Drugs".

### **Centres of expertise**

There are currently three Referral Centres for rare diseases acknowledged by the Croatian Ministry of Health and Social Welfare: the Referral Centre for Birth Defects (Children's University Hospital Zagreb, Decision UP/I-510.01/02-01/18, No 534-05-01/8-03-10), the Referral Centre for Rare Diseases and Metabolic Disorders (Department of Internal Medicine, Clinical Hospital Centre Zagreb; Decision UP/I-510-01/08-01/11, No 534-07-1-2/6-08-12), and the Referral Centre for the Medical Genetics and Metabolic Diseases in Children (Department of Paediatrics, Clinical Hospital Centre Zagreb, Decision UP –I-510-01/95-01/0005, No534-02-10-99-0003). These centres of expertise foster a multidisciplinary approach to rare disease patient care adhering to high medical standards. There are some other centres dealing with particular diseases, for instance the Referral Centre for Haemophilia, Referral Centre for solid tumours in children, etc. The funding and designation of centres of expertise will be a focus of the national plan for rare diseases, according to EUCERD Recommendations.

### **Registries**

Currently, there is neither a national registry for rare diseases in Croatia, nor a national committee dedicated to registries for rare diseases nor designated registries for rare diseases. There are plans to establish a national registry in the future. However, many patients are registered through the mentioned referral centres and patient organisations (phenylketonuria, other inborn errors of metabolism in children, Prader-Willi syndrome, osteogenesis imperfecta, epidermolysis bulosa, etc.) or international on-line registries. These types of registries are not financed. The exception regarding financing are the E-IMD registry for urea cycle defects and some organic acidurias and the E-HOD registry for homocystinurias, folate metabolism disorders and methylation defects and which are parts of the related EC financed E-IMD and E-HOD projects. As a part of EUROCAT network of congenital anomaly registries, Zagreb Registry covers four regions of Croatia (17% of annual births) and this initiative was extended during 2011 to two new regions. This activity is funded as a part of Joint Action EUROCAT 2011-2013 by the Public Health Programme 2008-2013 of the European Commission. The establishment of the National EUROCAT Committee is in progress.. Croatia also contributes to the European registry EUROCAT, EUROCAT CF, PID, European registry for intoxication type metabolic diseases (E-IMD), European network and registry for homocystinurias and methylation defects (E-HOD) and TREAT-NMD.

### **Neonatal screening policy**

Neonatal screening is centralised in Croatia and is an obligatory part of health care. Neonatal screening is provided for phenylketonuria and hypothyroidism. In addition, in 2003 national screening for hearing impairment was implemented and covers the whole of the country. Preliminary activities to extend the newborn screening program by tandem mass spectrometry are underway. The national screening laboratory has been renovated and equipped with tandem mass spectrometry equipment. The remaining problems to extend the screening are to clarify legislation and funding of the running costs. In 2013 Committee for the Neonatal Screening of the Ministry of Health has been established in order to improve regulation of neonatal screening and foster the screening activities.

### **Genetic testing**

Genetic testing is available for the most common genetic conditions in laboratories of clinical hospitals or research institutes. Genetic testing is covered by the Croatian Institute for Health Insurance: when a certain test is not available in Croatia, a second medical opinion from 2-3 medical professionals is needed before a sample can be sent abroad. However there are still problems with these sorts of cross-border services. The reference laboratories in Croatia are based in the Children's University Hospital Zagreb and the University Hospital Centre of Zagreb's Clinical Institute for Laboratory Diagnosis, Clinical Unit for Molecular Diagnostics.

Diagnostic tests are registered as available in Croatia for 32 genes and an estimated 49 diseases in the Orphanet database<sup>62</sup>. According to data from Croatian Society of Human Genetics testing is available for 48 genetic disorders (some laboratories are not listed yet in Orphanet database). There are no national guidelines for genetic tests although there have been activities of Croatian Society for Human Genetics in this sense.

### **National alliances of patient organisations and patient representation**

Since its registration as a non-profit humanitarian organisation in April 2007, the Croatian Society of Patients with Rare Diseases<sup>63</sup> has been working on developing relations with the stakeholders who have an impact on the lives of patients with rare diseases. The Society works to raise general awareness concerning rare diseases and lobbies political stakeholders. The Croatian Alliance for Rare Diseases, replacing the Croatian Society of Patients with Rare Diseases was established in 2012 as the umbrella organisation for rare diseases that gathers 19 other non-profit organisations and more than 300 patients with rare diseases and members of their families who do not have patient organisation representation. At present there are more than 400 different rare diseases registered in the association.

Patient organisation activities are supported by the government and other non-governmental bodies: this financial support is intended for capacity building, networking activities, dissemination of information and information sharing and events.

Representatives of patient organisations are also invited to participate in the meetings of the Croatian Society for Rare Diseases when policy issues and other issues of interest are discussed, as well as the Committee on Newborn Screening. Financial support is available for patients to attend these meetings. Most patient organisations' boards usually include a medical professional involved with patients in consultations, policy making etc.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Croatia***

Since 2006, there is a dedicated Orphanet team in Croatia, currently hosted by the Zagreb University School of Medicine. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. There is an Orphanet national website which was launched in 2013<sup>64</sup>. Since 1 July 2013 Croatian Alliance for Rare Diseases is collecting data.

#### ***Official information centre for rare diseases***

Apart from the national Orphanet team there is no official information centres on rare diseases in Croatia. However, from 2011 the new office of the Croatian Society for Rare Diseases, part of the Croatian Medical Association, started to function as an information centre, financed primarily by donations. This service has the support of the government and is consulted by governmental institutions, but it is not designated as an official information centre.

#### ***Help line***

A rare disease helpline was established in Croatia in 2012 by the Croatian Alliance for Rare Diseases. It will be financed through the project and by donations. Informal help lines run by patient organisations provide general information for rare diseases diagnostic and management.

#### ***Other sources of information***

Information on rare diseases is provided by the Croatian Society for Rare Diseases and by institutions hosting the mentioned referral centres. There are also certain public information sources on rare diseases, including help lines and websites run by patient organisations and non-governmental organisations. The site run by the Croatian Society of Patients with Rare Diseases (<http://www.rijetke-bolesti.hr/>) includes information on certain diseases and groups of diseases. The Croatian Society for Rare Diseases has developed a website which contains comprehensive information for professionals and patients ([www.rijetke-bolesti.org](http://www.rijetke-bolesti.org)).

### **Guidelines**

Guidelines have been developed for the treatment of adult patients with Gaucher and Fabry disease.

<sup>62</sup> Information extracted from the Orphanet database in January 2014.

<sup>63</sup> <http://www.rijetke-bolesti.hr>

<sup>64</sup> <http://www.orpha.net/national/HR-HR/index/homepage/>

### **Training and education initiatives**

Current university training courses do not yet provide specific training on rare diseases. Information on rare diseases is included in curricula for medical students, students at Faculty of Education and Rehabilitation Sciences and students at Faculty of Pharmacy and Biochemistry, University of Zagreb.

### **National rare disease events in 2013**

The Croatian Alliance for Rare Diseases organised a number of events to mark Rare Disease Day in 2013. Promotion of National plan and Help Line, as well as presentation of activities of patient organisations throughout 7 towns in Croatia was organised.

### **Hosted rare disease events in 2013**

The EUROCAT 12th European Symposium on Congenital Anomalies was held on 14 June 2013 in Zagreb. The Eurordis Membership Meeting was held in Dubrovnik, 30 May – 2 June 2013.

### **Research activities and E-Rare partnership**

#### ***Research activities***

There are around 40 projects funded by the Ministry of Science, Education and Sports for the investigation of genetic diseases and various other groups of rare diseases. Some pharmaceutical companies involved in the management of rare diseases support investigations of specific rare diseases. There is a database of clinical studies in Croatia ([www.regpok.hr](http://www.regpok.hr)) in the Croatian language.

#### ***Participation in European research projects***

There is one rare disease related FP7 project with Croatian participation.

#### ***E-Rare partnership***

Croatia is currently not an E-Rare partner and has not yet participated in these calls.

#### ***IRDiRC***

Croatian funding agencies have not yet committed funding to IRDiRC.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

In Croatia there is no orphan medicinal product committee, although the Croatian Health Insurance Institute has a drug committee which controls drug use and makes any drug available if approved after individual request by selected national experts.

#### ***Orphan medicinal product incentives***

No specific activity reported.

#### ***Orphan medicinal product market availability situation***

The availability of orphan medicinal products has been improved since the establishment of the Fund for Especially Expensive Drugs at the Croatian Institute for Health Insurance, and a regulation for orphan medicinal products is being prepared by a working group to be presented to the Ministry of Health and Social Care.

A tender for drugs for rare diseases was introduced in 2009. This resulted in introduction of only one drug for the treatment of a certain disease, for example for Fabry disease this is agalsidase alfa, whilst agalsidase beta was put on the hospital budget. This caused problems for patients treated with agalsidase beta, as hospital management has asked treating physicians to change the treatment to agalsidase alfa. These problems have later been solved. In 2013 Croatian Institute for Health Insurance released updates of the List of Especially Expensive Drugs which includes drugs for several rare diseases (drugs for multiple sclerosis, some cancers, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, home treatment of hemophyllia, peginterferon, growth hormone, enzyme replacement therapy). Orphan medicinal products approved for treatment of rare and severe diseases can be found on the web pages of the Croatian Agency for Drugs and Medicinal Products<sup>65</sup>. There is a detailed procedure regulating the inclusion of a drug on the List of Especially

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<sup>65</sup>[www.halmed.hr](http://www.halmed.hr)



Expensive Drugs. The final decision is taken by the Board of the Croatian Institute for Health Insurance, based on the report of Committee for drugs and medicinal products.

**Orphan medicinal product pricing policy**

No specific activity reported.

**Orphan medicinal product reimbursement policy**

In Croatia, treatment for rare diseases was originally covered using the hospitals' budget and hospitals were reluctant to begin a therapy presenting such a heavy financial burden. After a long negotiation between patients' organisations and professionals involved in the treatment of rare diseases with authorities, the Ministry of Health established in 2006 a "List of Especially Expensive Drugs" (Legislative Decree Class: 025-04/06-01/91, No: 338-01-01-06-1, Zagreb, 9. March 2006.) and the treatment of rare diseases is now covered from specially allocated funds from general state health system budget. Orphan medicinal products are thus now approved by the Croatian Institute for Health Insurance: all available orphan medicinal products are reimbursed by the Croatian health insurance fund ("expensive drug fund") for rare diseases.

In 2010 the Croatian Institute for Health Insurance has introduced a regulatory method for the control of the consumption of drugs that are on the "List of Especially Expensive Drugs". Maximal spending budget is regulated by the 3-year contracts and monitored monthly. This policy sometimes makes difficult ensuring prompt treatment for newly discovered patients.

**Other initiatives to improve access to orphan medicinal products**

Compassionate use is possible from the time of diagnosis to the approval for the use of the drug. The importation of relatively cheap drugs is sometimes problematic, because there is no obligation for companies to provide the drug.

**Other therapies for rare diseases**

No specific activity reported.

**Orphan devices**

No specific activity reported.

**Specialised social services**

There are possibilities for different types of social and respite care services in some parts of the country, although not specifically for rare disease patients, but for those affected with chronic disorders in general: these services are fully reimbursed by national health care. Therapeutic recreational programmes such as summer camps are organised by patient organisations (e.g. children's camps for those affected by rare forms of solid tumours and lymphomas): this is fully reimbursed by the patient organisation. Social and/or financial support for families and patients with disabilities is regulated by a number of legislative decisions/regulations. Fostering of employment for the integration of handicapped individuals in daily life is partly financed by the government. The National Strategy for Equal Possibilities for Handicapped Individuals 2007-2015 (Class 562.01./07-01/02, No 5030108-07-1, June 2007) was introduced in order to regulate the area of services aimed at the integration of patients with handicaps in daily life. In 2013, there were no new initiatives in the field of respite care.

## RARE DISEASE ACTIVITIES IN 2013 IN CROATIA

**National plan/strategy for rare diseases and related actions**

During 2013 the National Committee for Rare Diseases met on the regular basis which resulted in creating the national plan for rare diseases.

The Croatian national plan for rare diseases has been developed around of the following nine priority areas:

1. Promotion of the knowledge and the availability of information on rare diseases;

2. Support of rare disease registries and securing of their sustainability;
3. Facilitation of referral centres and centres of expertise activities;
4. Improvement of the availability and quality of health services for rare disease patients (prevention, diagnosis, treatment);
5. Improvement of access to treatment with orphan medicinal products;
6. Securing the availability of special social services for rare diseases patients.
7. Empowerment of patient's organisations;
8. Encouraging research activities in the field of rare diseases;
9. International networking in the field of rare diseases.

The draft was presented to the Croatian Society of Patients with Rare Diseases in December 2012 and further amended in 2013 after public consultation. The Croatian national plan is currently awaiting the final acceptance by the MoH. The presentation to the Parliament was scheduled for 2014.

### **Neonatal screening policy**

In 2013 Committee for the Neonatal Screening of the Ministry of Health has been established in order to improve regulation of neonatal screening and foster the screening activities.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Croatia***

Since 1 July 2013 Croatian Alliance for Rare Diseases is collecting data.

### **Guidelines**

Guidelines have been developed for the treatment of adult patients with Gaucher and Fabry disease.

### **National rare disease events in 2013**

The Croatian Alliance for Rare Diseases organised a number of events to mark Rare Disease Day in 2013. Promotion of National plan and Help Line, as well as presentation of activities of patient organisations throughout 7 towns in Croatia was organised.

### **Hosted rare disease events in 2013**

The EUROCAT 12th European Symposium on Congenital Anomalies was held on 14 June 2013 in Zagreb. The Eurordis Membership Meeting was held in Dubrovnik, 30 May – 2 June 2013.

### **Orphan medicinal products**

#### ***Orphan medicinal product market availability situation***

In 2013 Croatian Institute for Health Insurance released updates of the List of Especially Expensive Drugs which includes drugs for several rare diseases (drugs for multiple sclerosis, some cancers, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, home treatment of hemophyllia, peginterferon, growth hormone, enzyme replacement therapy).

## **1.5. CYPRUS**

### **Definition of a rare disease**

Stakeholders in Cyprus accept the European Orphan Drug Regulation definition of a prevalence of no more than 5 in 10 000 individuals.

### **National plan/strategy for rare diseases and related actions**

The Cyprus National Strategic Plan for Rare Diseases<sup>66</sup> (CNSPRD) was established following the European Council's Recommendation that each Member State should develop a national plan or strategy on rare diseases, preferably by the end of 2013. The final version of the CNSPRD was developed by a national steering committee for rare diseases, which consisted of Ministry of Health officials, experts in various fields relating to

<sup>66</sup> [http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/\\$file/Strategic%20Plan%20Rare%20Diseases.pdf](http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/$file/Strategic%20Plan%20Rare%20Diseases.pdf)

rare diseases as well as patient representatives, following a public consultation (the second) with local stakeholders including patient's representatives, in March 2012. The CNSPRD was approved by the Council of Ministers of the Republic of Cyprus in November 2012.

The main objective of the National Strategic plan is to ensure that patients with rare diseases will have access to high quality care (diagnostics, treatments as well as rehabilitation for those living with the disease). The CNSPRD is based on the following 5 pillars:

- (a) Prevention – Early Diagnosis
- (b) Treatment and Management
- (c) Palliative Care / Social Inclusion / Support
- (d) Registries/Epidemiology
- (e) Research

Following the approval of the CNSPRD, the National Committee for Rare Diseases was appointed by the Council of Ministers with the task of implementing as well as monitoring the progress of the plan. In addition, the National Committee for Rare Diseases is responsible for defining a number of priority actions with objectives and follow-up mechanisms. The Committee met for the first time in January 2013 and is having monthly meetings since then. Work is also being produced through subcommittees and devoted subgroups. During 2013, the actions of the CNSPRD were prioritised and those requiring little or no budget, such as training initiatives and public awareness raising activities were put into action, since due to current national financial circumstances no funding was available to implement the CNSPRD as a whole. In the past year, workshops, lectures, seminars and interviews addressing the general public, university students, health-care professionals and other relevant groups were organised. In addition, during 2013 the CNSPRD addressed the three relevant ministries, those of Health, Education and Culture and Labour and Social Insurance in order to establish a dialogue with authorities on important policy matters. Furthermore the CNSPRD contacted all University schools that offer education in fields relevant to rare disorders such as Medicine, Nursing, Physiotherapy, Speech therapy, Biology etc requesting the incorporation of rare disorders into their teaching curriculum. Collaboration with National Medical Associations and scientific societies has also been established. Finally, although rare cancers are included in the CNSPRD, since they are also addressed by the National plan against Cancer and the National Committee for Cancer, collaboration between the two committees has been initiated.

Among steps of action the necessity of introducing a help line has been discussed as well as the introduction of a special medical card and an alert card for patients.

### **Centres of expertise**

Currently, no officially designated centres of expertise for rare diseases exist in Cyprus since official guidelines and procedures are yet to be established at the administrative level. Nevertheless, a number of institutions are currently functioning at the level of centres of expertise. Among these are the Cyprus Institute of Neurology and Genetics, the Makarios Hospital for Mother and Child and its specialised clinics, the Cyprus Thalassaemia Centre, the Centre for the Study of Haematological Malignancies, the Bank of Cyprus Oncology Centre as well as a number of specialised clinics and departments at the Nicosia General Hospital and other hospitals. The Cyprus Institute of Neurology and Genetics operates as a centre of research, treatment and management for various rare neurological and genetic conditions. The Clinical Genetics Clinic, located both at the Cyprus Institute of Neurology and Genetics and the Archbishop Makarios III Hospital, is involved in the management of over 4000 patients and their families living with or at risk of a genetic condition in Cyprus. The Archbishop Makarios III Hospital for Mother and Child, in Nicosia, is the main referral hospital for children and adolescents where most young patients with rare diseases are referred for diagnosis and management. Several specialised clinics in this hospital operate as referral clinics for rare diseases by specialty such as, neonatology-NICU, paediatric endocrinology/ nephrology/ cardiology/ neurology/ pulmonology/ infectious diseases, etc. The Cyprus Thalassaemia Centre is the main centre for screening (premarital), counselling and management of thalassaemia on the island. The Centre is based in Nicosia but also holds special clinics for the management and care of patients with hemoglobinopathies in all other public hospitals on the island. The Centre for the Study of Hematological Malignancies operates as a centre of research and diagnosis of various rare haematological malignancies while management is offered by the Haematology clinics of the Nicosia and Limassol General Hospitals. The Bank of Cyprus Oncology Centre and the Oncology department of the Nicosia General Hospital are the main referral centres for the diagnosis, management and treatment of rare cancer syndromes. Several other departments and specialised clinics serve as referral centres for rare disorders including but not limited

to rare haematological and congenital heart disorders, cardiomyopathies, etc. The majority of these clinics are based at the Nicosia General Hospital.

The procedure for officially designating Centres of Expertise for rare diseases in Cyprus is currently under discussion.

### **Registries**

There is currently no designation process for rare disease registries in Cyprus, but this will be one of the considerations of the National Plan for Rare Diseases. Several registries have been formed by physicians and scientists at various specialised clinics and laboratories. Also a few patient organisations have their own registries based on their members. Cyprus participates in the EURO CARE CF European registry. The possibility of introducing a common platform for registries of rare disorders is under consideration. Currently there is no specific funding for rare disease registries.

### **Neonatal screening policy**

There are nationwide schemes for neonatal screening, which include screening for phenylketonuria and congenital hypothyroidism. Also a nationwide screening for congenital hearing deficit exists.

In June 2013 a National Committee for Neonatal Screening was appointed by the Ministry of Health, with the task of revisiting the current practices, discussing the possible need for expansion of the current policy and providing a plan of action in the field. The committee is multidisciplinary and consists of experts as well as stakeholder representatives. It is expected to complete its work by the end of 2015. This appointment was the reflection of the Ministry of Health to the report and recommendations of an Advisory Committee, works held between 2011 and 2013. This advisory committee addressed the current situation of newborn screening in Cyprus and evaluated the new emerging needs and possible expansion of the offered screening program. The advisory committee prepared a report summarising their findings and recommending the establishment of a National Committee. This report was accepted and endorsed by the Ministry of Health.

### **Genetic testing**

Genetic testing is available for several genetic disorders. This includes conventional and molecular cytogenetics, screening for metabolic disorders, neurogenetics, genetic testing for inherited cancers as well as for other predisposition genes, thalassemia molecular diagnostics, screening for other haematological genetic disorders and many others. In summary, diagnostic tests are available in Cyprus for around 220 genes and an estimated of 110 rare diseases<sup>67</sup>. Furthermore several tests are underway or performed as part of research projects. Specialised laboratories participate in appropriate external quality control schemes, while relevant legislation is currently under discussion between stakeholders and the parliament. At the same time samples for molecular testing are often sent and performed abroad after sufficient genetic counselling is offered. Special attention is taken in the selection of laboratories that are approved by relevant authorities and hold all necessary accreditation.

### **National alliances of patient organisations and patient representation**

In June 2010, the Cyprus Alliance for Rare Disorders (CARD)<sup>68</sup> was established with the aim of uniting the voices of all patients with rare diseases at a national level. The principal goals of the Alliance are the following: to lend support to the national rare disorders programme; to support the efforts of rare disease patients for improvement of prevention, medical treatment, as well as social and other services related to each of the rare disorders to improve the health and quality of life rare diseases patients; to provide support and continuous education to the patients and their families concerning the latest developments in medicine and research; and to raise awareness regarding rare diseases in the Cypriot society. Now legally registered, the Cyprus Rare Disease Alliance is becoming Cyprus' representative for patients in health organisations and institutions at European and international level. In 2013 two new patient organisations addressing rare diseases have been established, the Inherited Metabolic Disorders organisation 'Aspida Zois' and the Rare Genetic Disorders organisation 'Monadika Hamogela' or 'Unique Smiles'. Both these organisations became members of the Cyprus Alliance for Rare Disorders (CARD). Furthermore many other patient organisations exist, representing (but not exclusively) rare disease patients with a disability such as vision deficit or hearing loss, patients with mental retardation, patients with Down syndrome, patients with congenital heart disorders, etc.

<sup>67</sup> Source : Cyprus Institute of Neurology and Genetics

<sup>68</sup> [http://www.thalassaemia.org.cy/cyprus\\_alliance.html](http://www.thalassaemia.org.cy/cyprus_alliance.html)

## **Sources of information on rare diseases and national help lines**

### ***Orphanet activities in Cyprus***

Since 2004 there is a dedicated Orphanet team in Cyprus, currently hosted by the Archbishop Makarios III Medical Centre Clinical Genetics Department. This team was designated in 2010 as the Orphanet National team for Cyprus by the Medical and Public Health Services of Cyprus. The Orphanet Cyprus team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Cyprus for entry into the Orphanet database. A national website of Orphanet Cyprus<sup>69</sup> is also operational aiming to provide information on local activities in the field of rare diseases.

### ***Official information centre for rare diseases***

There is no official information centre for rare diseases in Cyprus apart from Orphanet.

### ***Help line***

Currently, no rare disease help line is operational in Cyprus.

### ***Other sources of information***

The Cyprus Institute of Neurology and Genetics is the main source of information for several neurological and other genetic disorders. Information on rare diseases is also published by Gene Net Cyprus<sup>70</sup>, a project that aimed to create a bicomunal network for genetic diseases bringing together health professionals patients and families. The project has produced trilingual leaflets on genetic conditions in Cyprus: 6 leaflets were published in English, Turkish and Greek. All these documents are available on the Gene Net website which provides links to Orphanet. Furthermore, the Thalassaemia National Centre is the main source of information for haemoglobinopathies. In addition, several specialised clinics and organisations, which operate in Cyprus are functioning as sources of information for specific disorders.

### **Guidelines**

Internationally accepted best clinical practice guidelines are being used in Cyprus as reference documents.

### **Training and education initiatives**

Activities have been organised in this field with a training/education angle, including conferences, courses and lectures within main and teaching hospitals, especially the paediatric department of the Makarios Hospital and the Cyprus Institute of Neurology and Genetics, and also within meetings of local scientific societies. These included teaching lectures and presentations on rare genetic syndromes and rare metabolic disorders. The Cyprus Institute of Neurology and Genetics serves also as a satellite centre to the EGF courses which include several activities on rare genetic disorders.

### **National rare disease events in 2013**

The National Committee for Rare Diseases celebrated Rare Diseases Day 2013 on the 6 March 2013 inviting stakeholders including patients, organisations, physicians, researchers, scientists, authorities, pharmaceutical companies, the public and the media to an open meeting/ discussion. The agenda consisted of short introductory presentations by experts in rare diseases and by patients outlining their experiences in living with a rare disorder in Cyprus. The discussion, which was vivid, addressed the problems and expectations of patients as well as the application of the National plan and the prioritization of actions. The event took place at the Makarios Medical centre.

A Europlan national conference was held on the 14 & 15 November 2013, bringing together stakeholders to discuss the implementation of the National Plan for rare diseases. The workshops of this conference addressed the following fields: Strategy to action plan and indicators, Registries, Social Inclusion and Centres of Expertise and European Reference Networks. The participation was very active and the discussion revealed many aspects of the present situation, including weaknesses, obstacles and strengths as well as actions to be taken.

### **Hosted rare disease events in 2013**

No hosted events reported.

<sup>69</sup> <http://www.orpha.net/national/CY-EL/index/homepage/>

<sup>70</sup> <http://www.genenet.org.cy/English/index.htm>

## **Research activities and E-Rare partnership**

### ***National research activities***

There are no dedicated research funds for rare diseases in Cyprus. In general funding opportunities are offered by the Cyprus Research Promotion Foundation.. In addition, Telethon is organised by the Cyprus Institute of Neurology and Genetics (CING) to support scientific research, including research on rare diseases.

### ***Participation in European research projects***

Teams in Cyprus participate/participated in 3 FP7 rare disease related projects.

### ***E-Rare***

Cyprus is currently not a member of E-Rare and does not participate in their calls.

### ***IRDiRC***

Cyprus is not currently a committed member of the IRDiRC.

## **Orphan drugs**

### ***Orphan drug committee***

No specific activity reported.

### ***Orphan drug incentives***

No specific activity reported.

### ***Orphan drug market availability situation***

No specific information was reported on the orphan drugs marketed in Cyprus. Several orphan drugs have been requested through the Department of Pharmaceutical Services of the Ministry of Health and they were approved for use by the Drug Committee on a patient name basis i.e. Enzyme Replacement Treatment namely for Gaucher, Maroteaux–Lamy and Pompe disease.

### ***Orphan drug pricing policy***

No specific activity reported.

### ***Orphan drug reimbursement policy***

No specific activity reported.

### ***Other initiatives to improve access to orphan drugs***

No specific activity reported.

## **Other therapies for rare diseases**

No specific activity reported.

## **Orphan devices**

No specific activity reported.

## **Specialised social services**

Social services for patients suffering of disabilities as a result of rare disorders are in place. The legislation is not specific to rare diseases but concerns the nature of the disability.

## DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 IN CYPRUS

### National plan/strategy for rare diseases and related actions

The Cyprus National Strategic Plan for Rare Diseases<sup>71</sup> (CNSPRD) was approved by the Council of Ministers of the Republic of Cyprus in November 2012. Following the approval of the CNSPRD, the National Committee for Rare Diseases was appointed by the Council of Ministers with the task of implementing as well as monitoring the progress of the plan. In addition, the National Committee for Rare Diseases is responsible for defining a number of priority actions with objectives and follow-up mechanisms. The Committee met for the first time in January 2013 and is having monthly meetings since then. Work is also being produced through subcommittees and devoted subgroups. During 2013, the actions of the CNSPRD were prioritised and those requiring little or no budget, such as training initiatives and public awareness raising activities were put into action, since due to current national financial circumstances no funding was available to implement the CNSPRD as a whole. In the past year, workshops, lectures, seminars and interviews addressing the general public, university students, health-care professionals and other relevant groups were organised. In addition, during 2013 the CNSPRD addressed the three relevant ministries, those of Health, Education and Culture and Labour and Social Insurance in order to establish a dialogue with authorities on important policy matters. Furthermore the CNSPRD contacted all University schools that offer education in fields relevant to rare disorders such as Medicine, Nursing, Physiotherapy, Speech therapy, Biology etc requesting the incorporation of rare disorders into their teaching curriculum. Collaboration with National Medical Associations and scientific societies has also been established. Finally, although rare cancers are included in the CNSPRD, since they are also addressed by the National plan against Cancer and the National Committee for Cancer, collaboration between the two committees has been initiated.

Among steps of action the necessity of introducing a help line has been discussed as well as the introduction of a special medical card and an alert card for patients.

### Centres of expertise

The procedure for officially designating Centres of Expertise for rare diseases in Cyprus is currently under discussion.

### Registries

The possibility of introducing a common platform for registries of rare disorders is under consideration.

### Neonatal screening policy

In June 2013 a National Committee for Neonatal Screening was appointed by the Ministry of Health, with the task of revisiting the current practices, discussing the possible need for expansion of the current policy and providing a plan of action in the field. The committee is multidisciplinary and consists of experts as well as stakeholder representatives. It is expected to complete its work by the end of 2015. This appointment was the reflection of the Ministry of Health to the report and recommendations of an Advisory Committee, works held between 2011 and 2013. This advisory committee addressed the current situation of newborn screening in Cyprus and evaluated the new emerging needs and possible expansion of the offered screening program. The advisory committee prepared a report summarising their findings and recommending the establishment of a National Committee. This report was accepted and endorsed by the Ministry of Health.

### National alliances of patient organisations and patient representation

In 2013 two new patient organisations addressing rare diseases have been established, the Inherited Metabolic Disorders organisation 'Aspida Zois' and the Rare Genetic Disorders organisation 'Monadika Hamogela' or 'Unique Smiles'. Both these organisations became members of the Cyprus Alliance for Rare Disorders (CARD).

### National rare disease events in 2013

The National Committee for Rare Diseases celebrated Rare Diseases Day 2013 on the 6 March 2013 inviting stakeholders including patients, organisations, physicians, researchers, scientists, authorities, pharmaceutical companies, the public and the media to an open meeting/ discussion. The agenda consisted of short introductory presentations by experts in rare diseases and by patients outlining their experiences in living with a rare disorder in Cyprus. The discussion, which was vivid, addressed the problems and expectations of patients

<sup>71</sup> [http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/\\$file/Strategic%20Plan%20Rare%20Diseases.pdf](http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/$file/Strategic%20Plan%20Rare%20Diseases.pdf)

as well as the application of the National plan and the prioritisation of actions. The event took place at the Makarios Medical centre.

A Europlan national conference was held on the 14 & 15 November 2013, bringing together stakeholders to discuss the implementation of the National Plan for rare diseases. The workshops of this conference addressed the following fields: Strategy to action plan and indicators, Registries, Social Inclusion and Centres of Expertise and European Reference Networks. The participation was very active and the discussion revealed many aspects of the present situation, including weaknesses, obstacles and strengths as well as actions to be taken.

## 1.6. CZECH REPUBLIC

### Definition of a rare disease

Stakeholders in the Czech Republic accept the definition outlined in the European Regulation on Orphan Medicinal Products of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

In October 2010, the Czech Republic released for the first time a ten-year strategy (2010-2020) for rare diseases. The strategy was approved by the government on 14 June 2010. The Czech strategy intends to “ensure the effective diagnosis and treatment of rare diseases, ensure that all patients with rare diseases have access to the indicated, high-quality health care, and ensure their subsequent social integration on the basis of equal treatment and solidarity”, and is “fully compliant with the European Council’s recommendation mainly concerning improved identification of rare diseases, support for the development of health policy and the development of European-level cooperation, coordination and regulation in this field”. The Strategy outlines existing efforts and proposes major targets and measures for improving the situation in the Czech Republic, which are to be subsequently specified in more detail in the context of a three-year National Action Plan that will establish “sub-tasks, instruments, responsibilities, dates and indicators for fulfilling individual tasks”.

The first meeting of the working party for the preparation of the National Action Plan convened on 12 November 2010 in Prague and since then a dedicated taskforce (“*Meziresortní a mezioborová komise pro vzácná onemocnění* – Interministerial and interdisciplinary commission for rare diseases”, henceforward “Taskforce”), under scientific coordination of Prof. Milan Macek (Czech National Orphanet Coordinator and Representative of the Czech Republic on the EUCERD, together with his deputy Dr. Kateřina Kubáčková who serves at Czech representative in the European Medicines Agency’s Committee on Orphan Medicinal Products committee) comprised of leading rare diseases experts, biotech industry, lawyers, the State Institute for Drug Control, medical statisticians and health insurance representatives, has convened every other month. This Taskforce created dedicated working parties with the aim fulfil the aims of the National Action Plan for 2013. The Czech ten-year strategy<sup>72</sup> reveals the budgetary sources for the plan, which will include “existing budgetary chapters and domestic and foreign subsidies” such as the Ministry of Health<sup>73</sup>, Ministry of Labour and Social Affairs<sup>74</sup> and the country’s public health insurance companies (e.g. the General Health Insurance Company<sup>75</sup>). A budget for the strategy has not yet been announced. The Ministry of Health has been trying to assure funding within the framework of the EEA Norway Grants Public Health “Predefined projects” scheme (this project is expected to start in mid-2014) for the National Coordination Centre at University Hospital Motol<sup>76</sup>, and its contractual partners. In addition, the Czech Ministry of Health annually offers targeted appropriation schemes for rare disease initiatives. The aforementioned Coordination Centre received this appropriation for awareness and education of lay and/professional communities in March 2013.

A group of stakeholders gathered in 2011 (including the Ministry of Labour and Social Affairs, experts and payers) to elaborate the Czech National Plan for Rare Diseases for 2012-2014<sup>77</sup>, which on 29 August 2012,

<sup>72</sup> [http://ec.europa.eu/health/rare\\_diseases/docs/national\\_czech\\_en.pdf](http://ec.europa.eu/health/rare_diseases/docs/national_czech_en.pdf)

<sup>73</sup> [www.mzcr.cz](http://www.mzcr.cz)

<sup>74</sup> [www.mpsv.cz](http://www.mpsv.cz)

<sup>75</sup> [www.vzp.cz](http://www.vzp.cz)

<sup>76</sup> [http://www.mfcr.cz/cps/rde/xchg/mfcr/xsl/Financial\\_Mechanism\\_EEA.html](http://www.mfcr.cz/cps/rde/xchg/mfcr/xsl/Financial_Mechanism_EEA.html)

<sup>77</sup> [http://www.eucerd.eu/?post\\_type=document&p=2105](http://www.eucerd.eu/?post_type=document&p=2105)



the Czech government adopted via Decree 633. The plan delineates concrete actions identified in the 2010-2020 Czech National Strategy<sup>78</sup>. Specific areas include: Improving information; Education; Prevention; Improving screening and diagnosis; Improving the availability and quality of care; Improving quality of life and social inclusion; Support for rare disease science and research; Unification and development of data collection and rare disease biological samples; Supporting and strengthening patient organisations; Interdepartmental and interdisciplinary collaboration; and International cooperation. Besides diagnostics and treatment, the Czech National Plan encompasses research, public information, training for health professionals (both paediatric and adult specialists), and quality of life for patients in collaboration with the Ministry of Social Affairs.

In order to fulfill the priority aims of the Czech National Plan for 2013 the Taskforce met four times and among others endorsed presentations of representatives of various professional societies for the establishment of respective centers of expertise in the country (e.g. for neurology, endocrinology, rheumatology, orofacial abnormalities, immune deficiencies, oncology, nephrology, hematology). Based on the endorsements of the Czech Ministry of Health envisages to publish official tenders for their establishment using EUCERD criteria<sup>79</sup>. The aforementioned EUCERD guidelines are intended to serve as basis for the crossborder health care in rare diseases related to the implementation of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare<sup>80</sup>.

The Czech National Action Plan originally included provisions for the continuous monitoring of International Classification of Functioning, Disability and Health (ICF) codes by general practitioners and a specific article was included in "Act No 372/2011". However, this article was deleted in subsequent amendments of this Act in 2013 based on protests of general practitioners who asserted that collection of ICF codes is not feasible in the absence of dedicated funding from health insurance companies.

### Centres of expertise

Based on the work of the Taskforce and including the entry into force of Law 372/2011Sb which in its article 112 provided legal basis for establishment of expert centres (not only for rare diseases), a group of rare disease centres was officially established on 28 May 2012 and published in Bulletin n. 4 / 2012 of the Czech Ministry of Health<sup>81</sup> – section 4 "Basic network of rare disease centres". These centres include:

- The National Coordination Centre for rare diseases in the Prague-Motol Teaching Hospital of Charles University Prague<sup>82</sup> in collaboration with the University Hospital of Masaryk University Brno<sup>83</sup> for the sake of regional representation,
- Five regional centres of cystic fibrosis (Prague – Motol Teaching Hospital of Charles University Prague<sup>84</sup>, Brno Teaching Hospital of Masaryk University<sup>85</sup>, Olomouc Teaching Hospital<sup>86</sup> of Palacky University, Hradec Králové Teaching Hospital of Charles University Prague<sup>87</sup> and Pilsen Teaching Hospital of of Charles University Prague<sup>88</sup>) covering all regions of the country (children and adults with the disease), linked via a dedicated disease-specific registry<sup>89</sup>,
- The national centre for epidermolysis bullosa at the Faculty Hospital Brno of the Masaryk University associated with DebraCZ<sup>90</sup>,
- The Centre for inherited metabolic disorders<sup>91</sup> at the General Teaching Hospital of Charles University Prague<sup>92</sup>.

These centres received their status for the next three years and could be renewed following audit by the Ministry of Health. Following the presentation of *de facto* activities of various professional groups (see above),

<sup>78</sup> [http://ec.europa.eu/health/rare\\_diseases/docs/national\\_czech\\_en.pdf](http://ec.europa.eu/health/rare_diseases/docs/national_czech_en.pdf)

<sup>79</sup> [http://www.eucerd.eu/?post\\_type=document&p=1224](http://www.eucerd.eu/?post_type=document&p=1224)

<sup>80</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF>

<sup>81</sup> [http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c4/2012\\_6288\\_2510\\_11.html](http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c4/2012_6288_2510_11.html)

<sup>82</sup> [www.ublg.lf2.cuni.cz](http://www.ublg.lf2.cuni.cz)

<sup>83</sup> [www.fnbrno.cz](http://www.fnbrno.cz)

<sup>84</sup> [www.fnmotol.cz](http://www.fnmotol.cz)

<sup>85</sup> [www.fnbrno.cz](http://www.fnbrno.cz)

<sup>86</sup> [www.fnol.cz](http://www.fnol.cz)

<sup>87</sup> [www.fnhk.cz](http://www.fnhk.cz)

<sup>88</sup> [www.fnplzen.cz](http://www.fnplzen.cz)

<sup>89</sup> [www.cfregistr.cz](http://www.cfregistr.cz)

<sup>90</sup> <http://www.debra.cz/>

<sup>91</sup> [www.udmp.cz](http://www.udmp.cz)

<sup>92</sup> [www.vfn.cz](http://www.vfn.cz)

active mainly within the major faculty hospitals (e.g. FN Brno<sup>93</sup>, FN Motol<sup>94</sup>, VFN Praha<sup>95</sup>, FN HK<sup>96</sup>, FN Olomouc<sup>97</sup> and FN Plzen<sup>98</sup>), *de iure* recognition of their “centre status” activities will be carried out by the Ministry of Health during 2014. However, it needs to be noted that establishment of centres from the Ministry of Health does not entitle them to “centre-based health care reimbursement”, which has to be assured independently through subsequent and complicated negotiations with the various health insurance companies. There are no legal provisions which would guarantee that *de iure* rare disease centers of expertise are eligible to become “centres with a specific contract”, an issue particularly important for reimbursement of orphan medicinal products. In 2013 new rare disease centres were not established.

The value of these centres has been acknowledged by many of the country’s major stakeholders including the State Institute for Drug Control, the Czech General insurance company and health insurance companies associated within the Czech Association of health insurance companies (mainly having regional coverage)<sup>99</sup>, the Ministry of Health, Czech Rare Disease Association<sup>100</sup>, researchers and physicians. Treatment with orphan medicinal products is reimbursed where contracts with insurance companies have been assured and these centres manage the provision of very expensive orphan medicinal products. Another important issue discussed with the Ministry of Health is the lack of guidelines and/or procedures for transition from paediatric to adult care.

In addition, it is expected that in duly justified instances (e.g. very rare diseases) care will be assured within European Reference Networks (i.e. in line with the EU Directive on cross-border healthcare sections 54 and 55). Currently, cross-border healthcare falls into the domain of the Centre for International Reimbursements<sup>101</sup>.

### Registries

The Czech Republic contributes to some European registries such as ECFS.eu for cystic fibrosis<sup>102</sup> and TREAT-NMD for muscular dystrophies, European Porphyria Network (EPNET), EUROCAT for rare birth defects<sup>103</sup>, as well as the SCNIR international registry<sup>104</sup>. The National Registry for Cancer<sup>105</sup> also contains information on the distribution of rare cancers in the Czech Republic. The Interministerial and interdisciplinary commission for rare diseases is in the process of establishing the National registry of rare diseases, which will serve as a “confederated database” of all other disseminated registries in centres to be established. As a pilot projects serves the dedicated registry initiative of the Institute of Biostatistics and Analysis<sup>106</sup> at the Masaryk University in Brno<sup>107</sup>. Finally, the National centre for cystic fibrosis in University Hospital Motol was accepted into the Clinical Trial Network<sup>108</sup> of the European Cystic Fibrosis Society<sup>109</sup>.

Teams in the Czech Republic contribute to the following European registries: EUROCARE CF, EUROCAT, SCNIR registry and TREAT-NMD. In 2013 the Czech Institute of medical informatics and statistics<sup>110</sup> started a compilation of rare disease registries in the country and established collaboration with the EPIRARE<sup>111</sup> and RD-Connect<sup>112</sup> projects in terms of mapping and standardisation of registries.

### Neonatal screening policy

Neonatal screening is now available for 13 disorders<sup>113</sup>. Neonatal screening is routinely performed for phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, hyperphenylalaninemia, maple

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<sup>93</sup> [www.fnbrno.cz](http://www.fnbrno.cz)

<sup>94</sup> [www.fnmotol.cz](http://www.fnmotol.cz)

<sup>95</sup> [www.vfn.cz](http://www.vfn.cz)

<sup>96</sup> [www.fnhk.cz](http://www.fnhk.cz)

<sup>97</sup> [www.fnol.cz](http://www.fnol.cz)

<sup>98</sup> [www.fnplzen.cz](http://www.fnplzen.cz)

<sup>99</sup> <http://www.szpcr.cz/>

<sup>100</sup> [www.vzacna-onemocneni.cz](http://www.vzacna-onemocneni.cz)

<sup>101</sup> <http://www.cmu.cz/en?Itemid=224>

<sup>102</sup> [www.cregistr.cz](http://www.cregistr.cz)

<sup>103</sup> [www.vrozene-vady.cz](http://www.vrozene-vady.cz)

<sup>104</sup> <http://depts.washington.edu/registry/>

<sup>105</sup> <http://www.linkos.cz/odbornici/onkologie/nor.php>

<sup>106</sup> <http://www.iba.muni.cz/index-en.php>

<sup>107</sup> [www.registry.cz](http://www.registry.cz)

<sup>108</sup> <http://www.ecfs.eu/ctn>

<sup>109</sup> [www.ecfs.eu](http://www.ecfs.eu)

<sup>110</sup> [www.uzis.cz](http://www.uzis.cz)

<sup>111</sup> <http://www.epirare.eu/>

<sup>112</sup> [www.rd-connect.eu](http://www.rd-connect.eu)

<sup>113</sup> <http://www.novorozenecky-screening.cz/>

syrup urine disease, isovaleric aciduria, glutaric aciduria type I, medium-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, carnitine palmitoyl transferase 1 deficiency, carnitine palmitoyl transferase 2 deficiency, carnitine acylcarnitine translocase deficiency and cystic fibrosis. There are follow-up clinical services available for all screened disorders and an *ad hoc* working group comprising representatives of the Czech Ministry of Health and screening institutes meets at a tri-monthly basis. Neonatal screening is fully reimbursed by the General Insurance Company<sup>114</sup> from 2010. In early 2011 the National Coordination Centre for Neonatal Screening was officially established by the Czech Ministry of Health<sup>115</sup> and its operation is funded by targeted annual appropriation schemes. In 2012 the ongoing research grant from the Czech Ministry of Health enabled a pilot project for broadening of the scope of screened metabolic diseases by mass spectrometry. Although the outcomes of this project suggested broadening of the screening for three additional metabolic diseases<sup>116</sup>, the Ministry of Health needs to issue a methodology and negotiate reimbursement with health insurance companies. The information portal for lay public and physicians on neonatal screening was established and financed by the Czech Ministry of Health<sup>117</sup>.

### Genetic testing

Genetic tests are registered for 223 genes and 285 diseases in the Orphanet database<sup>118</sup>. Genetic counselling exists for all families at risk and 51 such facilities are currently registered<sup>119</sup>, which mostly collaborate with molecular genetic and cytogenetic laboratories. Clinical genetics services are available throughout the entire country, with every major district having such services, both at private and/or state based levels. Genetic services are carried out in compliance with all international professional standards and are fully covered by the national health insurance system.

Act 373/2011 Sb regulates genetic testing for rare diseases and reflects the Council of Europe's Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes (CETS No 203) which regulates Direct to Consumer (DTC) testing via specific informed consent provisions. It stipulates (Part 6; section 28) that germinal genome is allowed to be tested within the context of rare diseases in genetic laboratories that are accredited according to the ISO 15189 norm, in accordance with "OECD guidelines for quality assurance in molecular genetic testing"<sup>120</sup>. Moreover, new law 372/2011 Sb stipulates provisions regarding informed consent procedures in the domain of health care services. This law came into effect in the Czech Republic on 1 April 2012.

### National alliances of patient organisations and patient representation

The Czech Association for Rare Diseases<sup>121</sup> (ČAVO) was founded in Spring 2012. At the end of 2013 it counted 30 members - patient organisations representing various rare diseases and 10 individual members who represent Ultra rare diagnoses. ČAVO organised meetings with members every month, published a newsletter, run awareness campaign for both public and health professionals, educated the member platform in areas of interest, such as centralised care, social and legal issues in relation to rare diseases. ČAVO held two major seminars in 2013 for its members and co-organised one Czech Parliament hearing on rare diseases in May 2013. It also works in association with the Coalition for Health Association<sup>122</sup>, which has common disease representatives. Both organisations collaborate on topics of common interest, mainly in the domain of care improvement. ČAVO is an associate member of Eurordis since May 2012 and attends its Council of National Alliances meetings regularly. In June 2012 the ČAVO representatives joined the Taskforce and became active in the fulfilment of the National Action Plan for Rare Diseases.

### Sources of information on rare diseases and national help lines

#### **Orphanet activities in the Czech Republic**

Since 2006 there is a dedicated Orphanet team in the Czech Republic, currently hosted by the University Hospital Motol and the Second Faculty of Medicine of Charles University Prague, that has been transformed by the Bulletin n4/2012 into the National Coordination Centre for Rare Diseases (see above). The team was designated as the Czech national Orphanet team by the Ministry of Health in 2010. This team is in charge of

<sup>114</sup> [www.vzp.cz](http://www.vzp.cz)

<sup>115</sup> [www.novorozenecky-screening.cz](http://www.novorozenecky-screening.cz)

<sup>116</sup> <http://www.novorozeneckyscreening.cz/studie-dlouhodobeho-vlivu-fp>

<sup>117</sup> <http://www.novorozeneckyscreening.cz/>

<sup>118</sup> Data extracted from Orphanet in January 2014.

<sup>119</sup> <http://www.slg.cz/pracoviste/klinicka-genetika/>

<sup>120</sup> <http://www.oecd.org/dataoecd/43/6/38839788.pdf>

<sup>121</sup> [www.vzacna-onemocneni.cz](http://www.vzacna-onemocneni.cz)

<sup>122</sup> [www.koaliceprozdravi.cz](http://www.koaliceprozdravi.cz)

collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also maintains the Orphanet Czech Republic national website<sup>123</sup> in the Czech language providing an entry point to the database. The informatics group of the National Coordination Centre for Rare Diseases also runs the dedicated website financed by the Ministry of Health for the general population and physicians on rare diseases<sup>124</sup>.

#### **Official information centre for rare diseases**

There is no official information centre for rare diseases in the Czech Republic other than Orphanet and activities of the National Coordination Centre for Rare Diseases at University Hospital Motol<sup>125</sup>.

#### **Help line**

A help line for rare diseases was not active in 2013, but the National Coordination Centre for Rare Diseases and ČAVO responded to lay and professional public enquiries by email. A dedicated help email is planned for operation from May 2014.

#### **Other sources of information**

Patient organisation web sites are one of the few national sources of information for rare diseases in the Czech language<sup>126</sup>. The National Alliance for Rare Diseases<sup>127</sup> has started to prepare an integrated server which will unify all disseminated resources under one web portal, including current and expanded neonatal screening<sup>128</sup>.

#### **Guidelines**

Best practice guidelines for genetic diagnosis are listed at the website of the Czech Medical Genetics Society of Czech Medical Association of Jan Evangelista Purkyně for the more common rare diseases<sup>129</sup> and reflect e.g. the EMQN.org and Eurogentest.org guidelines.

#### **Training and education initiatives**

Rare disease information was added into the medical genetics training curriculum at the Masaryk University Brno<sup>130</sup> (4<sup>th</sup> year) and Charles University Prague – 2 Faculty of Medicine (5<sup>th</sup> year<sup>131</sup>).

#### **National rare disease events in 2013**

A number of events were organised by rare disease patient organisations in the Czech Republic to mark Rare Disease Day 2013, mainly in collaboration with ČAVO and Debra<sup>132</sup>.

#### **Hosted rare disease events in 2013**

EuroGentest organised its 3rd International Symposium “Moving Next Generation Sequencing into Diagnostics” in (7 March 2013)<sup>133</sup>. IRDiRC organised together with the National Centre for Rare Diseases an international workshop “Rare Genetic Diseases: Diagnosis and Discovery Workshop Partnership Opportunities with Central/Eastern Europe and the Middle East” on 3 December 2013<sup>134</sup>, following the meeting of the IRDiRC Diagnostics Committee.

#### **Research activities and E-Rare partnership**

##### **National research activities**

Rare diseases research is conducted under several funding bodies: the internal grant agency of the Czech Ministry of Health ([www.mzcr.cz](http://www.mzcr.cz)), the grant agency of the Czech Republic ([www.gacr.cz](http://www.gacr.cz)), and the grant agency of the Charles University Prague ([www.gauk.cz](http://www.gauk.cz)). No new grant calls were issued in 2013.

<sup>123</sup> <http://www.orphanet.cz/national/CZ-CS/index/%C3%BAvod/>

<sup>124</sup> [www.vzacnenemoci.cz](http://www.vzacnenemoci.cz)

<sup>125</sup> [www.vzacnenemoci.cz](http://www.vzacnenemoci.cz)

<sup>126</sup> <http://vzacna-onemocneni.cz/odkazy/>

<sup>127</sup> [www.vzacna-onemocneni.cz](http://www.vzacna-onemocneni.cz)

<sup>128</sup> <http://novorozenecky-screening.cz>

<sup>129</sup> <http://www.slg.cz/koordinacni-centrum-geneticky-laboratori>

<sup>130</sup> [www.muni.cz](http://www.muni.cz)

<sup>131</sup> [www.lf2.cuni.cz](http://www.lf2.cuni.cz)

<sup>132</sup> <http://www.debra-cz.org/>

<sup>133</sup> [http://www.eurogentest.org/index.php?id=213&tx\\_ttnews\[tt\\_news\]=38&cHash=26c3f0e62805fc74baf31dda47d5a069](http://www.eurogentest.org/index.php?id=213&tx_ttnews[tt_news]=38&cHash=26c3f0e62805fc74baf31dda47d5a069)

<sup>134</sup> [http://www.irdirc.org/wp-content/uploads/2014/02/Rare-Genetic-Diseases-Workshop\\_final-version\\_public.pdf](http://www.irdirc.org/wp-content/uploads/2014/02/Rare-Genetic-Diseases-Workshop_final-version_public.pdf)

### **Participation in European research projects**

Czech teams participate or have participated in 13 FP7 projects related to rare diseases.

### **E-Rare**

The Czech Republic is not currently a partner of the E-Rare research programme on rare diseases.

### **IRDiRC**

Czech funding agencies have not yet committed funding to the IRDiRC.

### **Orphan medicinal products**

SUKL<sup>135</sup>, the State Institute for Drug Control, is the regulatory body in the Czech Republic responsible for the regulation and surveillance of human medicinal products and medical devices, including orphan medicinal products.

### **Orphan medicinal product committee**

There is no permanent committee for orphan medicinal products in the Czech Republic.

### **Orphan medicinal product incentives<sup>136</sup>**

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, the Czech Republic has a number of mechanisms in place to encourage orphan medicinal product development. For example *“administrative fees are not charged for applications for the registration of medicinal products or for an amendment, extension or transfer of registration of a medicinal product or for authorisations for parallel import of a medicinal product, if the application concerns a medicinal product included in the register of orphan medicinal products under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.*

*“Under §65(2)(b) of Act No 79/1997 Coll. on medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may refrain from recovering costs where these concern operations which are in the public interest or may have especially important implications for the wider population. These operations include applications for: authorisation/registration of clinical assessments of medicinal products and notification to the submitter of additions to the records in cases concerning the evaluation of an orphan medicinal product, and consultation and opinions on such applications; application for registration of an orphan medicinal product and application for amendment, extension or transfer of registration or application for authorisations for parallel import of an orphan medicinal product and consultation and opinions on applications concerning orphan medicinal products.*

*“Under §26d(1) of Act No 79/1997 Coll. On medicines, amending and supplementing other acts, as amended, the State Institute for Drug Control may, in the case of orphan medicinal products in justified cases meeting the conditions laid down by decree, allow the registration of a medicinal product or the placing on the market of individual batches of a medicinal product even where the data are indicated on the packaging in a language other than Czech.<sup>137”</sup>*

### **Orphan medicinal product pricing policy**

There is no specific pricing mechanism for orphan products. The prices of pharmaceuticals in Czech Republic are based mainly on reference ex-factory prices in reference basket countries (i.e. all European Union countries except of Bulgaria, the Czech Republic, Estonia, Luxemburg, Germany, Austria, Romania, Cyprus and Malta). The maximum ex-factory price is calculated as average of three lowest prices in reference basket countries. The ex-factory price is then increased by wholesaler and pharmacy margin and value added tax.

### **Orphan medicinal product market availability situation**

In 2013, 71 orphan medicinal products were registered in the Czech Republic, of which 43 have been launched on the market (Adcetris, Aldurazyme, Arzerra, Atriance, Cystadane, Diacomit, Elapraxe, Esbriet, Evoltra, Exjade,

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<sup>135</sup> [www.sukl.cz](http://www.sukl.cz)

<sup>136</sup> This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp9-10)

<sup>137</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp9-10)

Firazyr, Gliolan, Increlex, Inovelon, Jakavi, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Peyona, Revatio, Revlimid, Signifor, Tasigna, Tepadina, Tobi Podhaler, Torisel, Tracleer, Vidaza, Volibris, Votubia, Vpriv, Vyndaqel, Wilzin, Yondelis, Zavesca).

#### **Orphan medicinal product reimbursement policy**

The State Institute for Drug Control (SUKL) is the body in charge of reimbursement of out-patient drugs. In case the drug is used in in-patient settings, it is fully reimbursed by hospital lump sum. 30 orphan medicinal products which are distributed on a centre basis are reimbursed (Afinitor, Aldurazyme, Arzerra, Busilvex, Cystadane, Duodopa, Elaprase, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Ilaris, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedeia, Peyona, Prialt, Replagal, Revlimid, Revolade, Somavert, Tasigna, Tepadina, Torisel, Tracleer, Trisenox, Ventavis, Vidaza, Volibris, Wilzin, Yondelis, Zavesca). In some cases the level of reimbursement for out-patient drugs is based on individual negotiation between expert centres and marketing authorization holders. Establishment of official expert centres via Bulletin 4/2012 (see above) will facilitate subsequent reimbursement negotiations with health insurance funds or pharmaceutical companies (e.g. clinical trials, compassionate use programmes, risk sharing strategies etc.). Alternatively, there is the possibility to use art. 16 of Law No. 48/1997 Coll. for the "Individual patient reimbursement scheme". This scheme is applicable only in the case of unavailability of alternative treatments. Specialised centres can apply within a revolving application scheme to a revisional doctor of a particular health insurance fund until reimbursement is officially decided by SUKL. This measure is mainly intended to "bridge" the period between e.g. phase 3 clinical trials and introduction of a successful drug into health insurance reimbursement schemes.

Currently there is no special reimbursement procedure for orphan medicinal products and they are assessed similarly to non-orphan medicines. Since 2008 reimbursement procedure for medicines for out-patient use is run by SUKL in administrative proceedings with the involvement of the marketing authorization holder and payers (insurance funds). Patient groups are not directly involved in the procedure. Healthcare professionals can give their opinion on the assessment report and in many cases are engaged as consultants. All documentation is publicly accessible on internet. The assessment takes into account effectiveness (therapeutic benefit) and safety profile of the medicine, severity of disease (usually high in orphan drugs), treatment alternatives (usually not existing in orphan drugs), recommendation of expert doctors' associations or guidelines as well as budget impact and cost effectiveness.

Reimbursement price is calculated as the EU lowest price. Since the beginning of 2013 willingness to pay threshold has been introduced reflecting 3-times GDP per capita (est. 1,1 mil. CZK/QALY). The orphan drugs are sometimes not able to provide the cost/QALY results below this threshold either they do not have sufficient and long-term clinical data or their ICERs are exceeding the threshold. However assessment of all above mentioned criteria plays an important role. In case of orphan drugs severity of disease is usually high and lack of other treatment options is another crucial factor in the final decision. In case that the drug meets specific criteria (the new drug is safer or more effective compared to current treatment or it is the only existing treatment or there is few knowledge about cost-effectiveness of the drug and its real life effectiveness) it can be appointed so called "highly innovative drug" status. In this case reimbursement is granted temporarily for maximum 3 years even without sound cost-effectiveness analysis. The real-life clinical data must be collected and analysed during this period. At the end of the provisional period cost-effectiveness (cost per QALY) is re-evaluated and permanent reimbursement can be granted.

#### **Other initiatives to improve access to orphan medicinal products**

The country has compassionate use programme for specific orphan medicinal products, and therapeutic programmes that allow for the use of certain non-authorized medicinal products, usually coordinated by specific centres, on a named-patient basis. *Ad hoc* committees exist for very expensive orphan medicinal products, which are centre-based.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Orphan devices**

No specific information reported.

### Specialised social services

A few patient organisations also offer recreational services, such as summer camps for children or rehabilitation/therapeutic weekends for adult patients. These are usually fully reimbursed by the Ministry of Social Affairs. The *Act on social services for people with disabilities* came into force in 2007, improving the access to social services for rare disease patients: these schemes are reimbursed and are fully funded from social insurance and are coordinated by the Ministry of Social Affairs.

## RARE DISEASE ACTIVITIES IN 2013 IN THE CZECH REPUBLIC

### National plan/strategy for rare diseases and related actions

In order to fulfill the priority aims of the Czech National Plan for 2013 the Taskforce met four times and among others endorsed presentations of representatives of various professional societies for the establishment of respective centers of expertise in the country (e.g. for neurology, endocrinology, rheumatology, orofacial abnormalities, immune deficiencies, oncology, nephrology, hematology). Based on the endorsements of the Czech Ministry of Health envisages to publish official tenders for their establishment using EUCERD criteria<sup>138</sup>. The aforementioned EUCERD guidelines are intended to serve as basis for the crossborder health care in rare diseases related to the implementation of the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare<sup>139</sup>.

### Centres of expertise

Based on the work of the Taskforce and including the entry into force of Law 372/2011Sb which in its article 112 provided legal basis for establishment of expert centres (not only for rare diseases), a group of rare disease centres was officially established on 28 May 2012 and published in Bulletin n. 4 / 2012 of the Czech Ministry of Health<sup>140</sup> – section 4 “Basic network of rare disease centres”. Following the presentation of *de facto* activities of various professional groups, active mainly within the major faculty hospitals (e.g. FN Brno<sup>141</sup>, FN Motol<sup>142</sup>, VFN Praha<sup>143</sup>, FN HK<sup>144</sup>, FN Olomouc<sup>145</sup> and FN Plzeň<sup>146</sup>), *de iure* recognition of their “centre status” activities will be carried out by the Ministry of Health during 2014. However, it needs to be noted that establishment of centres from the Ministry of Health does not entitle them to “centre-based health care reimbursement”, which has to be assured independently through subsequent and complicated negotiations with the various health insurance companies. There are no legal provisions which would guarantee that *de iure* rare disease centers of expertise are eligible to become “centres with a specific contract”, an issue particularly important for reimbursement of orphan medicinal products. In 2013 new rare disease centres were not established.

### Registries

The Interministerial and interdisciplinary commission for rare diseases is in the process of establishing the National registry of rare diseases, which will serve as a “confederated database” of all other disseminated registries in centres to be established. As a pilot projects serves the dedicated registry initiative of the Institute of Biostatistics and Analysis<sup>147</sup> at the Masaryk University in Brno<sup>148</sup>.

In 2013 the Czech Institute of medical informatics and statistics<sup>149</sup> started a compilation of rare disease registries in the country and established collaboration with the EPIRARE<sup>150</sup> and RD-Connect<sup>151</sup> projects in terms of mapping and standardisation of registries.

<sup>138</sup> [http://www.eucerd.eu/?post\\_type=document&p=1224](http://www.eucerd.eu/?post_type=document&p=1224)

<sup>139</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF>

<sup>140</sup> [http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c4/2012\\_6288\\_2510\\_11.html](http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c4/2012_6288_2510_11.html)

<sup>141</sup> [www.fnbrno.cz](http://www.fnbrno.cz)

<sup>142</sup> [www.fnmotol.cz](http://www.fnmotol.cz)

<sup>143</sup> [www.vfn.cz](http://www.vfn.cz)

<sup>144</sup> [www.fnhk.cz](http://www.fnhk.cz)

<sup>145</sup> [www.fnol.cz](http://www.fnol.cz)

<sup>146</sup> [www.fnplzen.cz](http://www.fnplzen.cz)

<sup>147</sup> <http://www.iba.muni.cz/index-en.php>

<sup>148</sup> [www.registry.cz](http://www.registry.cz)

<sup>149</sup> [www.uzis.cz](http://www.uzis.cz)

<sup>150</sup> <http://www.epirare.eu/>

<sup>151</sup> [www.rd-connect.eu](http://www.rd-connect.eu)

### **National alliances of patient organisations and patient representation**

The Czech Association for Rare Diseases<sup>152</sup> (ČAVO) counted 30 members - patient organisations representing various rare diseases and 10 individual members who represent Ultra rare diagnoses. ČAVO organised meetings with members every month, published a newsletter, run awareness campaign for both public and health professionals, educated the member platform in areas of interest, such as centralised care, social and legal issues in relation to rare diseases. ČAVO held two major seminars in 2013 for its members and co-organised one Czech Parliament hearing on rare diseases in May 2013.

### **Sources of information on rare diseases and national help lines**

#### **Help line**

A help line for rare diseases was not active in 2013, but the National Coordination Centre for Rare Diseases and ČAVO responded to lay and professional public enquiries by email. A dedicated help email is planned for operation from May 2014.

#### **Other sources of information**

The National Alliance for Rare Diseases<sup>153</sup> has started to prepare an integrated server which will unify all disseminated resources under one web portal, including current and expanded neonatal screening<sup>154</sup>.

### **Training and education initiatives**

Rare disease information was added into the medical genetics training curriculum at the Masaryk University Brno<sup>155</sup> (4<sup>th</sup> year) and Charles University Prague – 2 Faculty of Medicine (5<sup>th</sup> year<sup>156</sup>).

### **National rare disease events in 2013**

A number of events were organised by rare disease patient organisations in the Czech Republic to mark Rare Disease Day 2013, mainly in collaboration with ČAVO and Debra<sup>157</sup>.

### **Hosted rare disease events in 2013**

EuroGentest organised its 3rd International Symposium “Moving Next Generation Sequencing into Diagnostics” in (7 March 2013)<sup>158</sup>. IRDiRC organised together with the National Centre for Rare Diseases an international workshop “Rare Genetic Diseases: Diagnosis and Discovery Workshop Partnership Opportunities with Central/Eastern Europe and the Middle East” on 3 December 2013<sup>159</sup>, following the meeting of the IRDiRC Diagnostics Committee.

## **1.7. DENMARK**

### **Definition of a rare disease**

There is no official absolute definition for rare diseases at the moment in Denmark. The Danish Health and Medicines Authority (formerly National Board of Health) defines rare diseases as affecting no more than 500 - 1000 patients, 1-2 per 10,000 in the Danish population. Rare Disorders Denmark (The national alliance of patient organisations for rare disorders) defines rare diseases as affecting no more than 1 000 patients in the Danish population. The Danish definition also takes into account the degree of complexity of the disease, and the general rules that the disease must be severe, genetic or congenital, therefore rare cancers and infectious

<sup>152</sup> [www.vzacna-onemocneni.cz](http://www.vzacna-onemocneni.cz)

<sup>153</sup> [www.vzacna-onemocneni.cz](http://www.vzacna-onemocneni.cz)

<sup>154</sup> <http://novorozenecky-screening.cz>

<sup>155</sup> [www.muni.cz](http://www.muni.cz)

<sup>156</sup> [www.lf2.cuni.cz](http://www.lf2.cuni.cz)

<sup>157</sup> <http://www.debra-cz.org/>

<sup>158</sup> [http://www.eurogentest.org/index.php?id=213&tx\\_ttnews\[tt\\_news\]=38&cHash=26c3f0e62805fc74baf31dda47d5a069](http://www.eurogentest.org/index.php?id=213&tx_ttnews[tt_news]=38&cHash=26c3f0e62805fc74baf31dda47d5a069)

<sup>159</sup> [http://www.irdirc.org/wp-content/uploads/2014/02/Rare-Genetic-Diseases-Workshop\\_final-version\\_public.pdf](http://www.irdirc.org/wp-content/uploads/2014/02/Rare-Genetic-Diseases-Workshop_final-version_public.pdf)



diseases are usually not considered to be part of the concept of “rare diseases” in Denmark, but it is recognised that they have similar problems.

### **National plan/strategy for rare diseases and related actions**

Access to health care at hospitals and GPs is free of charge for all citizens independently of diagnoses and prevalence. Patients also have a right to choose between relevant hospitals. Access to social services and support for patients is also free of charge and given depending on need not diagnosis.

There is currently no specific national/strategy plan for rare diseases in Denmark involving all sectors, but regarding the hospital sector the Danish Health and Medicines Authority as the statutory competent authority has approved centres of expertise/referral centres for rare diseases in 2010 as part of a comprehensive planning of highly specialized hospital services in Denmark accordingly to the health care act.

Since 1993 The National Board of Health has published a list of centres of expertise designated by the National Board of Health. This list of centres has been revised regularly through the years and is now developed to the above mentioned approval system.

In 2001 the Danish National Board of Health launched a special report on rare diseases with recommendations regarding rare diseases in general and specific recommendations for 14 rare diseases to be cared for at two specialised Rare Diseases Centres. These two centres were established in Copenhagen and Aarhus respectively. In the beginning the centres were mainly focused on paediatric patients. Now about one third of the patients are adults. The two centres work continuously on strengthening the interdisciplinary and cross professional activities. The 2001 report also gave a number of other recommendations which have not yet all been implemented. The report described an ideal general model for development of activities regarding rare diseases in the health care sector and cooperation with other sectors. Many of the EUROPLAN-recommended elements of a national strategy for rare diseases are dealt with in this report.

Current expenditure for rare diseases, as for all other diseases, is within in the general health system budget of the regions and municipalities. There are no dedicated funds for rare diseases, except for the dietary treatment of phenylketonuria which is directly financed from the state budget. In 2010 special funding was obtained from the state budget to implement a National Center for Rett syndrome within the Kennedy Center.

On 19 November 2010, Rare Disorders Denmark in collaboration with EURORDIS held a National Conference on Rare Diseases<sup>160</sup> in the context of the Europlan project in order to discuss the elaboration of a national plan for rare diseases in Denmark. In 2011 it was decided to let the National Board of Health establish a working group to elaborate a national strategy for Rare Diseases.

The working group with the task to elaborate a national plan for RD has a broad representation of stakeholders and was founded at the end of 2011 and met at the start of February 2012 for the first time. The recommendations in the previous report on rare diseases from 2001 are being assessed to see what is still needed, what has changed and what new recommendations can be added considering the European perspective and the recommendations for a national strategy. The subject of centres of expertise is a key area of consideration but many other subjects are dealt with. The working groups’ proposal for a national strategy/ is scheduled to be submitted to the Ministry of Health early 2014. There is no a specific budget for the strategy.

In October 2013, with a new disability policy action plan, entitled "A Society for All" was launched which will hopefully improve aspects of care for all disabled people and patients, including rare disease patients.

### **Centres of expertise**

The Danish Health and Medicines Authority has the authority to approve centres of expertise accordingly to the Health Care Act.

As mentioned above two centres of expertise specific for rare diseases have been functioning officially since 2001 in the health care system in Denmark at university hospital level. There are also a number of other established referral centres/centres of expertise approved by the Danish Health and Medicines Authority with the task to maintain a specific or several specific rare diseases<sup>161</sup>.

The two centres, Centre for Rare Diseases CSS RH in Copenhagen and Centre for Rare Diseases – CSS AUH in Aarhus, were established in 2001, being responsible centres for 14 specific diagnoses. The special remit

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<sup>160</sup> [http://download.EURORDIS.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/final report denmark europlan.pdf](http://download.EURORDIS.org/europlan/2%20EUROPLAN%20Guidance%20Documents%20for%20the%20National%20Conference/final%20report%20denmark%20europlan.pdf)

<sup>161</sup> For more information

[http://www.sst.dk/Planlaegning%20og%20kvalitet/Specialplanlaegning/specialplan\\_2010.aspx](http://www.sst.dk/Planlaegning%20og%20kvalitet/Specialplanlaegning/specialplan_2010.aspx)

Centres of Reference for RD in Europe: State of the art in 2006 and recommendations of the RDTF (p.9)

<http://www.eucerd.eu/upload/file/Publication/RDTFCR2006.pdf>

of these centres is the co-ordination of patient-care programs, treatment protocols and databases, and taking care of medical highly specialised tasks in agreed partnerships. Two years after the establishment of the centres, Rare Diseases Denmark conducted a survey that revealed that 75% of patients felt they had received better and more coherent treatment when treated at the centres. The two centres also have an important function in assessing patients, who do not have a diagnosis, but where a rare disease is suspected. Today the centres take care of many more different diagnoses, which do not have another nominated centre of expertise.

According to the Danish Health Care Act from 2007 the National Board of Health began a comprehensive work going through the organisation of specialized diagnoses, treatments and medical technologies across 36 surgical, medical and diagnostic specialties. The main goal was to improve quality through sufficient volumes of patients and experienced professionals. The general criteria for establishing centers of expertise in this context are rareness, complexity, multidisciplinary and costly technologies. In 2009 public and private hospitals could apply to the National Board of Health for approval to maintain specific specialised treatments. In 2010 the National Board of Health announced the approved hospital departments in specific lists for each medical specialty. The two Centres of Rare Diseases have also been approved in this context. The departments that host the two Centres of Rare Diseases have also been approved for a number of different rare diseases, e.g. in Copenhagen for inborn errors of metabolism (IEM).

The number of centres of expertise for a single condition or groups of conditions depends on rarity (estimated number of patients), competence and available technology. A specific condition might thus be treated at only one specialised hospital department or up to five different hospital departments. Some geographical considerations will usually play a role in the decision making process if there is room for more than one centre. The approved departments are required to secure and develop their expertise, establish a quality improvement programme, document their activities and take part in teaching and research activities. The system is focused on treatment of patients.

The National Board of Health has in the National Plan for highly specialised hospital services issued about 1100 approvals of medical highly specialised functions and estimates that about 100 -120 of these are related to various diseases or groups of diseases which can be classified as rare. In General the approvals will last for a duration of 3 years. A revision process for these services will start in March 2014.

### **Registries**

No single centralised register for rare diseases currently exists in Denmark, but a number of different registries and biobanks exist although there is currently no public register giving an overview of the existing registries and biobanks dealing with rare diseases. The Serum Institute has hosted registry and biobank of all newborn screening blood samples since 1980. The Kennedy Centre maintains biobanks on specific rare disorders as Menkes disease and various genetic eye diseases. All visually handicapped children are registered until the age of 18. Furthermore, several research departments have registries of rare diseases patients. The Raredis database which collects clinical data has been developed in Denmark in accordance to the recommendations in the Danish report of rare diseases from 2001 and has been in function since 2007 at the two Centres of Rare Diseases in Denmark. There is now collected data on more than 3000 patients with more than 500 different diagnoses seen at the two centres. Centres of rare diseases in the Nordic countries use their local version of Raredis for collecting clinical data. The hereby collected information can be used for research projects and bench marking at a Nordic level for different rare diseases. Several specific research projects are performed and planned.

The Danish National Patient Registry (NPR) exists since 1977 and collects systematic information on diagnoses, surgical treatment, and various demographical parameters on all patients admitted to hospital or similar institutions in Denmark. The Danish personal identity numbers give possibilities to follow up patients through the years and combine data with other national registries as the cancerregistry, registry for cause of death etc and to clinical databases and more specific registries. In 2013 an article with an overview of Danish registries for studies of medical genetic diseases was published<sup>162</sup>.

Danish teams contribute to some European registries such as EURO CARE CF, EIMD, EMHG and EUROCAT.

### **Neonatal screening policy**

National neonatal screening schemes are in place for phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, maple syrup urine disease, ASL, carnitine transporter defect, medium chain acyl-CoA

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<sup>162</sup> Mary Nguyen Nielsen et al. Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. Clinical epidemiology 2013, 3:5 249-262

dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, very long chain acyl-coA dehydrogenase deficiency, glutaric acidemia type 1, methyl malonic acidemia, propionic acidemia, multiple carboxylase defect, arginino succinic aciduria, tyrosinemia type 1 and biotinidase defect. Furthermore, the timing for drawing the blood samples (done by heel-prick) has been brought forward from five days to within 48-72 hours following birth, allowing for earlier intervention and treatment. Neonatal hearing screening has also been introduced as part of the national policy.

### **Genetic testing**

There are 6 approved highly specialised centres for clinical genetic testing and counselling. Some genetic testing is also carried out in a few clinical biochemistry laboratories (e.g. BRCA testing). Genetic testing abroad is possible mediated by the clinical genetics centres. Genetic testing for medical reasons is part of the national health care system and free of charge. State reimbursement of costs for tests abroad can be effected after approval from the Danish Health and Medicines Authority.

Diagnostic tests are registered as available in Denmark for 114 genes and an estimated 226 diseases in the Orphanet database<sup>163</sup>.

### **National alliances of patient organisations and patient representation**

Rare Diseases Denmark (RDD), founded in 1985, is the national alliance of 48 rare disease patient organisations/societies covering 11,500 members. In addition there are around 12 - 15 other patient organisations for rare diseases. Patient organisations are eligible to receive limited funding from the Ministries of Health and Social Affairs. RDD facilitates exchange of experience between the member societies, creates and disseminates new knowledge about living with rare diseases and advocates for the rights of all rare disease patients. From December 2012, RDD has established its own secretariat situated in an accessible building, which has offices for 24 disability-related organisations. RDD also publishes a newsletter.

RDD holds a mini-roundtable with relevant pharmaceutical companies. The mini-roundtable currently has 6 members.

RDD has developed a tool, Social Profiles, to promote dialogue between rare disease patients and professionals. The profiles are currently available for 35 rare diagnoses, with more to come. The profiles are published on the "Rare Citizen" website<sup>164</sup>.

Over 2009 -2012 RDD developed a special training programme for families with children affected by rare diseases under the age of 18 called "Rare Family Days". Some preliminary results were presented by RDD at the ECRD conference in Brussels and the final results were published in 2013<sup>165</sup>, along with a new concept for "Rare Family Days".

RDD cooperates with the National Board of Social Services. In 2012 RDD through NBSS adopted a Focus Point of Contact for very rare disease patients and relatives with no possibility to join or form a patient organisation/society. More than 500 rare citizens adhere to the Focus Point, representing more than 170 rare diseases.

Also in 2013, RDD contributed to the work of National Board of Health's working group to elaborate a national strategy for Rare Diseases.

Patients' organisations are, in general, consulted regarding legalisation concerning issues relevant to rare diseases and, in general, participate in the relevant boards and official bodies/working groups. RDD is represented in a number of these groups including the working group of National Strategy for rare diseases, constituted by the National Board of Health in December 2011.

Patient organisations are eligible for some limited funding from the Ministries of Health and Social Affairs for capacity building work. RDD received funding recently to lead a survey of RD patients' families concerning their perception of everyday life and the cross-over between healthcare and social support.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Denmark***

From 2004-2010 there was a dedicated Orphanet team in Denmark, hosted by the John F. Kennedy Institute. This team was in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in the country for entry into the Orphanet database.

<sup>163</sup> Information extracted from the Orphanet database (January 2014).

<sup>164</sup> [www.sjaeldenborger.dk](http://www.sjaeldenborger.dk)

<sup>165</sup> <http://www.sjaeldnediagnoser.dk/documents/9FE7D7DD-09F7-48AF-93AC-D41985D643EC.pdf>

### **Official information centre for rare diseases**

The state-funded information centre on rare diseases, the Danish Centre for Rare Diseases and Disabilities (*Center for små handicapgrupper*<sup>166</sup>) functioned from 1994 - 2010 with a public database containing short descriptions in Danish on rare diseases. The centre provided information, as well as guidance, especially on social issues, and provided contact with patient organisations. The CSH also ran a rare disease help line which provided information and support. The CSH maintained a database of approximately 400 rare disease patients who are currently without patient organisation representation for their disease. The CSH also contributed to Rarelink.eu, the Nordic website compiling links relating to information on rare diseases.

At the end of 2010, the Ministry for Social Affairs closed the Centre for Rare Diseases and Disabilities (*Center for Små Handicapgrupper* – CSH) as an independent institution. This decision was a consequence of the merger of 3 information and knowledge networks and 13 research centres in areas overseen by the Ministry of Social Affairs to form a new Centre for Disability and Social Psychiatry (*Videnscenter for Handicap og Socialpsykiatri* - ViHS<sup>167</sup>) as of 1 January 2011. The experience of the first years of the new structure is that the help line is less sought after than before and that the knowledge-based work with diagnosis descriptions has become more difficult and is not at the same level as before. The future general information about rare diseases is expected to be discussed in the working group of the National Strategy

### **Help line**

After the closure of CSH in 2010 the ViHS ran the help-line until the end of 2012.

### **Other sources of information**

No specific activity reported.

### **Guidelines**

The 2001 report from the National Board of Health laid down guidelines concerning 11 specific rare diseases. These guidelines also serve as template concerning other rare diseases. Health care professionals consult published international guidelines.

### **Training and education initiatives**

The two Rare Diseases Centres participate in educational activities for nurses and doctors. Furthermore, they provide teaching for other health care professionals, families, teachers and caretakers.

### **National rare disease events in 2013**

Rare Diseases Denmark led the celebration of Rare Disease Day 2013 with a Rare Market in Flensburg and a balloon launch, as well as the annual holding of hands to show solidarity

A conference on patient education for families with children with severe chronic illness and disability was organised on 8 May 2013 by Rare Disorders Denmark in Taastrup to discuss the concept of Rare Family Days with stakeholders.

Rare Diseases Denmark also wrote letters to the Ministers of Health and European Affairs and the corresponding parliamentary committees in order to raise awareness of the needs of rare diseases patients, especially the need to implement the Cross-Border Healthcare Directive into Danish law so as to benefit rare disease patients.

### **Hosted rare disease events in 2013**

In October 2013, Rare Diseases Denmark hosted a EUCERD Joint Action Workshop on training of social service providers, - organised through the EUCERD Joint Action N°2011 22 01.

### **Research activities and E-Rare partnership**

#### **National research activities**

There are no specific programmes for rare diseases research in Denmark or focussed calls/grants. Although there are no specific initiatives to support research into rare diseases in Denmark, Danish researchers are active in the field and there are resources in place (biobanks, registries, databases) for rare disease research.

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<sup>166</sup> [www.csh.dk](http://www.csh.dk)

<sup>167</sup> More information on the organisation of the ViHS can be accessed here [http://www.csh.dk/fileadmin/pdf/Rapporter\\_og\\_andet/Organisering\\_af\\_ViHS-1.doc](http://www.csh.dk/fileadmin/pdf/Rapporter_og_andet/Organisering_af_ViHS-1.doc) (accessed 27/01/2011)

### **Participation in European research projects**

Danish teams participate/have participated in 30 FP7 rare disease related projects.

#### **E-Rare**

Denmark is not an E-Rare partner.

#### **IRDIRC**

Danish funding agencies have not committed funding to the IRDiRC.

### **Orphan medicinal products**

#### **Orphan medicinal product committee**

There is currently no committee dedicated to Orphan medicinal products and/or rare diseases in Denmark.

#### **Orphan medicinal product incentives**

Upon request, the Danish Medicines Agency may provide free scientific advice in the development of orphan medicinal products<sup>168</sup>.

#### **Orphan medicinal product market availability situation**

Out of 68 orphan medicinal products with an EU market authorisation, 58 are approved in Denmark and are on the Danish national formulary of medicines<sup>169</sup>. The approval process usually takes 6-8 weeks.

The list of orphan medicinal products approved and launched on the market in Denmark includes<sup>170</sup>: Afinitor, Aldurazyme, Arzerra, Atriance, Busilvex, Carbaglu, Cayston, Ceplene, Cystadane, Diacomit, Elaprase, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyr, Firdapse, Gliolan, Glivec, Increlex, Inovelon, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Prialt, Replagal, Revatio, Revlimid, Revolade, Savene, Soliris, Somavert, Sprycel, Tassigna, Tepadina, Teysuno (S-1), Thalidomide Celgene, TOBI Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, VPRIV, Vyndaqel, Wilzin, Xagrid, Yondelis, Zavesca.

#### **Orphan medicinal product pricing policy**

Manufacturers and importers of pharmaceutical products are free to set the price of each pharmaceutical. However, orphan medicinal products are mostly hospital-only pharmaceuticals, and the drugs used at hospitals are bought via public procurement. Most public tenders are carried out by AMGROS which is a hospital purchasing agency owned by the five regions in Denmark.

#### **Orphan medicinal product reimbursement policy**

There is no reimbursement policy that pertains specifically to orphan medicinal products. In many cases, orphan medicinal products are restricted to hospitals. All medicines dispensed at hospitals are free of charge to the patient, and if dispensed from a pharmacy on prescription there is a needs-based co-payment<sup>171</sup>.

#### **Other initiatives to improve access to orphan medicinal products**

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, there are no specific programmes to facilitate the provision of medicines to rare diseases patients in Denmark (i.e. compassionate use). However, in special circumstances and to a limited degree the Danish Medicines Agency can authorise "the sale or dispensing of medicinal products that are not marketed in Denmark for other purposes than clinical investigations (cohort or named patient supply). Patients with life-threatening diseases for which there are no well-documented treatment options can be offered experimental treatment (named patient supply only)"<sup>172</sup>.

<sup>168</sup> This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*. Revision 2005 (pp10-11)

<sup>169</sup> Data from last year's edition has not been able to be updated, [www.medicinpriser.dk](http://www.medicinpriser.dk)

<sup>170</sup> Data from last year's edition has not been able to be updated.

<sup>171</sup> EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Hahl & Florian Bachner, p.47.

<sup>172</sup> This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*. Revision 2005 (p10)

### **Other therapies for rare diseases**

No specific activity reported.

### **Orphan devices**

No specific activity reported.

### **Specialised social services**

The National Board of Social Services is an independent subdivision of The Ministry of Social Affairs, Children and Integration. Founded on 1 January 2007, the Board is located in Odense, Denmark, with units in Copenhagen, Esbjerg and Aarhus. Through its two departments – the Department of Social Services and the Department known as VISO – the Board aims to promote new development and initiatives in social services while also supporting and counselling local authorities in providing services to citizens. VISO is the Danish abbreviation for "National Videns- og specialrådgivningsorganisation" which translates into the National Organisation for Knowledge and Specialist Consultancy. VISO offers specialist consultancy and specialist assessments in complicated and specialised individual cases in the field. In such cases, the Board also offers specialist consultancy to citizens. Both departments offer assistance for all citizens, including persons with rare diseases/disabilities.

In 2007 Denmark went through a structural reform, which reduced the number of municipalities from 275 to 98 and reduced the 14 counties to 5 regions. As a part of the reform the municipalities are to take care of all social services – also the specialised ones, previously organised at county level. An evaluation of the reform conducted in 2012-13 has shown that the reform seems to have had serious consequences on the specialised functions. Therefore it was decided by the parliament that the National Board on Social Services from 2014 will have a new monitoring role, keeping an eye on the need for and development in specialised social and educational services – with a special focus on citizens with rare diseases/disabilities.

Respite care services are sometimes provided by municipalities. Patient organisations organise informal therapeutic recreational activities and can sometimes receive government financial support. Services are provided and funded by the government to enable help integrate patients with rare diseases into daily life, both at school and work.

## **RARE DISEASE ACTIVITIES IN 2013 IN DENMARK**

### **National plan/strategy for rare diseases and related actions**

Access to health care at hospitals and GPs is free of charge for all citizens independently of diagnoses and prevalence. Patients also have a right to choose between relevant hospitals. Access to social services and support for patients is also free of charge and given depending on need not diagnosis.

There is currently no specific national/strategy plan for rare diseases in Denmark involving all sectors, but regarding the hospital sector the Danish Health and Medicines Authority as the statutory competent authority has approved centres of expertise/referral centres for rare diseases in 2010 as part of a comprehensive planning of highly specialized hospital services in Denmark accordingly to the health care act.

Since 1993 The National Board of Health has published a list of centres of expertise designated by the National Board of Health. This list of centres has been revised regularly through the years and is now developed to the above mentioned approval system.

The working group with the task to elaborate a national plan for RD has a broad representation of stakeholders and was founded at the end of 2011 and met at the start of February 2012 for the first time. The recommendations in the previous report on rare diseases from 2001 are being assessed to see what is still needed, what has changed and what new recommendations can be added considering the European perspective and the recommendations for a national strategy. The subject of centres of expertise is a key area of consideration but many other subjects are dealt with. The working groups' proposal for a national strategy/ is scheduled to be submitted to the Ministry of Health early 2014. There is no a specific budget for the strategy.

In October 2013, with a new disability policy action plan, entitled "A Society for All" was launched which will hopefully improve aspects of care for all disabled people and patients, including rare disease patients.

### Centres of expertise

The National Board of Health has in the National Plan for highly specialised hospital services issued about 1100 approvals of medical highly specialised functions and estimates that about 100 -120 of these are related to various diseases or groups of diseases which can be classified as rare. In General the approvals will last for a duration of 3 years. A revision process for these services will start in March 2014.

### Registries

In 2013 an article with an overview of Danish registries for studies of medical genetic diseases was published<sup>173</sup>.

### National alliances of patient organisations and patient representation

Rare Diseases Denmark (RDD), founded in 1985, is the national alliance of 48 rare disease patient organisations/societies covering 11,500 members.

Over 2009 -2012 RDD developed a special training programme for families with children affected by rare diseases under the age of 18 called "Rare Family Days". Some preliminary results were presented by RDD at the ECRD conference in Brussels and the final results were published in 2013<sup>174</sup>, along with a new concept for "Rare Family Days".

Also in 2013, RDD contributed to the work of National Board of Health's working group to elaborate a national strategy for Rare Diseases.

### Hosted rare disease events in 2013

In October 2013, Rare Diseases Denmark hosted a EUCERD Joint Action Workshop on training of social service providers, - organised through the EUCERD Joint Action N°2011 22 01.

### Specialised social services

The National Board of Social Services is an independent subdivision of The Ministry of Social Affairs, Children and Integration. In 2007 Denmark went through a structural reform, which reduced the number of municipalities from 275 to 98 and reduced the 14 counties to 5 regions. As a part of the reform the municipalities are to take care of all social services – also the specialised ones, previously a organised at county level. An evaluation of the reform conducted in 2012-13 has shown that the reform seems to have had serious consequences on the specialised functions. Therefore it was decided by the parliament that the National Board on Social Services from 2014 will have a new monitoring role, keeping an eye on the need for and development in specialised social and educational services – with a special focus on citizens with rare diseases/disabilities.

## 1.8. ESTONIA

### Definition of a rare disease

Stakeholders in Estonia accept the definition of the European Regulation on Orphan Medicinal Products of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

In 2008, Estonian Government adopted Eesti Rahvastiku Arengukava 2009-2020 (*Estonian National Health Plan 2009-2020*, hereafter referred to its Estonian acronym, ERTA). ERTA 2009-2020 provides recommendations and indicates the directions to be taken to improve healthcare and brings together the tasks necessary to achieve this. The plan also assembles a large number of strategic documents which have already been implemented or which are soon to be implemented in other fields that have a role to play in achieving ERTA's objective.

In September 2012 a working group was set up to discuss the activities on the field of rare diseases to be added to the implementation plan of ERTA: the working group includes professionals in the field of rare diseases (doctors, medical geneticists, representatives of patient organisations, representatives from the Estonian Board of Disabled People, etc.). A draft plan for rare diseases was drawn up at the end of 2012. The

<sup>173</sup> Mary Nguyen Nielsen et al. Existing data sources for clinical epidemiology: Danish registries for studies of medical genetic diseases. *Clinical epidemiology* 2013, 3:5 249-262

<sup>174</sup> <http://www.sjaeldnediagnoser.dk/documents/9FEED7DD-09F7-48AF-93AC-D41985D643EC.pdf>

plan was finalised in 2013 and urgent activities have been selected and added to the activity plan of the Estonian National Health Plan 2009-2020.

In the National Cancer Plan 2007-2015 there is no separate mention of rare cancers.

There is no plan to pass develop a separate rare diseases emergency card. All such document is regulated in Estonia.

### **Centres of expertise**

The development of centre(s) of expertise depends on the concentration of competences. In Estonia, the competence in the sphere of rare diseases (diagnostics, treatment, research work) is mostly concentrated under the University of Tartu, where doctors are also educated, using the resources of the Tartu University Hospital. The research potential is also concentrated under the same institution. Tartu University Hospital also runs the Genetic Centre of Joint Laboratory of Tartu University Hospital that offers studies and advice in the sphere of clinical genetics in its departments in both Tartu and Tallinn.

Tartu University Hospital fulfils the criteria approved by EUCERD. Consequently there are no plans to elaborate special designation procedure for centres expertise in Estonia.

### **Registries**

Estonia does not have a national committee on registries nor national registers for groups of diagnoses and does not plan for rare disease specific registries. In Estonia all health-related information (including health investigations, diagnosis, medication etc) is collected into the Tervise Infosüsteem (Health Information System). In Estonia E-Health Foundation is the developer of health-related information systems. Depending on the needs the Health Information System could be updated. Instead of a national registry, overview and statistical data from about diseases, including rare diseases can be extracted from the electronic health information system using ICD-10. Estonia participates in the EUROCARE CF and EURO-WABB European registries.

### **Neonatal screening policy**

For early detection of all developmental disorders, including rare disorders, there is a consensus agreement that all infants and children with any developmental disorders should be referred to one of tertiary children's hospitals in Estonia: Children's Clinic of Tartu University Hospital or Tallinn Children's Hospital. Both hospitals have quick access to medical genetics services for early detection and prevention<sup>175</sup>. Early detection or treatment of rare diseases is provided using metabolic testing, chromosomal analyses, DNA diagnostics and neonatal screening programmes are in place for phenylketonuria since 1993 and congenital hypothyroidism since 1996.

There was a request to the Health Insurance Fund to enlarge the screening policy in 2009, and it is hoped that the widened policy will come into effect in 2015. There are plans to introduce tandem mass-spectrometry analysis at Tartu University Hospital in 2013 to provide screening for 10 further diseases (fatty acid oxidation defects – MCAD, LCHAD, VLCAD, CACT, CPT I and II; amino acid disorders – tyrosinemia and maple syrup urine disease; organic acidurias – isovaleric aciduria type I and glutaric aciduria type I).

### **Genetic testing**

Genetic testing is organised as a part of regular medical service. There is one Department of Genetics in Tartu University Hospital which performs genetic counseling and genetic testing<sup>176</sup>. This department is located in two main cities – Tartu and Tallinn and has two laboratories – molecular genetic and cytogenetic laboratories, which perform most genetic testing for everyday clinical practice. Genetic counseling is always provided before and after testing.

There are no national guidelines for genetic testing; the official guidelines<sup>177</sup> of European Union and European Society of Human Genetics are used.

All genetics tests which are available locally in Estonia and there are clinical indication, are reimbursed by Estonian Health Insurance Fund. Genetic testing in abroad is possible. If there are clinical indications and this test is not available locally, the assembly of doctors (minimum 3 doctors) will apply for the payment of specific genetic test abroad to the Estonian Health Insurance Fund. In case of a positive decision, the Estonian Health Insurance Fund will give out the E112 form or a guarantee letter for this specific investigation.

<sup>175</sup> <http://www.kliinikum.ee/geneetikakeskus/>

<sup>176</sup> See the regularly updated list in Estonian for further information: <http://www.kliinikum.ee/geneetikakeskus/>

<sup>177</sup> [http://www.coe.int/t/dg3/healthbioethic/Activities/07\\_Human\\_genetics\\_en/Brochure/default\\_en.asp](http://www.coe.int/t/dg3/healthbioethic/Activities/07_Human_genetics_en/Brochure/default_en.asp)



Diagnostic tests are registered as available in Estonia for 183 genes and an estimated 127 diseases in the Orphanet database<sup>178</sup>.

### **National alliances of patient organisations and patient representation**

Considering the size of Estonia the organisational capabilities of organisations of patients who suffer from rare diseases is small, as the probability of the presence of some families that are more active and with more organisational abilities among the few is relatively small. There is currently no national alliance for rare disease patient organisations in Estonia. There are only a few non-profit patients associations in the field of rare diseases (Estonian Association of Phenylketonuria, Estonian Association of Haemophilia, Estonian Association of Coeliac Disease, Estonian Association of Cystic Fibrosis, the Prader-Will Syndrome Association). But mostly rare disease patients' and patient organisations are supported by the Estonian Chamber of Disabled People (hereinafter the ECDP). ECDP is an organisation that was established in 1993 and has consistently operated as an NGO, protecting public interests, being the umbrella organisation for organisations of disabled people all over Estonia.

Patient organisations are represented on the council of the Estonian Health Insurance Fund and grants are available for patient organisations to attend these meetings.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Estonia***

Since 2004, there is a dedicated Orphanet team in Estonia, currently funded by the Department of Paediatrics at the University of Tartu. The team was designated as the Orphanet team for Estonia by the Ministry of Social Affairs in 2010 to which an application was made in 2012 for future funding. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. In 2011 the Orphanet Estonia national website<sup>179</sup>, in Estonian, was launched by the Orphanet Estonia team.

#### ***Official information centre for rare diseases***

There is no official information centre for rare diseases in Estonia other than Orphanet.

#### ***Help line***

There is currently no help line for rare diseases.

#### ***Other sources of information***

All information on rare diseases is concentrated at the Tartu University Hospital, and the Agrenska Foundation provides additional information on the social aspects of rare diseases.

### **Guidelines**

Estonia is a small country and the medical field is rapidly evolving. There are special requirements for the development of medical guidelines. It is typically a 2-3 year process. The translation of internationally recognised guidelines is difficult to organise. Therefore doctors use internationally recognised guidelines in English.

### **Training and education initiatives**

There are special advanced courses for physicians (2-3 courses per year) on rare disorders, aimed at improving the early detection and diagnosis of certain rare diseases (Prader-Willi syndrome, Angelmann syndrome, SMA, Dravet Syndrome, etc) organised by the Department of Continuing Education at Tartu Medical University. In 2009-2013 the number of advanced courses on rare disorders organised by the Department of Continuing Education at the Tartu Medical University increased, due to rising interest in the subject. Training is dependent on the offer of the University.

### **National rare disease events in 2013**

Due to Estonia's small size, there are no special annual rare disease events, nonetheless rare diseases are given a spotlight during the annual meetings of the Estonian Society of Human Genetics and Estonian Society of Laboratory Medicine.

<sup>178</sup> Information extracted from the Orphanet database (January 2014).

<sup>179</sup> <http://www.orpha.net/national/EE-ET/index/avalet/>

### **Hosted rare disease events in 2013**

No events reported in *OrphaNews Europe*.

### **Research activities and E-Rare partnership**

#### ***National research activities***

The population of Estonia is small, but it is highly important to participate in the various international clinical research programmes in the field. Continued and extended international co-operation is highly important in this sphere.

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, *Eesti Teadusfond* (Estonian Science Foundation) supports research on rare diseases at national level on the basis of appropriate applications, but there is no distinction from other projects not related to rare diseases (approximately 40,000-65,000 EUR available over four years)<sup>180</sup>. Some projects that involve research on rare diseases are financed by Targeted Financing from the Estonian Government (dysmorphic syndromes, methylation defects such as Prader-Willi, Silver-Russell and Beckwith-Wiedemann syndrome, metabolic diseases such as phenylketonuria, classical galactosemia, mucopolysaccharidoses, fatty acid oxidation defects and mitochondrial diseases, and congenital adrenal hyperplasia).

#### ***Participation in European research projects***

Teams from Estonia participate/have participated in 6 FP7 rare disease related projects.

#### ***E-Rare***

Estonia is not currently a partner of the E-Rare consortium.

#### ***IRDiRC***

Estonian funding agencies have not yet committed national funding to the IRDiRC.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

There is currently no orphan medicinal product committee in Estonia. On the sphere of drugs the main adviser is the Drug Committee. The main objective of the Drug Committee is to advise the Ministry of Social Affairs on the positive list of reimbursement medicines and to debate about the use of pharmaceuticals and about the need to update the reimbursement rules for some product or group of products. Orphan medicinal products are subject to Drug Committee on the same basis as other medicines.

#### ***Orphan medicinal product incentives***

There are no specific incentives for orphan medicinal products in Estonia.

#### ***Orphan medicinal product market availability situation***

In theory, all orphan medicinal products with EU market authorisation can be bought in Estonia. All information concerning drugs, including orphan medicinal products is available in Ravimiamet<sup>181</sup> (*Stage Agency of Medicine of Estonia*).

#### ***Orphan medicinal product pricing policy***

There is no specific pricing policy for orphan medicinal products in Estonia.

#### ***Orphan medicinal product reimbursement policy***

There is no concrete list of orphan medicines for reimbursement and no specific programmes to facilitate the provision of medicines to rare disease patients. Reimbursement of the cost of medicines to patients comes from joint medical-insurance funds on the basis of *Eesti Haigekassa's* (Estonian Health Insurance Fund) medicine reimbursement budget in accordance with the diagnosis, where the criterion for establishing the selection of corresponding diagnoses is not so much the incidence of the disease as its seriousness and mortality, the possibility of an epidemic, the need for alleviating the associated pain or other humane

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<sup>180</sup> This section is written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*. Revision 2005 (p 11)

<sup>181</sup> <http://www.sam.ee/>

considerations, the chronic nature of the disease together with the impairment caused to the quality of life, and the match with the financial possibilities of the medical insurance scheme. Children under the age of 4 are entitled to 100% drug reimbursement. Rare diseases are also included in the catalogue of described diagnoses for reimbursement.

Mostly orphan drugs that are reimbursed by Estonian Health Insurance Fund (EHIF) or other funds (e.g. charity funds) are available in Estonia.

The orphan drugs Busilvex, Exjade, Kuvan, Nexavar, Nplate, Revatio, Revlimid, Sprycel, Tasigna, Thalidomide, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Wilzin, Xagrid, Xaluprine, Zavesca are reimbursed by EHIF. Also many drugs without orphan designation are reimbursed, like Fabrazyme, Revolade, Replagal, Glivec, Alimta, Ammonaps, Avastin, Filgrastim, Cancidas, Cerezyme, Vfend etc.

Due to the high cost of these orphan medicinal products, only those which are reimbursed by *Eesti Haigekassa* (Estonian Health Insurance Fund) are easily accessible. Patients can access all other orphan medicinal products if they are willing to pay the cost of the drug.

#### **Other initiatives to improve access to orphan medicinal products**

There are no specific programmes to facilitate the provision of medicines to rare disease patients, however the Estonian Health Insurance Fund has previously reimbursed off-label drugs for rare diseases.

#### **Other therapies for rare diseases**

The Estonian Health Insurance Fund has reimbursed medical food if used for rare diseases.

#### **Orphan devices**

No specific information reported.

#### **Specialised social services**

The Estonian Agrenska Foundation, founded by several sources including Agrenska Sweden, the University of Tartu, the Estonian Board of Disabled People, the Tartu University Hospital Foundation, and *Stenstroms Skjortfabrik Eesti* provides counselling and care for families with children with rare disorders. Like its Swedish counterpart, the Estonian Agrenska Foundation<sup>182</sup> targets the family, offering a family-centred counselling system that should be able to cover all of Estonia in the coming future. The service focuses on families of children with disabilities, offering psychosocial, educational and medical information and support. In 2013, several respite camps were organized by the Estonian Agrenska Foundation. The reimbursement of these services varies from full reimbursement to partial payment by patients. Every family with a disabled child is entitled to a fixed sum per year from the government for respite care services. The Maarja Village Foundation (founded by the Tartu Toome Rotary Club) runs a residential centre which accommodates up to 33 young people with mental disabilities. Therapeutic recreational programmes exist for certain rare diseases (Prader Willi for example) and are provided by patient organisations and are partially reimbursed. Services exist to promote the integration of patients with disabilities in schools and in the work place and are financed by the government.

## **RARE DISEASE ACTIVITIES IN 2013 IN ESTONIA**

#### **National plan/strategy for rare diseases and related actions**

The plan for rare diseases was finalised in 2013 and urgent activities have been selected and added to the activity plan of the Estonian National Health Plan 2009-2020.

#### **Centres of expertise**

Tartu University Hospital fulfils the criteria approved by EUCERD. Consequently there are no plans to elaborate special designation procedure for centres expertise in Estonia.

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<sup>182</sup> <http://www.agrenska.ee/>

### National rare disease events in 2013

Due to Estonia's small size, there are no special annual rare disease events, nonetheless rare diseases are given a spotlight during the annual meetings of the Estonian Society of Human Genetics and Estonian Society of Laboratory Medicine.

## 1.9. FINLAND

### Definition of a rare disease

There is no official definition for rare diseases in Finland. At present the parties involved in the field of rare diseases normally use the common EU definition of no more than 5 in 10 000 individuals. In matters concerning orphan medicinal products Finland officially applies the same definition used in European Regulation on Orphan Medicinal Products.

### National plan/strategy for rare diseases and related actions

There is currently no officially accepted national plan/strategy for rare diseases, but a draft plan prepared by the RD Steering Committee has been handed to the Ministry of Social Affairs and Health. The process towards national plan started already 2011 when funding specifically focused on national plan related activities was applied from the Ministry of Social Affairs and Health (this was accepted in 2012). During 2011 a nationwide survey was performed to identify centres who consider themselves as experts related to a rare disease or disease group. The Ministry of Social Affairs and Health decided to invite stakeholders in the field to become members of a steering committee, including hospital districts, governmental institutes like the National Institute for Health and Welfare, Väestöliitto, the Orphanet National Advisory Board, the umbrella organisation for rare diseases HARSO, Helsinki University Hospital, and the Harvinaiset Network for Rare Diseases to name representatives for the steering committee to elaborating the national plan<sup>183</sup>. Discussions focused on establishing centres of expertise, with a step which will include patients before they reach the centres (i.e. early health care pathways to diagnostic processes). This multi-disciplinary steering group finalised its report which introduces a suggestion for the Plan by the end on 2013 (some final reviewing still took place in early 2014) and handed the Plan to the Ministry of Social Affairs and Health in March 2014. However, a healthcare reform is underway which may slow down the work on the plan

The draft of the Plan focuses on the following themes:

1. Rare diseases research
2. Diagnostics and its challenges
3. The development of care
4. Centres of expertise However, a healthcare reform is underway which may slow down the work on the plan
5. The development of social services
6. The empowerment of rare disease patients
7. The implementation, monitoring and financing of the national plan as well as international networking

Current expenditures for rare diseases fall within the general health system budget with additional ad hoc funding on the basis of rare disease projects.

Finland participated in a project (which ran from 2009 to 2010) focusing on cooperation possibilities between Nordic countries in the field of rare diseases. The project was supported by the Nordic Council of Ministers, and was entitled "*Kartläggning av möjliga nordiska samarbetsområden anknutna till små och sällsynta diagnosgrupper*" ("Report on possibilities for co-operation between the rare disease groups in Nordic Countries"). The goal of the project was to create recommendations for Nordic cooperation in all fields: medical, social, psychological and pedagogical. The project came to the conclusion<sup>184</sup> that co-operation with the Nordic countries should involve continuous exchange of experiences and knowledge of rare diseases

<sup>183</sup> <http://www.stm.fi/ylakulma/artikkeli/-/view/1814973>

<sup>184</sup> <http://www.nordicwelfare.org/filearchive/1/119089/Rapport%20med%20bilagor%20final.pdf>

through regular conferences and seminars, increasing co-operation with small separate projects in the field of rare diseases, and joint Nordic training in the field.

Planning is also underway for a national plan for cancer treatment and research with the hope that the process for the rare disease and cancer plans to feed into one another.

### **Centres of expertise**

There are currently no official centres of expertise for rare diseases in Finland. However, the departments for different medical specialities in university hospitals act as reference centres for rare diseases, and certain university hospitals specialise in specific rare operations related to rare diseases, such as congenital heart defects, cleft lip or palate, craniofacial malformations, glaucoma, retinoblastoma and biliary atresia according to the decree of the Ministry of Social Affairs and Health (767/2006) based on a law for specialised medical treatment (1062/1989).

The establishment of centres of expertise and healthcare pathways will be one of the first topics to be dealt with in the elaboration of a national plan for rare diseases with a stepwise approach for designation envisaged. There are already officially designated expert centres, though not for specific diagnoses but for specific treatments (craniofacial surgery, childhood rheumatoid arthritis, hematologic malignancies in children).

### **Registries**

In general, all the main health care registries are under the National Institute for Health and Welfare, for example Hospital Discharge Registry, Cancer Registry, Malformation Registry and Birth Registry. There is a need for new legislation related to registries; this is in the pipeline in the Ministry of Social Affairs and Health. Finland has not decided how to approach the question of rare disease registries, this will be part of the national plan. The other registries are financed by the government.

There are two legally specified registries concerning rare diseases: the Finnish register of congenital anomalies and the Finnish register of visual impairment. However, there is no designation process for rare disease registries.

The Finnish Haematology Registry and Clinical Biobank was established in 2010 by the Finnish Association of Haematology (FAH). In addition, rare inherited cancers are included in the Cancer Register and rare kidney diseases are included in the Finnish registry for Kidney Diseases. There is a national registry for primary and specialised health care<sup>185</sup>) but in this registry rare diseases are difficult to trace due to the problems of ICD10. Finland contributes to European registries including TREAT-NMD and EUROCAT.

### **Neonatal screening policy**

All newborns are screened for hypothyroidism but not for phenylketonuria as it is practically absent in the Finnish population. A pilot scheme for screening additional metabolic diseases including congenital adrenal hyperplasia (CAH), MCAD deficiency, LCHAD deficiency, Glutaricaciduria type 1 (GA1), and phenylketonuria was started in 2007 in the Turku area, concerning around 3000 newborns per year. No decision has at present been made concerning the continuation of the pilot beyond the year 2012 or widening of the pilot to other areas in Finland, though experts representing university hospitals now suggest that screening for newborn congenital metabolic diseases should be widened in 2015, so that the screening practice in Finland would be similar to other western countries. A screening recommendation was handed over to the Ministry of Social Affairs and Health in 2012. In addition to this, hospitals organise screening for phenylketonuria in newborns of non-Finnish origin.

### **Genetic testing**

Genetic testing on the national level is not centrally organised but has developed partly based on needs for certain tests but partly due to local desire to have a molecular laboratory also for training/educational purposes. There are laboratories offering selections of genetic tests (especially the founder mutations of the so called Finnish Disease Heritage) in connection with University Hospitals, the largest in Helsinki.

In addition, there is one major private laboratory offering testing, also to public health care.

There are no national guidelines, but most of predictive testing (including familial cancer) happens in genetic clinics. According to the law on the patient's status and rights (1992/785) informed consent is always sought for medical tests but it does not have to be written. Clinical geneticists have agreed among themselves that tests for adult-onset diseases or carriership are not performed in minors. Most physicians representing

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<sup>185</sup> [www.thl.fi/tietokantaraportit](http://www.thl.fi/tietokantaraportit)

other specialties agree to this principle. Some of the laboratories are accredited, some are still in the process of being accredited but they all belong to larger laboratory units which are, at least partly, accredited.

Tests are part of the hospital fee of which the patients pay a nominal sum. The municipalities then are responsible for paying for the tests: the rest is paid by the municipalities. It is rather rare that the payment would create a problem: usually if the physician in charge of diagnosis/treatment of a patient suggests genetic test(s), they are always paid without any discussion.

Genetic testing abroad creates usually no problems, many even quite common diseases like NF1, Marfan and related disorders etc are regularly bought elsewhere, from Europe or the USA. Then, usually, a laboratory that performs the required test is sought for from Orphanet. Also Finnish laboratories carry out genetic tests for foreign customers, especially in case of the diseases of the so called Finnish Disease Heritage.

Diagnostic tests are registered as available in Finland for 182 genes and an estimated 230 diseases in the Orphanet database<sup>186</sup>. Other tests are available abroad.

### **National alliances of patient organisations and patient representation**

Representatives of patient associations decided to set up a national alliance at their meeting at the Family Federation Finland, in Helsinki on 6 June 2011. During this meeting it was decided to set up a work group, led by Elina Nykyri, head of the Finnish Turner Association, to prepare a constitutive meeting held on 8 October 2011. A first statutory meeting was held on 21 January 2012. The new alliance, named HARSO, HARvinainen (rare) Sairauksien (diseases) Organisaatio (organisation) welcomes all Finnish patient organisations that represent one or more rare diseases or disabilities. Harso is run by patients themselves. There were 29 rare disease patient organisations out of a total of 51 in Finland present at the launch of the association. The new umbrella group will advocate for the rare disease patients, their families and their organisations in Finland, aiming for the best possible health and social care for the entire rare disease community. One of the main objectives will be to raise awareness of rare diseases and disabilities in order to facilitate diagnosis. Rare diseases and/or disabilities affect the daily lives of approximately 250 000 people in Finland. Harso will provide the rare disease community with strength in numbers for the first time. The organisation unites the rare disease community, creating a common voice and more visibility. So far, some rare disease organisations have chosen to stay outside Harso.

At present, individual patient organisations may be consulted on their opinion about forthcoming legislation, but the bodies to be consulted on such matters have not been defined. The Ministry of Social Affairs and Health has a council of the disabled which represents all groups of the disabled including rare disease patients.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Finland***

Since 2004 there is a dedicated Orphanet team in Finland, previously hosted by the Medical Genetics Clinic of Vaestoliitto, the Family Federation of Finland, and now hosted by the Norio-centre. The team was designated as the Finnish national Orphanet team by the Ministry of Social Affairs and Health in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database, as well as maintaining the Orphanet Finland national website<sup>187</sup> in Finnish.

Orphanet and Terveysportti<sup>188</sup> have established a collaboration to add links from Terveysportti's Finnish texts to the relevant Orphanet disease page were added: Orphanet is thus included in Terveysportti's searches for these 300 "most common rare diseases" and will make Orphanet better known amongst Finnish healthcare professionals. Terveysportti is maintained by Duodecim, the Finnish Medical Society, a scientific society adhered to by almost 90% of Finnish doctors and medical students. The Terveysportti portal is for healthcare professionals and is used nationwide in public health care units, hospitals, private practices and pharmacies as well as the universities' medical faculties. The service consists of more than 35 databases and helps professionals find day-to-day medical information quickly and reliably from one source.

<sup>186</sup> Information extracted from the Orphanet database (January 2014).

<sup>187</sup> <http://www.orpha.net/national/FI-FI/index/kotisivu/>

<sup>188</sup> <http://www.terveysportti.fi/>

### **Official information centre for rare diseases**

There is no official information centre for rare diseases in Finland other than the services provided by Orphanet, however the Norio-centre serves unofficially this function for health care providers, students, teachers, parents etc.

### **Help line**

There is no official help line for rare diseases. The Norio-centre has a nationwide phone and e-mail service for matters concerning rare diseases, which operates on work-days: the Norio-centre receives part of its funding from Finland's Slot Machine Association (RAY). The main purpose of RAY is to raise funds through gaming operations to promote Finnish health and welfare.

### **Other sources of information**

Established in 1993, the Harvinaiset Network is a network of 18 non-governmental, non-profit organisations funded by RAY, Finland's Slot Machine Association. The members of the network have signed a partnership agreement and are regarded as equal partners in the network.

The Network provides information on rare diseases and services, raises awareness of the needs of people with rare diseases and organises courses for patients and their families. Harvinaiset also maintains an internet portal with information about rare diseases in Finnish. An updated website was launched in 2010 as well as a web based service to help individuals without patient organisations for their disease to find other individuals with the same rare disease. The Harvinaiset network also participates in the maintaining of the Nordic website [www.rarelink.fi](http://www.rarelink.fi).

Most providers of services for rare diseases also have web-based information and phone or web answering services: they provide general information about diseases, contacts for treatment, advocacy, rehabilitation, psychological support and support from patient organisations or peer support groups.

### **Guidelines**

Finland has a strong tradition of producing best practice guidelines. They, however, are written based on Cochrane reviews and as this is not possible in case of rare diseases, such guidelines have not been produced. Health care personnel in Finland, especially medical doctors, have no difficulties in accessing and using guidelines written in English.

Information on 35 monogenic diseases belonging to the Finnish Disease Heritage<sup>189</sup> can be found at a database [findis.org](http://findis.org). For each disease, the prevalence or incidence and a short description of clinical symptoms are provided, as well as genetic locus and a molecular description for identified mutations. As the character and consequences of all known mutations, Finnish and foreign, are described at the DNA and polypeptide level and disease allele frequencies reported for Finnish mutations, the database can be used as a best practice guideline for molecular diagnostics of these diseases. However, this database does not provide guidelines or information related to treatment or follow up of these diseases.

The database follows the Quality Criteria for Health Related Websites recommended by the European Commission: funding for the database has been provided by the Academy of Finland, Centre of Excellence in Disease Genetics.

### **Training and education initiatives**

There are regular "dysmorphology afternoons" twice a year, especially planned to support young doctors in training.

### **National rare disease events in 2013**

International Rare Disease Day 2013 was coordinated by The Finnish Network for Rare Diseases, Harvinaiset-verkosto. A « rare market » was organised at the Helsinki Vocational College which gave a place for patient organisations and stakeholders to meet.

The fifth National Rare Diseases Day took place in Helsinki on 25 October 2013. The annual event is organised by Swedish Orphan Biovitrum and provides a forum for the discussion of questions concerning research and management of rare diseases. Amongst the 180 participants were healthcare and social care professionals and representatives of patient organisations.

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<sup>189</sup> <http://www.findis.org/main.php?action=disease>

### **Hosted rare disease events in 2013**

On 21 September 2013, a Europlan national conference was organised in Helsinki by HARSO.

### **Research activities and E-Rare partnership**

#### ***National research activities***

There are no specific programmes for rare disease research and projects compete with other topics in the calls of Finnish Academy and various foundations. Fundraising events do not belong to the research funding traditions in Finland, except for the research related to cancer and paediatric diseases.

Research in the field of rare disease has been focused on diseases of so-called Finnish Disease Heritage; nearly 40 rare inherited diseases are over-represented in Finland in comparison to other populations. Most of the genes associated with these diseases have been mapped and cloned in Finland during the last 20 years. Also rare forms/founder mutations amongst more common ones, like hereditary nonpolyposis colorectal cancer (HNPCC), hereditary connective tissue diseases, and long QT syndrome, have been studied.

Many different bodies fund medical research programmes in Finland. There are no specific programmes for research of rare diseases, which compete with more common diseases for the funds. Part of this funding for research goes towards research on orphan medicinal products. Five universities with medical faculties have programmes of their own, which are partly funded by a special State contribution (EVO). The Finnish Academy and private foundations finance substantially medical research and some rare disease research programmes amongst others.

#### ***Participation in European research projects***

Teams from Finland participated in 15 FP7 projects related to rare diseases and coordinated one other such project.

#### ***E-Rare***

Finland is not currently a partner of the E-Rare consortium.

#### ***IRDiRC***

The Academy of Finland is a member of the IRDiRC.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

No specific information reported.

#### ***Orphan medicinal product incentives<sup>190</sup>***

The Finnish Medicines Agency (*Fimea*, which before the 1<sup>st</sup> November 2009 was known as the National Agency for Medicines *Lääkelaitos*) gives free administrative and scientific advice to bodies developing orphan medicinal products. Furthermore, the special status of orphan medicinal products has been taken into account in inspection and authorisation procedures. *Fimea* also maintains a registry of clinical trials.

The evaluation criteria are the same for all medicinal products; no exceptions for orphan medicinal products are stated in the Health Insurance Act. However, the health economic evaluation is not always required from the marketing authorisation holder of orphan medicinal product if justified by the applicant.

#### ***Orphan medicinal product market availability situation***

Of the orphan medicinal products with EU market authorisation, 51 were available on the market in 2013 in Finland in at least one form, if not in all forms. The *Fimea*<sup>191</sup> lists the following orphan medicinal products as available on the market in Finland: Adcetris, Aldurazyme, Arzerra, Atriance, Busilvex, Cystadane, Diacomit, Elaprase, Esbriet, Evoltra, Exjade, Fabrazyme, Firazyf, Firdapse, Gliolan, Increlex, Inovelon, Jakavi, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Pedeia, Prialt, Revatio, Revlimid, Revolade, Savene, Signifor, Soliris, Somaver, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, Vpriv, Xagrid, Yondelis, Zavesca.

<sup>190</sup> This section was written with information from the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (pp11-12)

<sup>191</sup> <http://www.fimea.fi/medicines/fimeaweb>



### **Orphan medicinal product pricing policy**

According to the 2005 *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*<sup>192</sup> in the section concerning Finland, "A reasonable wholesale price refers to the maximum price at which the product may be sold to pharmacies and hospitals. The holder of marketing authorisation must be able to justify the reasonableness of the proposed wholesale price for a medicinal product that is to serve as a basis for the reimbursement payments. The application must include a detailed, comprehensive assessment of the cost of the drug therapy and the benefits expected to be gained thereby. Moreover, the application must include an evaluation of the product in relation to alternative drug treatments and other therapies. The application must also include the validity period of the pharmaceutical patent or a supplementary protection certificate, an estimate of the sales volume and number of users of the product over the next three years as well as the approved price and ground for reimbursement of the product in other EEA countries.

"Applications concerning medicinal products containing a new active substance must contain a health economic evaluation. When considering the reasonableness of the proposed wholesale price, the Pharmaceuticals Pricing Board takes into account the cost of the drug therapy and the benefits to be gained from its use as regards both the patient and the overall health care and social costs. The Pricing Board will also consider the cost of the treatment alternatives, the prices of comparable medicinal products and the price of the medicine in question in other EEA countries. Manufacturing, research and development costs are also taken into consideration when making a decision on application, if they are considered relevant by the applicant, as are the funds allocated for reimbursement payments."

### **Orphan medicinal product reimbursement policy**

All medicines with a wholesale price approved by the Pharmaceuticals Pricing Board are automatically entitled to reimbursement under the basic refund category. The basic reimbursement is currently 35% of the purchasing price. In certain diseases or conditions, lower (65%) or higher (100%) special reimbursement is available.

In October 2010 Harvinaiset, the Finnish Network for Rare Diseases, sent a letter<sup>193</sup> to the Ministry of Social Affairs and Health concerning the reimbursement of orphan medicinal products in Finland in order to expose the need for an improved approach to the issue especially for Fabry disease, Myasthenia gravis and Long QT syndrome. The Ministry wrote back to assure that the pharmaceutical policy foreseen for 2020 would deal with many of the concerns raised by the network including the development of medications towards more specific treatments (including orphan medicinal products), price regulations, updating the list of diseases for which reimbursement is provided through the Government Regulation in place, uniform payments and payment caps for social and health care.

### **Other initiatives to improve access to orphan medicinal products**

No specific information reported.

### **Other therapies for rare diseases**

No specific information reported.

### **Orphan devices**

No specific information reported.

### **Specialised social services**

Respite care services are available and local authorities are responsible for their provision, but some are equally provided by private institutions: patients and families often have to provide co-payment. Therapeutic recreational programmes are available under different forms and patients have to partially pay for these services though some funding can be provided by RAY. Services for transport, modifications for housing arrangements, day-care, interpreter (sign language etc), personal assistants etc are available for those with handicaps by local authorities, provided for by the law 380/1987 in 1987 (updated 1267/2008 and 981/2008).

Patients with a rare disease, as well as all others with a severe disability, were given new possibilities from 2009 with the update of the legislation for personal assistance. This update follows the principles of Independent Living Movement. Personal assistance for persons with a severe functional disability is free of

<sup>192</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005* (p12)

<sup>193</sup> [http://harvinaiset.fi/ajankohtaista/stm-n-vastaus-kannanottoon-laeaekehoidon-korvauksista&rurl=translate.google.fr&twu=1&usg=ALKJrh-90epLiXoahxcmk5V47DH0lr\\_Av](http://harvinaiset.fi/ajankohtaista/stm-n-vastaus-kannanottoon-laeaekehoidon-korvauksista&rurl=translate.google.fr&twu=1&usg=ALKJrh-90epLiXoahxcmk5V47DH0lr_Av)

charge. Besides the support in the daily living, work and education this now also includes assistance with participation in recreational activities, social activities and education. The service is financed by the municipalities.

## RARE DISEASE ACTIVITIES IN 2013 IN FINLAND

### National plan/strategy for rare diseases and related actions

There is currently no officially accepted national plan/strategy for rare diseases, but a draft plan prepared by the RD Steering Committee has been handed to the Ministry of Social Affairs and Health. The process towards national plan started already 2011 when funding specifically focused on national plan related activities was applied from the Ministry of Social Affairs and Health (this was accepted in 2012). During 2011 a nationwide survey was performed to identify centres who consider themselves as experts related to a rare disease or disease group. The Ministry of Social Affairs and Health decided to invite stakeholders in the field to become members of a steering committee, including hospital districts, governmental institutes like the National Institute for Health and Welfare, Väestöliitto, the Orphanet National Advisory Board, the umbrella organisation for rare diseases HARSO, Helsinki University Hospital, and the Harvinaiset Network for Rare Diseases to name representatives for the steering committee to elaborating the national plan<sup>194</sup>. Discussions focused on establishing centres of expertise, with a step which will include patients before they reach the centres (i.e. early health care pathways to diagnostic processes). This multi-disciplinary steering group finalised its report which introduces a suggestion for the Plan by the end on 2013 (some final reviewing still took place in early 2014) and handed the Plan to the Ministry of Social Affairs and Health in March 2014. However, a healthcare reform is underway which may slow down the work on the plan

The draft of the Plan focuses on the following themes:

8. Rare diseases research
9. Diagnostics and its challenges
10. The development of care
11. Centres of expertise However, a healthcare reform is underway which may slow down the work on the plan
12. The development of social services
13. The empowerment of rare disease patients
14. The implementation, monitoring and financing of the national plan as well as international networking.

Planning is also underway for a national plan for cancer treatment and research with the hope that the process for the rare disease and cancer plans to feed into one another.

### National rare disease events in 2013

International Rare Disease Day 2013 was coordinated by The Finnish Network for Rare Diseases, Harvinaisetverkosto. A « rare market » was organised at the Helsinki Vocational College which gave a place for patient organisations and stakeholders to meet.

The fifth National Rare Diseases Day took place in Helsinki on 25 October 2013. The annual event is organised by Swedish Orphan Biovitrum and provides a forum for the discussion of questions concerning research and management of rare diseases. Amongst the 180 participants were healthcare and social care professionals and representatives of patient organisations.

### Hosted rare disease events in 2013

On 21 September 2013, a Europlan national conference was organised in Helsinki by HARSO.

<sup>194</sup> <http://www.stm.fi/ylakulma/artikkeli/-/view/1814973>

## 1.10. FRANCE

### Definition of a rare disease

Stakeholders in France accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 people.

### National plan/strategy for rare diseases and related actions

#### **First French National Plan for Rare Diseases 2005-2008**

France was the first EU country to set up a comprehensive rare diseases plan in 2004 for the period 2005-2008 with allocated funding. This first plan, entitled “Ensuring equity in the access to diagnosis, treatment and provision of care”, included 10 objectives:

- Increase knowledge of the epidemiology of rare diseases;
- Recognise the specificity of rare diseases;
- Develop information on rare diseases for patients, health professionals and the general public;
- Train health professionals to better identify rare diseases;
- Organise screening and access to diagnostic tests;
- Improve access to treatment and quality of healthcare provision for patients;
- Continue efforts in favour of orphan medicinal products;
- Respond to the specific needs of accompaniment of patients suffering from a rare disease and develop support for patients’ organisations;
- Promote research and innovation on rare diseases, in particular on treatments;
- Develop national and European partnerships in the domain of rare diseases.

The first national plan provided for the official recognition in four yearly waves and funding of 131 centres of expertise, called “*centre de référence maladies rares*” in France (“Reference Centres for Rare Diseases”). This national network was completed in 2008 by the recognition of a second level network of 500 centres working in close connection with the Reference Centres. They are called “*centre de compétences maladies rares*” (“Competence Centres for Rare Diseases”), and are the equivalent of regional centres of expertise. Unlike Reference Centres, Competence Centres received no specific funding for their activity and are not evaluated. New rare disease research networks and research projects were supported by a national call for proposals. Information on rare diseases, orphan medicinal products and related fields was developed by Orphanet (established in 1997, but whose budget was increased significantly thanks to the plan). A national helpline for patients (called “*Maladies Rares Info Services*”<sup>195</sup> – MRIS - French “Rare Disease Information Service Helpline”) was developed. Several new information products for health professionals were developed such as emergency guidelines, developed by Orphanet, and specific clinical practice guidelines (called “*protocole national de diagnostic et de soins*” – PNDS – “national diagnosis and treatment protocol for a rare disease”), developed by the Reference Centres; all these guidelines are published on the Orphanet website. Emergency cards to be used by the patients if necessary were also developed by the French Ministry of Health.

Funding for this first national plan was provided within the general health system budget with ad hoc funding on the basis of rare disease projects (over €100 million for the duration of the plan).

#### **Evaluation of the first plan**

The first French National Plan for Rare Diseases underwent intense scrutiny when its four-year term ended in 2008. The main goal of the evaluation was to provide data to serve for the elaboration of a second national plan, initially expected in 2010. An Evaluation Committee consisting of health, economics and sociology experts, under the authority of the French Council for Public Health, measured the initial objectives of the plan against the corresponding actions undertaken during the four years of the plan. The official evaluation report was rendered to the French Minister of Health in May 2009. The document provided an analysis of the accomplishments, advances, and shortcomings of each of the ten objectives of the plan. A series of propositions and recommendations for the elaboration of a second plan was also provided.

Throughout the evaluation, the Evaluation Committee underscored the satisfaction of the different stakeholders towards the overall results of the plan. The objectives judged most pertinent – access to information (Orphanet and *Maladies Rares Info Service*), new healthcare organisation (Reference Centres), research funding, orphan product accessibility, and partnerships with European institutions – have benefited from corresponding actions that have satisfactorily fulfilled the planned goals. The need to strengthen these

<sup>195</sup> <http://www.maladiesraresinfo.org>

successful actions was underlined in the evaluation. However, some objectives – specifically those concerning epidemiology, professional training for rare diseases, and screening and diagnostic programmes – were considered insufficiently developed. The strategies to meet these goals needed to be reformulated taking stock of the difficulties encountered and planning actions to overcome obstacles.

The tenth objective of the plan, “Develop national and European partnerships in the field of rare diseases”, received an overall favourable evaluation with propositions formulated to enhance and encourage European collaboration. Furthermore, the Evaluation Committee proposed the development of measures to bring non-European industrialised and developing countries into the fold. Indeed, throughout the evaluation of the plan, the necessity for European and international-level coordination and resource-sharing was emphasised.

The Evaluation Committee’s report<sup>196</sup> was completed by a self-assessment report<sup>197</sup> drawn up by the Steering Committee of the plan within the Ministry of Health. These two reports and the testimonies of rare disease health professional, industry and patients’ organisation stakeholders who had contributed to the first plan were presented and discussed at the final meeting of the Follow-up Committee of the plan.

In 2009, the external evaluation of the 131 Reference Centres, planned to take place during the fifth year after their designation, began according to a method (self-evaluation on the third year and external evaluation on the fifth one) which was developed and implemented by the French National Authority for Health (“*Haute Autorité de santé*” – HAS). At the end of the complete process, the designation of all the 131 Reference Centres was renewed.

On 30 September 2010, the French Alliance for Rare Diseases (“*Alliance Maladies Rares*”), in collaboration with EURORDIS, organised a national conference on rare diseases<sup>198</sup> in the context of the Europlan project. The theme of the conference was “The French plan in the European landscape”. This conference gathered a large range of stakeholders and focused on lessons drawn from the first plan for the benefit of other European countries.

### **Second French National Plan for Rare Diseases 2011-2014**

The second French National Plan for Rare Diseases<sup>199</sup> was elaborated during 2009-2010 by the Ministry of Health with the collaboration of the Ministry of Higher Education and Research from the results of the evaluation of the first plan and from the conclusions of seven working groups, which had gathered during 34 meetings 184 representatives of health professionals, rare disease experts, researchers, patients’ organisations and administration. The second plan was launched on 28 February 2011 on the occasion of Rare Disease Day, with a budget of €180 million for the period 2011-2014. The ten objectives of the first plan have been consolidated into three main objectives:

- Improve the quality of care for rare disease patients;
- Develop research on rare diseases;
- Amplify European and international cooperation in the field of rare diseases.

These three objectives encompass actions such as:

- Quality assessment and networking of the existing French Reference Centres;
- Improvement of access to genetic diagnosis;
- Development of neonatal screening of rare diseases;
- Proper use and facilitated access to drugs, orphan medicinal products and any other medical product necessary for the patients;
- Information and training of health professionals;
- Information for patients;
- Strengthening of research.

The second plan includes 15 measures and 47 specific actions. The key measures of the plan are:

- Creation of a Foundation for Scientific Cooperation on Rare Diseases (“*Fondation maladies rares*” – French Foundation for Rare Diseases - FFRD) to coordinate and facilitate research on rare diseases;
- Creation of a National Rare Diseases Databank (called “*Banque nationale de données maladies rares*” - BNDMR) to allow mapping of patients’ needs and delivered healthcare, and to facilitate their recruitment for clinical and epidemiological studies and clinical trials. The national registry BNDMR will

<sup>196</sup> [http://www.hcsp.fr/docspdf/avisrapports/hcspr20090317\\_maladiesRares.pdf](http://www.hcsp.fr/docspdf/avisrapports/hcspr20090317_maladiesRares.pdf)

<sup>197</sup> [http://www.sante.gouv.fr/IMG/pdf/Evaluation\\_interne\\_Plan\\_National\\_Maladies\\_Rares\\_2005-2008.pdf](http://www.sante.gouv.fr/IMG/pdf/Evaluation_interne_Plan_National_Maladies_Rares_2005-2008.pdf)

<sup>198</sup> [http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/final\\_report\\_france\\_europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_france_europlan.pdf)

<sup>199</sup> [http://www.sante.gouv.fr/IMG/pdf/Plan\\_national\\_maladies\\_rares.pdf](http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf)

be based on the collection of a minimum data set, common to all patients and rare diseases and all the Reference and Competence Centres;

- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature for the patients' follow-up;
- Access to next-generation sequencing (NGS) technology for genetic diagnosis. Most of the French academic laboratories will be equipped at the end of the second year of the plan with NGS facilities to optimise genetic diagnosis of a large set of rare diseases. Various levels of NGS will be implemented during the plan for speeding up and maximal diagnosis coverage;
- Coordination of rare diseases Reference Centres and their regional centers into a limited number (around twenty) of coherent "national networks for rare diseases" (called "*filières de santé maladies rares*"), gathering all rare disease relevant stakeholders and centered on a homogeneous group of rare diseases. These networks aim to allow a better and easier orientation of patients towards appropriate diagnosis, treatment, social care and follow-up anywhere in France. They aim also to allow better coordinated initiatives of the Reference Centres in their research, information and education activities. These French networks would be connected to the future European Reference Networks (ERN) developed for rare diseases.

The additional actions foreseen in the plan to improve the quality of care are:

- Creation of a "Permanent Working Group" for the monitoring of Reference Centres and the future national networks;
- Measures to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed out of their marketing authorisation;
- Enhancement of rare disease clinical practice guidelines ("PNDS") development;
- Training of medical doctors and paramedical professionals;
- Better coordination of health care and social care;
- Improvement of information for rare disease patients supporting Orphanet and *Maladies Rares Info Service*, and helping the creation of a European unique number for rare disease help lines.

The implementation and the follow-up of the plan is the mission of a dedicated Steering Committee (called "*Comité de suivi et de prospective*" – "Follow-up and Prospective Committee") which held its first meeting on 19 May 2011 and meets at least once a year. This committee is chaired by the General Director for Provision of Healthcare in the French Ministry of Health. Five thematic working groups reporting to the Steering Committee were established in 2011 to help implement the plan: one dedicated to draw up a new evaluation process of the Reference Centres, a second one to define the specifications, scope and organisation of the future national networks for rare diseases, a third one to help improve the quality of information, a fourth one to develop the access to NGS, and the last one to help developing the National Rare Disease Database. The Steering Committee is in charge of the follow up of the plan, its implementation according to schedule, the effective involvement of relevant bodies and institutes, as well as the survey of new methods for diagnosis, prevention, treatment and care for rare disease patients which might justify the adaptation of the plan during its progress.

An "information and experience sharing meeting" concerning the implementation of the Second Plan was organised on 19 December 2012 for over 300 participants, in particular for all the coordinators of the 131 Reference Centres. The meeting objectives were to share information with the coordinators and patients' association on the progress of the plan. In particular the new evaluation procedures for Reference Centres were presented and discussed, as well as the future national networks for rare diseases and the new method to develop "PNDS" (See section on *Good Practice Guidelines*).

The Steering Committee of the plan held two meetings in 2013 on 19 March and 19 November. These meetings concluded that significant progress has been made to date which is in line with the objectives of the Second French National Plan.

In the area of research, a significant development has been the setting up of a funding process to support Preclinical and Early Clinical Research. This is especially important as France provides sources of funding for basic research (from the "*Agence nationale de la recherche*" – ANR – "National Research Agency", financed by the Ministry for Research) and for academic clinical research (from the "*Programme hospitalier de recherche Clinique*" – PHRC – "Hospital Clinical Research Programme" - financed by the Ministry of Health), but not for research projects that fall somewhere in between basic and clinical research. An annual call for proposals for translational research in health was announced and launched in 2013. It was financed both by ANR and Ministry of Health. Basic research for rare diseases was granted €113 million between 2005 and 2011, representing 327 projects over these 7 years. Clinical research received €9 million (36 projects) in 2010, €8.3 million (23 projects) in 2011 and €8.5 million (21 projects) in 2012.

One of the research priorities of the second plan was to set up a national scientific cooperation structure to coordinate and accelerate rare diseases research. To this end, the French Foundation for Rare Diseases (“Fondation maladies rares” - FFRD<sup>200</sup>) was approved by a decree of the French Ministry of Research and Higher Education on 6 February 2012, and officially launched on 29 February 2012. The FFRD is an innovative framework gathering all fields of rare diseases research from biomedical research to social sciences and humanities research. Its founding bodies represent a unique alliance of research, care and patients’ organisations, namely the French Muscular Dystrophy Association (“Association française contre les myopathies” – “AFM-Téléthon”), the French Alliance for Rare Diseases (*Alliance Maladies Rares*), the National Institute of Health and Medical Research (INSERM), the Conference of General Directors of the University Hospitals and the Conference of University Presidents. The Executive Committee, composed of representatives from the founding members as well as 8 international experts in the rare diseases field, is supported by International Scientific Committees of leading medical specialists and scientists providing strategic advice. The Foundation operates as a private structure with a sustained source of funding, based on public/private partnerships, and acts a federative and strategic hub to accelerate scientific, clinical and social innovation by stimulating cross-sector cooperation to the benefit of patients affected by rare diseases. With headquarters at the heart of the French national Platform for Rare Diseases (“Plateforme maladies rares”) and seven field coordinators in direct contact with researchers all over the national territory, the priorities of the FFRD are driven by grounded needs and integrated into a national strategy with an international perspective. Its rapid development in 2012 and 2013 has been bringing new synergies to basic, translational and applied research (details in the “research activities” section of this report), with an active bridging of all rare diseases stakeholders leading to:

- Better understand rare diseases (facilitation of researchers’ access to cutting-edge technology, funding resources, R&D expertise);
- Develop new treatments (acceleration of clinical innovation thanks to the early detection of drug candidates, expert consulting and public-private partnerships);
- Improve patients’ care (support of societal advances through the funding of dedicated research, national think tanks on key issues and contribution to acquainted policies).

The implementation of necessary sequencing infrastructures to speed up genetic diagnosis was financed by the Ministry of Health in 2012 and 2013: a total of 34 university hospitals received funds (€9.6 million over 2 years) to obtain necessary equipment to provide new generation sequencing services to speed up standard diagnosis. An in-depth reflexion has been in progress in 2013 to design one national NGS platform for complex diagnosis and research.

Since December 2012, hospitals began one of the key actions of the second plan: coding in the National Database of In-patient Registrations (“PMSI”) all rare disease patients hospitalised in Reference Centres using Orphanet nomenclature. The goal is to begin to use systematically the codes Orpha for better identifying patients in the healthcare system so as to improve knowledge of their healthcare pathways. The pilot study performed in some hospitals found it difficult for coders. The outcomes were analysed by a working group composed of representatives of the Medical Information Coders Society (“Société francophone d’information médicale” – SOFIME), the French National Agency for Technical Coding in Health Information Systems (“Agence technique de l’information sur l’hospitalisation” - ATIH), the National Rare Disease Data Repository (BNDMR) and Orphanet. This group is currently working towards a simpler integration of Orphacodes in the French health information system in order to enable a wider coverage of coding (in- and out-patient clinics).

The initiative to establish a French national rare diseases databank (“Banque nationale de données maladies rares” - BNDMR<sup>201</sup>) in order to have a central data repository on rare disease patients from various existing sources, for health care planning and clinical research, began in 2011. The project is financed by the Ministry of Health. 2012 was dedicated to drawing up the minimum dataset for all rare diseases along with the 131 Reference Centres. The minimum dataset was approved during the Steering Committee meeting on 19 March 2013. A national interoperability framework was also defined in 2013. The project first aims at gathering qualified data from Reference and Competence Centres. The linkage with other national data sources will be enabled in 2015 onwards once patients are identified thanks to the Reference and Competence Centres and the minimum data set. A specific steering committee was created in November 2013 to follow the implementation of the BNDMR.

<sup>200</sup> <http://www.fondation-maladiesrares.org>

<sup>201</sup> <http://www.bndmr.fr/>

In the area of health care delivery, improving the way Reference Centres are evaluated is one of the main objectives of the second plan, to ease the reporting carried out by the centres and to create the tools for an accurate assessment on which to base decision on the renewal of the designation and on the allocation of funds. An annual reporting system and a new external evaluation process were defined after 2 years of solid effort by working groups composed of representatives of Reference Centres, patients' associations, French National Authority for Health ("HAS"), French Agency for the Evaluation of Research and Higher Education ("AERES") and Ministry of Health. The new process will be ready to be launched in 2014.

Another main objective of the second plan is to reorganise Reference Centres and group them in a functional way that maximises collaboration and allows better and easier orientation of patients. These "national networks for rare diseases" ("*filiales de santé maladies rares*") will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: Reference and Competence Centres, diagnostic and research laboratories, imaging, health and social care, professionals and patients' associations etc. Preliminary work and surveys in 2012 identified 23 possible groupings of Reference Centres. The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres. At the end of the call, in November 2013, 32 projects have been received. The "Permanent Working Group", planned to monitor the activity of Reference Centres and national networks, held a first meeting on 18 December 2013 and began to examine the submitted projects. The national networks will be designated by the Ministry of Health in early 2014.

Another objective of the plan was to increase the number of "*national diagnosis and treatment protocol*" ("PNDS"). These protocols were identified in the first plan as defining the national standard of care by rare disease (good practice guidelines). Each PNDS was completed with a list of the acts and products (drugs, medical devices) considered as essential for the patients care and therefore which may be reimbursed, including off-label products. The method of production was developed and implemented by the HAS ("French National Authority for Health"), which supervised very closely their elaboration by the Reference Centres. This high quality method was however too complicated to allow rapid publication of a significant number of protocols: in seven years, only 50 PNDS were published. To boost the production to 200 protocols in 4 years, as expected at the end of the second plan, the method was simplified by the HAS<sup>202</sup> and the task to produce the PNDS was completely delegated to the Reference Centres. However, the production of PNDS remains low: only 2 new PNDS were published in 2013. The PDNS developed with the HAS new method are not yet completed with a list of the acts and products.

One of the burning issues discussed by the Steering Committee of the plan was the off-label use of drugs for treating rare diseases. A survey carried out in 2012 in 50% of the Reference Centres demonstrated that over 500 medicinal products are regularly used off-label, especially in children with rare diseases. A recent French law (December 2011) makes necessary to have "temporary use recommendations" published by the French National Agency for the Safety of Medicine and Health Products ("ANSM") so that off-label products are reimbursed (this clause of the law is not specific for drugs used for rare diseases, and concerns any off-label use). The publication of "temporary use recommendations" requires data to support that the off-label use of the drug has probably a favourable benefit to risk ratio in the absence of any other effective product in this indication. Of course, this is highly difficult for rare diseases as the existence of such data is modest and often absent. The ANSM did not publish any temporary use recommendations in 2013. This new context has been a matter of concern for the professionals and patients. A specific working group has been created to follow this issue and make proposals to help the development of temporary use recommendations.

In conclusion, the second French plan is well on the way and several initiatives delineated in the plan have been implemented. A new leader of the implementation of the plan was named in July 2013. The Steering Committee recognises that the final months of the plan will present challenges as the rare disease community will have to prepare for the future in the context of a constrained budget but also to build on all the improvements resulting from the two national plans.

### **Second French National Plan for Cancers (including rare cancers) 2009-2013**

A second National Plan for Cancers<sup>203</sup> was launched on 2 November 2009 for the period 2009-2013. This plan is the continuation of the first national plan<sup>204</sup> which covered the period 2003-2007, during which pilot projects targeting an organisation of expert centres for rare cancer patients were supported. The six main domains concerned by the plan are: research, observation, prevention, screening, care, and "living with and after

<sup>202</sup> The HAS published its new method in December 2012: [http://www.has-sante.fr/portail/jcms/c\\_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=3](http://www.has-sante.fr/portail/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=3)

<sup>203</sup> [http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013\\_english.pdf](http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf)

<sup>204</sup> <http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20032007.pdf>

cancer". A specific action of the plan is dedicated to the development of specialised expert centres for rare cancer patients, labelled "Reference Centres for rare cancers". The term "rare cancers" applies to the following cancers: those which are diagnosed in fewer than 6/100 000 persons per year; or those requiring highly specialised management, owing to their unusual location, or to their occurrence at a specific or complex site.

The National Cancer Institute ("*Institut national du cancer*" – INCa) published a report entitled "The Situation of Cancer in France in 2011". This report gives an overview of the measures in place for cancers, including rare cancers, and gives key facts and figures concerning the cancer patients in France. It was published at the same time on the INCa site and on a new web portal on cancer data<sup>205</sup>. A second report concerning the activity of the "Expert Centres" was published in 2012<sup>206</sup>, as well as a document published in French<sup>207</sup> and in English<sup>208</sup> describing this specific organisation. Other reports on genetic testing and treatment for hereditary cancers were published in 2012: the first one summarised the 2011 activities of French oncogenetic platforms, and the second one focused on molecular genetic testing for targeted therapies in France in 2012<sup>209</sup>. In 2013, a report of their scientific council<sup>210</sup> was published including details of specific recommendations and activities in the field to date, as well as an overview of cancer in France<sup>211</sup> and a 2012 activity report<sup>212</sup> concerning the care of adult patients with rare cancers, including details of the number diagnoses, clinical trials and research collaborations in the area.

The final report concerning the implementation of the cancer plan, including a section on the actions in the field of rare cancers, was published in 2013<sup>213</sup>.

As for the preparation of the third French National Plan for Cancers (including rare cancers) 2014-2019: recommendations for a third plan for cancers<sup>214</sup> in the field were transmitted to the Minister of Health in autumn 2013. A third National Plan for Cancers was then prepared and published on 4 February 2014<sup>215</sup>. Organisation of care for adults with a complex cancer, improvement of the organisation of second opinion in pathology for rare cancers and organisation of care for very rare cancers in children are planned.

### **French National Plan for Rare Disabilities 2009-2013**

A "rare disability" is a French administrative concept which was defined in 2000<sup>216</sup>: the definition proposed is the coexistence of a prevalence of no more than 1 in 10 000 people, a rare combination of severe deficiencies or diseases (vision or hearing disability, dysphasia, severe epilepsy etc.), complex care and rarity of competent professionals. A plan aimed at rare disabilities<sup>217</sup> (of which rare diseases may be a cause) was adopted on 27 October 2009 for the period 2009-2013<sup>218</sup>. The National Solidarity Fund for Autonomy ("*Caisse nationale de solidarité pour l'autonomie*" – CNSA - in charge of funding for the autonomy of the elderly and disabled people) is in charge of its implementation. The main objectives of the plan are:

- The centralisation and dissemination of information on rare disabilities in collaboration with Orphanet;
- The consolidation, development and evaluation of specialised expertise at national level;
- The reinforcement and organisation of the identification of rare disabilities and multidisciplinary functional evaluation across France;

<sup>205</sup> <http://lesdonnees.e-cancer.fr/>

<sup>206</sup> [http://www.e-cancer.fr/component/docman/doc\\_download/9274-bilan-2011-de-la-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares](http://www.e-cancer.fr/component/docman/doc_download/9274-bilan-2011-de-la-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares)

<sup>207</sup> [http://www.e-cancer.fr/component/docman/doc\\_download/4692-cancers-rares-de-ladulte--lorganisation-en-centres-experts](http://www.e-cancer.fr/component/docman/doc_download/4692-cancers-rares-de-ladulte--lorganisation-en-centres-experts)

<sup>208</sup> [http://www.e-cancer.fr/component/docman/doc\\_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012](http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012)

<sup>209</sup> <http://www.e-cancer.fr/toutes-les-actualites/360-les-soins/7283-genetique-moleculaire-des-cancers-deux-nouveaux-rapports-sur-la-prise-en-charge-personnalisee-des-patients#>

<sup>210</sup> <http://www.e-cancer.fr/publications/87-rapports-scientifiques/742-rapport-scientifique-2012-2013>

<sup>211</sup> <http://www.e-cancer.fr/publications/69-epidemiologie/758-les-cancers-en-france-edition-2013>

<sup>212</sup> <http://www.e-cancer.fr/rss-soins/8591-prise-en-charge-des-patients-adultes-atteints-de-cancers-rares-donnees-dactivite-2012>

<sup>213</sup> <http://www.plan-cancer.gouv.fr/accueil/actualites/43-actualites/1204-publication-du-rapport-final-au-president-de-la-republique-du-plan-cancer-2009-2013.html>

<sup>214</sup> <http://www.sante.gouv.fr/IMG/pdf/Recommandations-pour-le-3e-plan-cancer.pdf>

<sup>215</sup> <http://www.e-cancer.fr/publications> (english) <http://www.e-cancer.fr/le-plan-cancer?gclid=CKLYntPlyb4CFbShtAodTDOAcA>

<sup>216</sup> <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000765671>

<sup>217</sup> One of the measures of the plan was to compare this concept with other concepts used in France or in other countries. The INSERM (French National Institute for Healthcare and Medical Research) set up an expert working group in charge of analysing this notion. The expert report has been published in May 2013: <http://www.inserm.fr/actualites/rubriques/actualites-societe/handicaps-rares-contextes-enjeux-et-perspectives-une-expertise-collective-de-l-inserm>. The 2000 definition of "rare disability" is currently in discussion in France, and may change in 2014.

<sup>218</sup> This plan is called "Schéma national handicaps rares" ("National Scheme for Rare Disabilities"):

[http://www.cnsa.fr/IMG/pdf/CNSA\\_Schema-national-Handicap-rare-2.pdf](http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf); [http://www.cnsa.fr/article.php?id\\_article=726](http://www.cnsa.fr/article.php?id_article=726)



- The creation of inter-regional relays;
- The development of the offer of services at home and in establishments for patients with rare disabilities.

Several levels of expertise for patients with a rare disability were planned. Three “national resource centres” (“Centres nationaux de ressources pour les handicaps rares” – CNRHR – “National Resource Centres for Rare Disabilities”) were created in 2011 for patients with a severe visual or hearing deficiency associated with other deficiencies or diseases. A fourth national resource centre for patients with rare disabilities and severe epilepsy was created in 2013. Inter-regional intermediary teams (“équipes relais”) of these national centres were launched in 2013 with the aim of their complete deployment in 2014-2015. Cooperation between national resource centres and inter-regional teams for rare disabilities and Reference Centres for rare diseases is also underway. A leaflet<sup>219</sup> was published describing the national organisation of care in this area.

In terms of improving knowledge, several research projects have been funded by the CNSA, in collaboration with the Institute of Public Health Research.

The Ministry of Social Affairs and Health has asked for an evaluation of the first plan and will announce a second one in 2014 based on various studies conducted during the first one, such as the expert report conducted by INSERM at the request of the CNSA entitled<sup>220</sup> “Rare handicaps: context, purposes, perspectives”. It highlights the need to describe rare disabilities with the International Classification of Functioning, Disability and Health (ICF), the utility of creating national and international registries or databases, and suggests strengthening the organisation created by the first plan.

#### **Other French national initiatives related to rare diseases**

On 2 May 2013, the third National Plan for Autism for the period 2013-2017 was published by the Ministry of Social Affairs and Health. This plan aimed at improving early diagnosis and early care, structuring healthcare, educational and social pathways for patients, supporting families, improving training for all the professionals in charge of patients, and strengthening research<sup>221</sup>.

In June 2008, a national plan concerning visual handicap (of which rare diseases may be a cause) for the period 2008-2011 was published. This plan aimed at improving treatment, social care, mobility and social integration of people with visual handicap<sup>222</sup>.

In February 2010, a national plan concerning deafness and hearing-impairment (of which rare diseases may be a cause) for the period 2010-2012 was published<sup>223</sup>, with 52 measures including: improvement of the prevention and screening of hearing disorders; better support of deaf and hearing-impaired people through their life; and enhanced access to social life.

The “dossier médical personnel” (“personal medical record” - DMP) is a national healthcare tool for sharing and exchanging information about individual patients. The DMP has been developed by the French Shared Healthcare Information Systems Agency (“Agence des systèmes d’information partagés de santé” – “ASIP Santé”) for the Ministry of Health. It is a secure electronic health record accessible on the Internet with full patient control of what it contains and what physicians may access. The aim is to provide physicians with a holistic picture of patients with complex conditions such as chronic diseases, and among them, rare diseases. It is thus expected to support the coordination of the different specialists, GPs and centers of expertise involved in the follow-up of patients and improve the quality of care. For rare diseases, the on-going limitation of DMP use is the current impossibility to create a DMP for children. Three years after the DMP was launched, there were about 420 000 DMP at the end of 2013.

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo (“Rare Diseases Cohorts”) project for duration of 10 years and for a total of €10 million. The RaDiCo project finality is to create and follow selected cohorts of rare disease patients in the perspective of better annotating the phenotypes, better understanding the genotype-phenotype relationship, the natural history of rare diseases, and improving physiopathological, therapeutic or prognostic research. The RaDiCo program is dedicated to set up a platform pooling all the resources needed for rare disease cohorts in order to:

- Establish a common set of meaningful rare disease data/indicators collected from all the Reference and Competence Centres;
- Provide appropriate resources to clinicians/biologists experts in rare diseases;

<sup>219</sup> <http://www.cnsa.fr/IMG/pdf/Memos23-WEB.pdf>

<sup>220</sup> The expert report has been published in May 2013: <http://www.inserm.fr/actualites/rubriques/actualites-societe/handicaps-rares-contextes-enjeux-et-perspectives-une-expertise-collective-de-l-inserm>

<sup>221</sup> <http://www.social-sante.gouv.fr/actualite-presse,42/breves,2325/presentation-du-3eme-plan-autisme,15797.html>

<sup>222</sup> [http://www.solidarite.gouv.fr/IMG/pdf/Dossier\\_de\\_presse\\_2JUN08.pdf](http://www.solidarite.gouv.fr/IMG/pdf/Dossier_de_presse_2JUN08.pdf); [www.cnsa.fr/IMG/doc/Plan\\_handicap\\_visuel\\_1\\_-2.doc](http://www.cnsa.fr/IMG/doc/Plan_handicap_visuel_1_-2.doc)

<sup>223</sup> [http://www.travail-emploi-sante.gouv.fr/IMG/pdf/Plan\\_en\\_faveur\\_des\\_personnes\\_sourdes\\_ou\\_malentendantes\\_-\\_10\\_02\\_2010.pdf](http://www.travail-emploi-sante.gouv.fr/IMG/pdf/Plan_en_faveur_des_personnes_sourdes_ou_malentendantes_-_10_02_2010.pdf)

- Be able to integrate rare disease data from different sources, requiring the development or improvement of the interoperability of different databases (data standardisation and harmonisation);
- Use common standards for data (including data description, data quality, interoperability, data exchange etc.);
- Ensure the long-term sustainability of these actions.

The RaDiCo project will take advantage of this platform to facilitate the emergence and the design of clinical and translational research programs on rare diseases in partnership with industry. Expected results of the above-mentioned actions are:

- Provision of methodological expertise to analyse rare disease data;
- Anticipation of future needs such as integration of data from systems biology and “omics” approaches.

The research programs resulting from this integrated view of rare diseases are:

- Economic and socio-economic aspects of rare diseases;
- Setting up a collection of induced pluripotent stem cells (iPS) for all rare diseases investigated in France.

The RaDiCo project showed accelerated development in 2013<sup>224</sup>, and prepared the launch its first call for rare diseases cohort proposals at the beginning of January 2014. The RaDiCo projet has developed very close links with the BNDMR.

In 2011, the web portal “Epidemiology – France”<sup>225</sup> was launched, aiming to provide a directory of databases to advance research and expertise in the field of health in France. The “Epidemiology – France” portal was created under the auspices of the Strategic Council for the Health Industries (“*Conseil stratégique des industries de santé*” - CSIS), in collaboration between:

- AVIESAN (“*Alliance nationale pour les sciences de la vie et de la santé*” - French National Alliance for Life Sciences and Health);
- The French Ministry of Economy, Finances and Industry (General Directorate for Competitiveness, Industry and Services - DGCI);
- The LEEM (“*Les entreprises du médicament*” - French pharmaceutical industry association).

This portal aims to :

- Improve the availability of information;
- Locate existing skills and data by theme;
- Encourage transparency;
- Contribute to cooperation between research networks;
- Reinforce research quality;
- Foster the generation of new research projects;
- Promote partnerships and collaboration and increase value of health data.

It brings together information on approximately 493 databases and includes a search by the theme “Rare Diseases”; 28 databases classified in “Rare Diseases” are included in this portal with theme including mostly nationally designated registries.

### Centres of expertise

The first National Plan for Rare Diseases (2005-2008) launched a structured organisation of healthcare for rare disease patients. A designation process was created to name centres of scientific and clinical expertise in the field of rare diseases. Four waves of designation took place between 2004 and 2007. By the end of the first plan, 131 Reference Centres (“*centre de référence maladies rares*” – CRMR) were named in university hospitals by the Ministry of Health and received a specific funding for their missions. A “coordinator” was designated officially in each Reference Centre. The centres have 6 main missions:

- To facilitate diagnosis and define the course of treatment. Each centre has a double role: it is an expert centre for one or several diseases for which it is designated, and it is a resource centre for patients referred to it.
- To define, publish and update national clinical practice guidelines for rare diseases (“PNDS”) in collaboration with the French National Authority for Health (HAS);
- To coordinate research and participate in epidemiological surveillance in collaboration with the French Institute for Public Health Surveillance (“*Institut de veille sanitaire*” – InVS);

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<sup>224</sup> <http://www.radico.fr>

<sup>225</sup> <http://epidemiologie-france.fr/>

- To participate in training and information programmes for health professionals, patients and their families, in collaboration with the French national Institute for Prevention and Health Education (*"Institut national de prévention et d'éducation pour la santé"* – INPES);
- To coordinate networks of health professionals and social workers;
- To be the contact point for patient organisations and social workers.

Between 2009 and 2012, the Reference Centres were evaluated over time, first through self-evaluation after 3 years as a designated centre, then through an external evaluation the fifth year. The external evaluation was organised by the HAS published its 2010 activity report in 2011, with one section dedicated to its activity in the evaluation of Reference Centres<sup>226</sup>. At the beginning of the first plan, a National Consultative Designation Committee (*"Comité national consultative de labellisation"*) analysed the proposals for creation of Reference Centres and the results of the external evaluation, and gave advice to the Ministry of Health. This Committee has not been continued. The second national plan has planned a revision of the evaluation process. The new process has been in progress in 2012 and was definitively specified at the beginning of 2013: each Reference Centre will establish an activity report each year and undergo an external evaluation at 4 years according to modalities still under discussion with the HAS. The second plan has planned the creation of a "Permanent Working Group", which will monitor the annual activity and external evaluation reports, and give an opinion to the Ministry of Health on the renewal of the designation of Reference Centres. It will also monitor the future "national networks for rare diseases". The permanent working group was officially created at the end of 2013, and held its first meeting on 18 December.

A second type of expert centre was designated in 2008, named "*centres de compétences maladies rares*". These regional centres were proposed by each Reference Centre and designated by French Regional Hospital Agencies (*"Agences Régionales d'Hospitalisation"* – ARH). The aim of these regional centres is to assume responsibility for diagnosis, treatment and follow-up of the patients close to their home, and to participate in the activities of the reference centres they are linked to. Unlike the Reference Centres, the regional centres do not receive dedicated funding for their rare disease activities, and have not to fill an annual activity report and to be evaluated. Currently about 500 regional centres have been named corresponding approximately to 1 expert centre per region for each of the 18 groups of rare diseases identified in Orphanet reports. These Competence Centres will be included into the future national networks for rare diseases in association with the Reference Centres they are linked to.

In 2013 major steps were made to coordinate individual Reference Centres and group them in a functional way that maximises collaboration across the country. The "national networks for rare diseases" (*"filiales de santé maladies rares"*) will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: not only Reference and Competence Centres, but also diagnostic and research laboratories, imaging, health and social care, professionals and patients' associations etc. The designated networks will receive funds from the Ministry of Health for their coordination activity. A preliminary survey identified 23 possible groups gathering nearly all the 131 Reference Centres (some centres do not fall in any of these groups). The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres: at the end of the call, in November, 32 projects have been received. The Permanent Working Group began to analyse these projects in December 2013. The result of this call is expected in early 2014<sup>227</sup>.

In July 2013, the Ministry of Health published a directive concerning the process for succession as coordinator of a Reference Centre, and for the creation or abrogation of a Competence Centre linked to a Reference Centre.

Rare cancers have been excluded from the first national plan for rare diseases (2005-2008) since a national plan for cancer including measures for rare cancers was already in place. The French National Cancer Institute (INCa) published a report<sup>228,229</sup> on the organisation of healthcare for rare adult cancers. This organisation was one of the key actions of the Second National Cancer Plan for the period 2009 -2013: this includes the creation of a system of national "Reference Centres" and a network of regional centres for rare adult cancers. Since 2009, 23 national clinical networks for 23 groups of rare adult cancers and four anatomical pathology networks - in charge of the double reading of sarcoma, rare malignant neuroendocrine tumours, malignant mesothelioma and lymphoma - have been set up and financed. Among their missions, these

<sup>226</sup> [http://www.has-sante.fr/portail/jcms/c\\_1070314/rapport-annuel-d-activite-2010](http://www.has-sante.fr/portail/jcms/c_1070314/rapport-annuel-d-activite-2010)

<sup>227</sup> The list of the first 15 accepted "national networks for rare diseases" was published on the website of the Ministry of Health on 28 February 2014. <http://www.sante.gouv.fr/les-filieres-de-sante-maladies-rares.html>

<sup>228</sup> <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

<sup>229</sup> [http://www.e-cancer.fr/component/docman/doc\\_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012](http://www.e-cancer.fr/component/docman/doc_download/9266-rare-adult-cancers--organisation-into-expert-centres-septembre-2012)

Reference Centres have to ensure diagnostic certainty by implementing a systematic second reading of the biopsy specimens, to assure a multidisciplinary expert discussion of the patient file for the choice of initial and subsequent treatments, and to facilitate the enrolment of patients in appropriate clinical trials.

Three “national resource centres” for rare disabilities have been designated in 2011, and a fourth one in 2013 thanks to the French National Plan for Rare Disabilities 2009-2013<sup>230</sup>.

In 2011 the university hospitals of Angers and Nantes, in association, with the French Alliance for Rare Diseases (“*Alliance Maladies rares*”), created a platform to support rare disease patients in the Pays de la Loire Region. This unique platform (called “*Plateforme régionale d’information et d’orientation sur les maladies rares*” – PRIOR – Regional platform for information and guidance concerning rare diseases) consists of a team including neurologists, a dermatologist, a psychologist, an occupational therapist, a social worker and a coordination assistant. It aims to help patients to find their way in the health and social care system. In Montpellier and the Languedoc-Roussillon Region, a network was created by the Reference Centre concerning rare malformation syndromes and developmental defects in association with the French Alliance for Rare Diseases to provide support to patients with developmental disorders and training sessions for professionals of health and social sector.

In June 2012, the French General Directorate for Provision of Healthcare launched a position paper<sup>231</sup> detailing the conditions for the establishment and renewal of “reference centres” so as to best respond to requests for designation of such centres. This position paper is not specific to rare diseases reference centres.

### Registries

A National Rare Disease Registry Committee was created in October 2006 as part of objective 1 - “Improve knowledge of epidemiology of rare diseases” - of the first National Plan for Rare Diseases. The Committee aims at:

- Proposing a policy for registries based on healthcare and epidemiological research needs;
- Giving an opinion on whether to create new registries or maintain existing registries, and on the management of registries;
- Evaluating the quality of registries submitted to the Committee after a call for proposals each year: only registries recognised as good quality registries (from then on called “qualified registries”) may receive a national public funding from INSERM, InVS or INCa);
- Helping to diffuse and valorise information produced by qualified registries.

Members of the Committee include official members (representatives of French Institute For Public Health Surveillance, French National Institute of Health and Medical Research, Ministry of Health, Ministry of Research etc.), professionals with expertise in the field of rare diseases, registries or public health, as well as two representatives of patients’ organisations. They were nominated for a 3-year term, with renewable mandate. The evaluation of the quality of registries was in fact the only activity of the Committee. In 2008, 6 national registries were qualified by the Committee for the period 2009-2011, and three new national registries in 2010 for the period 2011-2013. In 2011, seven national registries already qualified obtained a new qualification for the period 2012-2015, and one registry were qualified for the period 2012-2014. In 2012, one register was qualified for 3 years (2013-2015). At the end of 2012, 12 national registries were qualified: thalassemia, Gaucher disease, histiocytosis, congenital neutropenia, Pompe disease, cystic fibrosis, biliary atresia, esophageal atresia, arterial pulmonary hypertension, hereditary immune system disorders, SDH-dependant hereditary paraganglioma, and inherited deficiencies of coagulation. In 2012, a reflection began on a possible evolution of the Committee’s missions and the needs of the other registries and databases existing in France for support and evaluation and in April 2013 the committee was dissolved at the same time as the national committee created in 1996 for the evaluation of non-rare disease registries. The InVS, Inserm and INCa launched a call for experts in October 2013 in order to create a Registry Evaluation Committee which will consider, amongst others, rare disease registries. This committee will consist exclusively of experts of registries, epidemiology and public health.

The Second National Plan for Rare Diseases also has foreseen the creation of a National Rare Disease Database (BNDMR). Its primary objective is to describe the demand of care for rare diseases at a national level, as well as the offer of care, and to assess whether the offer matches the demand. A secondary objective is to help recruiting patients for clinical trials or rare diseases cohorts (“RaDiCo project”). The Reference and Competence Centres for rare diseases will be the primary data providers as well as diagnostic laboratories (genetic, cytogenetic, etc.) or existing rare disease registries if appropriate. To achieve these objectives, the

<sup>230</sup> [http://www.cnsa.fr/IMG/pdf/CNSA\\_Schema-national-Handicap-rare-2.pdf](http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf); [http://www.cnsa.fr/article.php3?id\\_article=726](http://www.cnsa.fr/article.php3?id_article=726)

<sup>231</sup> [http://circulaire.legifrance.gouv.fr/pdf/2012/06/cir\\_35428.pdf](http://circulaire.legifrance.gouv.fr/pdf/2012/06/cir_35428.pdf)

first step was to build a minimum data set (MDS) common to all rare disease centres of expertise and to all rare diseases. In 2012, a working group helped to build the MDS along with the 131 Reference Centres, which was discussed and validated by the Steering Committee of the plan in March 2013. The MDS will be entered through an application called BaMaRa (“Banque Maladies Rares” – Rare Diseases Databank), either directly by the centres of expertise, or through their own application if appropriate. To enable data flows between French hospitals and the BaMaRa, a national interoperability framework was defined in 2013. It consists in setting the necessary compatibility elements such as patient identification, data elements and nomenclatures, technical data flows and security. It will help gathering data at the Reference and Competence Centre level and linking this information to biobank data and other national databases (medico-economic databases, national health insurance databases etc.). A data warehouse, the National Rare Disease Database (BNDMR), will host several types of de-identified national rare disease data sets in accordance with the Data Protection Act. A steering committee specific of the BNDMR was set up in 2013 including representatives from the concerned ministries and stakeholders, including patients’ associations. In 2013, the BNDMR team also began to develop a specific application named LORD (Linking Open Rare Disease data) to help with rare disease diagnosis coding in hospital health information systems<sup>232</sup>. This application will be used at national level to help coding RD patients either in hospital information systems or registries.

Each of the national Expert Centres for rare adult cancers is requested to contribute to the epidemiological surveillance and observation of these cancers by establishing a database and collects all the cases. Almost 14 000 cases with a rare adult cancer were registered in 2012 in these databases.

France contributes to several European rare disease registries including EUROCAT, EUROHISTIONET, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EIMD, EUROWABB, EUROTRAPS, CHS, EURO CARE CF, ECFS, INFEVERS, EDMUS, EHN-EUROHISTIONET, ESCORT-HU, SCLS registry, EURORHETT, VALID and TREAT-NMD. In the domain of rare cancers, France contributes to European clinicobiological databases, as CONTICABASE (soft tissue and visceral sarcoma), CONTICAGIST (gastrointestinal sarcoma tumours), ENS@T-ACC (adrenal cortical carcinoma) and ENS@T-pheo (pheochromocytoma).

### Neonatal screening policy

A national neonatal screening programme exists in France for all newborns for the following four diseases: cystic fibrosis, phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, as well as for sickle cell anaemia only for newborns at risk of developing the disease<sup>233</sup>.

In 2010, an assessment of the opportunity to extend neonatal screening to one or more inborn metabolic errors of metabolism by tandem mass spectrometry in the general French population began. The first results were published in 2011 by the French National Authority for Health (HAS). The HAS has recommended the extension of the neonatal screening programme to medium chain acyl-CoA dehydrogenase deficiency<sup>234</sup>. The decision to put this recommendation into practice has not yet been taken. That requires reorganising first the neonatal screening programme because tandem mass spectrometry cannot replace all the existing screening techniques, and cannot be used in all the laboratories currently participating in the national programme. Furthermore the HAS is still working on the possibility of extending the programme to other inborn metabolic errors and on the generalisation of sickle cell anaemia screening to all newborns in France.

Neonatal screening programme for deafness (of which rare diseases may be a cause), on which the HAS had given recommendations in 2007, was approved on 23 April 2012<sup>235</sup>. Screening for deafness was already performed in 51% of the French maternity hospitals using different methods. National specifications on screening methods have not yet been published in 2013.

### Genetic testing

The French Biomedicine Agency (“*Agence de la Biomédecine*”), a public agency operating under the supervision of the Ministry of Health, was created under the Bioethics Law of August 2004. The agency oversees four key areas of human biology and medicine: organ tissue and cell transplantation, assisted reproductive technology, prenatal and genetic diagnosis and human embryo and embryonic stem cell research. On a national level, it provides professionals and researchers with collective answers, guarantees equity of access, ethics and transparency of these activities, organises information and awareness campaigns, and evaluates and publishes

<sup>232</sup> This application was launched in early 2014: <http://enlord.bndmr.fr>

<sup>233</sup> <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000021763691&dateTexte=&categorieLien=id>

<sup>234</sup> [http://www.has-sante.fr/portail/jcms/c\\_1069254/evaluation-de-lextension-du-depistage-neonatal-a-une-ou-plusieurs-erreurs-innees-du-metabolisme-par-spectrometrie-de-masse-en-tandem-1er-volet-deficit-en-mcad](http://www.has-sante.fr/portail/jcms/c_1069254/evaluation-de-lextension-du-depistage-neonatal-a-une-ou-plusieurs-erreurs-innees-du-metabolisme-par-spectrometrie-de-masse-en-tandem-1er-volet-deficit-en-mcad)

<sup>235</sup> <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000025794966&dateTexte=&categorieLien=id>

its activities in an annual report. Its 2012 annual report was published in 2013<sup>236</sup>. For the fourth consecutive year, the Agency included data on postnatal genetic testing carried out in France culled via a partnership with Orphanet. The number of diseases for which a genetic diagnosis is available is still increasing in 2012: 1526 genetic diseases can be diagnosed.

Guidelines for good practices related to the examination of genetic characteristics in the medical context in order to assure quality of care were finalised in at the end of 2012, and published in the form of an official text on 2 June 2013<sup>237</sup>. These guidelines describe in particular information to be delivered to patients before and after performing genetic tests.

Tests for 1472 genes and an estimated 1606 diseases are registered as available in France in Orphanet<sup>238</sup>.

### **National alliances of patient organisations and patient representation**

The *Alliance Maladies Rares* (French Alliance for Rare Diseases) is the national umbrella organisation dealing with rare diseases. It plays a major role in organising working groups, communicating on rare diseases, offering support to organisations of patients and families, and contributing to the development of the French National Plans for Rare Diseases and their evaluation. The Alliance played a major role in the elaboration of the first and second National Plan and in the evaluation of the Reference Centres. The Alliance celebrated its 10 anniversary in 2010 and marked the occasion with a meeting of its members on 15 February 2010 in Paris: the Alliance's new website was launched as were the forthcoming information documents created by the Alliance. In 2011 the Alliance launched a practical guide and made it available for its members and in centres of expertise for rare diseases. The guide is intended to patients and their families, and provides information on the organisation and availability of expert care and the services. The guide also gives information on the rare disease patients' organisations in France. The Alliance also launched an awareness raising campaign aimed at children via the newspaper for children called *Le Petit Quotidien*; information packs for teachers were also made available to help classes understand what is a rare disease and life for children with such a condition. In 2013, the Alliance has begun reflection and workshops to develop therapeutic patient education programs.

The *Alliance Maladies Rares* and other patients' organisations have received some public funding during the first and second National Plans for their various support activities and awareness campaigns.

Seventeen patients' organisations in the field of rare cancers collaborate daily with the existing rare cancer national expert centres. Several have been involved as soon as the designation of these centres. They play a major role in diffusing high quality information both on the healthcare services available and on access to innovative treatments.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in France***

Concerning actions to improve public information, financial support for the French Rare Disease Platform ("*Plateforme Maladies Rares*", established in 2001 in Paris), and more particularly for the Orphanet web portal, has been reinforced under the two National Plans. The French Ministry of Health has supported strongly the launch of the Orphanet Joint Action financed by the European Commission.

Orphanet was established in 1997 and is the reference for all rare disease information in France. The team, hosted by the French National Institute of Health and Medical Research (INSERM) in Paris, is in charge of collecting data on services for rare diseases (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patients' organisations) in France, and of coordinating the activity of Orphanet's external teams across Europe, as well as maintaining the encyclopaedia and inventory of rare diseases. The team also maintains the Orphanet France<sup>239</sup> national website. Recent new Orphanet features include the encyclopaedia for patients in French, emergency guidelines, a search by sign facility and a national entry point for France in French. Since 2003, Orphanet also edits a twice-monthly newsletter concerning political and scientific news in the field of rare diseases and orphan medicinal products entitled *OrphaNews France*.

In December 2009, Orphanet signed a partnership with the National Solidarity Fund for Autonomy (CNSA) and leads a project, in the framework of both the National Plan for Rare Disabilities and the National Plan for Rare Diseases, to develop and make available the information concerning the disabilities caused by rare diseases. Orphanet will introduce specific chapters on disability in the General Public encyclopedia

<sup>236</sup> [http://www.agence-biomedecine.fr/IMG/pdf/rapport\\_annuel\\_vdef.pdf](http://www.agence-biomedecine.fr/IMG/pdf/rapport_annuel_vdef.pdf)

<sup>237</sup> [http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v\\_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id](http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id)

<sup>238</sup> Data extracted from Orphanet in January 2014.

<sup>239</sup> <http://www.orphanet-france.fr/national/FR-FR/index/page-d-accueil/?lng=FR>

concerning rare diseases responsible for disability. In addition to this, the disabilities associated with rare diseases will be indexed with the WHO's ICF (International Classification of Functioning, Disability and Health), in order to allow rare diseases to be found when searched by any kind of disability. The first 3-year cooperation has been an opportunity to develop information on some crucial aspects of rare diseases that have not yet been specifically addressed before in Orphanet. This information will be useful to patients, families and professionals dealing with disabilities. The CNSA decided to maintain the cooperation for three more years in March 2013.

The INCa signed an agreement with Orphanet to share information on organisation for rare cancers. Recently, Orphanet published a document describing the clinical networks (national and regional expert centres) for rare cancers<sup>240</sup>.

#### **Official information centre for rare diseases**

Orphanet is the official source of information on rare diseases in France.

Information on rare cancers organisation is available on the INCa website<sup>241</sup>. Fourteen national expert centres have elaborated dedicated websites with high quality information available for the patients.

#### **Help line**

The help line *Maladies Rares Info Services* provides support and information on rare diseases. It is the first health information service in France to have a quality certification (ISO 9001). This service launched in 2011 and has continued in 2013 to propose a series of Internet chat sessions on the first Monday of each month: each session has a theme and Internet users can ask the team questions during the hour-long sessions. *Maladies Rares Info Services* also implemented a "rare diseases barometer". The purpose of this barometer is to collect objective data on the issues to which patients are confronted. Data were collected by means of qualitative and quantitative surveys targeting users of the information and support service. The results of the first round of these surveys were published in 2012<sup>242</sup>. The service also launched a forum for its users in 2012.

The AFM ("*Association française contre les myopathies*" - French Muscular Dystrophy Association) provides a help line for information on neuromuscular diseases.

#### **Other sources of information on rare diseases**

The French National Agency for the Safety of Medicine and Health Products ("*Agence Nationale de Sécurité du Médicament et des Produits de Santé*" – ANSM, ex-AFSSAP<sup>243</sup>) has published on its website since 2009 a registry of clinical trials on medicinal products conducted in France including those on rare diseases, an updated list of compassionate use authorisations (cohorts) with respective summary of product characteristics and leaflet, updated list of medicinal products available within nominative temporary use authorisations (ATU) with specific information if applicable and other general information on hospital preparations.

During the first National Plan for Rare Diseases, the French General Directorate for Health ("*Direction Générale de la Santé*" - DGS) in the Ministry of Health has produced some information cards to be used in case of emergency by rare disease patients. These cards were developed in close collaboration with health professionals, Reference Centres and patient organisations. Each card had two parts: a first one with information about the patient's health status intended for healthcare professionals, and a second one with brief general information on his/her disease for the patient and for non-specialist healthcare professionals<sup>244</sup>. These cards were distributed by the Reference Centre physicians. A simpler model is now envisaged, just specifying some information on the patient and on his/her disease (name of the disease, Orpha number, Reference Centre, what to do and not to do in case of emergency) to be used in case of emergency. It is not yet developed.

National Expert Centres for rare cancers are also requested to provide information to patients and their relatives and to develop close links with national and international patients' associations. Twenty patients associations were listed in 2012 in close active collaboration with the expert centres.

<sup>240</sup> [http://www.e-cancer.fr/component/docman/doc\\_download/9123-cahiers-dorphanet-centres-experts-cancers-rares](http://www.e-cancer.fr/component/docman/doc_download/9123-cahiers-dorphanet-centres-experts-cancers-rares)

<sup>241</sup> <http://www.e-cancer.fr/soins/prises-en-charge-specifiques/cancers-rares>

<sup>242</sup> <http://www.maladiesraresinfo.org/services-proposes/89.html>

<sup>243</sup> The AFSSAPS was given a new name and new missions on 1 May 2012, following the French law reinforcing the monitoring of safety of medicinal and other health products, published on 29<sup>th</sup> December 2011: *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (French National Agency for Medicine and Health Products) <http://www.ansm.sante.fr/>.

<sup>244</sup> <http://www.sante.gouv.fr/les-cartes-de-soins-et-d-informations-pour-les-personnes-atteintes-de-maladies-rares.html>

In 2010, the website [www.droitsdesmalades.fr](http://www.droitsdesmalades.fr), which informs all citizens about their healthcare rights, was launched. In addition, the patient organisation *Sparadrap*<sup>245</sup> has published an informative guide concerning children's rights when they are admitted into healthcare facilities, including issues such as consent to participate in research and financial aid.

The website *Intégrascol* gives information on chronic diseases, in particular rare diseases, for teachers and education professionals in charge of pupils with chronic disease or disabilities. This website free of access contains brief medical and educational information useful for education professionals to adapt teaching to the children with the aim of better integration into school<sup>246</sup>.

Since 2012, the website of the French Foundation for Rare Diseases (FFRD)<sup>247</sup> is integrating information dedicated to rare diseases researchers, including an extensive mapping of funding opportunities (institutional funding, FFRD funding, charities, private and EU/international opportunities). The portal is updated on a regular basis. Further advice is provided by the regional coordinators to better inform researchers about access, specificities and deadlines, guide them towards most adapted funding sources and support their applications, including through access to complementary partners and fulfillments of specific conditions.

### Guidelines

During the first national plan up to December 2012, the Reference Centres produced, with the sustained help of the HAS, 50 national good practice guidelines ("PNDS") for diagnosis, treatment and follow-up of patients with rare disease. Each PNDS of this first group were completed with a list of the acts and products (drugs, medical devices) considered as essential for the patients care and therefore which may be reimbursed, including off-label products. In December 2012, the HAS published a new simplified method to develop "PNDS"<sup>248</sup> to help the Reference Centres draft more quickly the PNDS to boost the production to 200 protocols in 4 years, as expected at the end of the second plan. The task to produce the PNDS is now completely delegated to the Reference Centres, and the HAS will just publish the PNDS on its website. The PNDS developed with the HAS simplified method will be no more completed with a list of the acts and products for patients care. However, the production of PNDS has remained low in 2013: only 2 new PNDS were published. All the PNDS are published on Orphanet, HAS<sup>249</sup> and Reference Centre websites. The HAS itself has published clinical practice guidelines<sup>250</sup> for the follow-up of children with deafness under the age of six and their family.

Concerning rare tumours, two national good practice clinical guidelines were published with the quality label of HAS and INCa respectively in 2010, the first one concerning surgical practices in digestive neoplasia including peritoneal pseudomyxoma, and the second one gestational trophoblastic disease<sup>251</sup>. Clinical guidelines are available on the dedicated websites of national Expert Centres, concerning most of the rare cancers, such as sarcomas, cutaneous lymphoma, rare head and neck cancers, thyroid carcinoma, rare ovarian carcinoma, thymus carcinoma.

National working groups coordinated by the French Foundation for Rare Diseases have also been working on complementary guidelines, including updated guidance concerning informed consent to the analysis of genetic characteristics, taking into account the rapid evolution of the field through the implementation of NGS at the crossing between research and healthcare. Work has also been undertaken to provide researchers with targeted guidelines on the use of databases in the evolving regulatory context. Consultation of all relevant national learned societies on those key issues is on-going.

### Training and education initiatives

All health professionals, medical doctors, midwives, nurses and paramedics follow two hours of training during their undergraduate medical studies on the topic of rare diseases.

Every year, 3<sup>rd</sup> year medical students at the Necker-Cochin faculty of medicine in Paris are offered an optional 30-hour training course on rare diseases during which experts in the field and representatives of rare disease patients' organisations are present. The Paris-based Institute of Myology organises an annual Summer School in Paris: this offers the possibility to train in myology via a condensed 10-day course.

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<sup>245</sup> <http://www.sparadrap.org/SPARADRAP>

<sup>246</sup> <http://www.integrascol.fr/>

<sup>247</sup> <http://fondation-maladiesrares.org>

<sup>248</sup> [http://www.has-sante.fr/portail/jcms/c\\_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=2](http://www.has-sante.fr/portail/jcms/c_1340205/fr/methode-d-elaboration-des-protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=2)

<sup>249</sup> [http://www.has-sante.fr/portail/jcms/c\\_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=1](http://www.has-sante.fr/portail/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds?xtmc=&xtcr=1)

<sup>250</sup> [http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite\\_de\\_lenfant\\_-\\_0\\_a\\_6\\_ans\\_-\\_recommandations.pdf](http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/surdite_de_lenfant_-_0_a_6_ans_-_recommandations.pdf)

<sup>251</sup> [http://www.has-sante.fr/portail/jcms/c\\_1147273/fr/tableau-des-recommandations-de-bonne-pratique-ayant-obtenu-le-label-methodologique-inca-has?xtmc=&xtcr=2](http://www.has-sante.fr/portail/jcms/c_1147273/fr/tableau-des-recommandations-de-bonne-pratique-ayant-obtenu-le-label-methodologique-inca-has?xtmc=&xtcr=2)



In 2013, the French Foundation for Rare Diseases organised 3 national workshops designed for rare diseases researchers. A total of 450 participants had the opportunity to meet up with technology platforms and scientific experts in the field of proteomics, animal models and molecular screening, with the objective to boost the development of cutting-edge research projects ahead of the launch of dedicated call for proposals by the FFRD. The FFRD also initiated a reflection on the first national academic training dedicated to rare diseases research. Partner universities have been contacted and details of the objectives, programme and access will be discussed over 2014 for a national implementation as early as 2015.

### **National rare disease events 2013**

To mark the Rare Disease Day 2013 in France, a gathering took place at the Pont des Arts in Paris including the members of the Rare Disease Platform to raise hands in solidarity. Orphanet also marked the day with the launch of their mobile application. From 28 February to 2 March for the third year in a row, an awareness raising campaign was organised on several train lines to raise awareness of this issue amongst the passengers using the service. The Rare Disease Platform also held a press conference on 21 February.

On 12 March, a regional event was organised in Limoges by the Regional Health Agency (“Agence régionale de santé”) to bring together healthcare professionals, regional administrative officers and patients’ associations, for discussions concerning rare diseases and implementation of the plans in Limousin Region, with presentations from actors in the field and regional decision makers.

On 23 September, Orphanet and the French Rare Disease Alliance organised in Paris their annual forum for patient organisations on the theme of information and communication technologies. This forum has become, over the years, a major event for many patients’ organisations, and this year’s event was attended by over 100 attendees. The theme for 2013 was “ICT for the collection and sharing of information on rare diseases”. The first part was dedicated to the latest news of the French rare diseases community, and then the role of patients and patient organisations in registries and cohorts was discussed. The second part focused on how patients can play a role in data collection by highlighting the benefits and the risks they are exposed to.

On 16 September, a regional event was organised in Marseille by the Rare Diseases Alliance, bringing together more than 150 participants from patients’ organisations and from the clinics, research and medico and social care areas with the participation of French Ministry of Health representative.

On 17-18 October, the French Foundation for Rare Diseases supported the organisation of Orphan Drug and Rare Disease Seminar in Marseille organised by Eudipharm, F-CRIN and OrphanDev with the aim to raise awareness among clinical research stakeholders on drug development specificities in the rare diseases field.

On 21 November, a Rare Diseases Conference, organized by the Regional Health Agency, in partnership with the Rare Diseases Alliance and the French Foundation for Rare Diseases, was organised in Rennes in order to inform the public about the availability of regional care, medical resources and technical facilities dedicated to rare diseases patients. This meeting also aimed at bridging teams and dedicated platforms at national and regional levels, raising awareness on latest developments of research as well as addressing social and ethical implications associated with rare diseases.

On 28-29 November, the third edition of the “Rare Conferences”, Rare2013<sup>252</sup>, was organised by Eurobiomed in Montpellier with over 300 participants attending the presentations and roundtables to hear about advances in the field of rare diseases.

Each year in December, an annual *Téléthon* is organised by the AFM-Téléthon (“Association française contre les myopathies” - French Muscular Dystrophy Association) over 30 hours to raise funds. The funds raised go towards rare disease research, information services (including the French Rare Disease Platform), awareness campaigns, patient care and patient organisations. In 2013, the 27<sup>th</sup> edition of the *Téléthon* took place on 6-7 December, raising over 78 million Euros. On the same weekend, the 14<sup>th</sup> Rare Disease March took place in Paris, organised by the Rare Disease Alliance, bringing together 2000 participants.

### **Hosted events in 2013**

Amongst the events hosted by France in the field of rare diseases were: the European Society of Human Genetics (Paris, 8-12 June 2013), Orphan Drug & Rare Disease Seminar “Accelerating access to therapeutic innovation” (17-18 October 2013, Marseille), 16th International Conference on Behçet’s Disease (18-20 September 2013, Paris), 2nd International Symposium on Hypothalamic Hamartomas (20-21 September 2013, Marseille), 2nd International Expert Meeting on Congenital Melanocytic Nevi and Neurocutaneous Melanocytosis (28-30 September 2013, Marseille), Fifth BHD Symposium and Second HLRCC Symposium (28-29

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<sup>252</sup> <http://www.rare2013.com/>

June 2013, Paris, France), Myasthenia 2013 (1-2 July 2013, Paris), European Human Genetics Conference 2013 (8-11 June 2013, Paris), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France).

The French National Cancer Institute, associated partner of EPAAC (European partnership action against cancer) work package 7 (WP7) organised a workshop on rare cancers in July 2013. The purpose of this workshop was to explore the feasibility and relevance to harmonize clinical practice guidelines at European level in the context of rare cancers (with sarcoma as an example), taking into account the results of the survey which has been conducted in the frame of EPAAC WP7 on existing rare cancer networks and patients groups in Europe. A report of this workshop was presented in Open Forum EPAAC in Slovenia in November 2013<sup>253</sup>.

## Research activities and E-Rare partnership

### National research activities

In France, public funding is available for rare disease research projects from:

- The National Agency for Research (*Agence Nationale de la Recherche – ANR*) for basic research;
- The General Directorate for Provision of Healthcare (*Direction Générale de l’Offre de Soins – DGOS*) of the Ministry of Health for clinical research via funding of the “PHRC” (“*Programme Hospitalier de Recherche Clinique*” – Hospital Clinical Research Programme) sponsored by National Health Insurance of the French Social Security System;
- The INSERM for translational research;
- The “*Fondation maladies rares*”<sup>254</sup> (*Rare Diseases Foundation*).

Basic research for rare diseases was granted €113 million between 2005 and 2011, representing 327 projects over these 7 years. Clinical research received €9 million (36 projects) in 2010, €8.3 million (23 projects) in 2011 and €8.5 million (21 projects) in 2012.

A specific chapter of the Second National Plan for Rare Diseases is dedicated to research, and several new initiatives have been planned, most of which have already been implemented.

Flagship of the Second National Plan, the French Foundation for Rare Diseases (FFRD) has been actively promoting rare diseases research since its launch in February 2012. The unique cooperative framework is proving to be an efficient design to implement the main objective to accelerate rare diseases research, and more specifically, to bridge all rare diseases stakeholders in order to:

(1) Understand rare diseases

The French Foundation for Rare Diseases carefully selected 7 technology platforms, both public and private, with whom it initiated partnerships in order to fulfil key needs in the area of rare diseases research: by the end of 2013, the FFRD had launched 4 calls for projects to facilitate researchers’ access to NGS technologies and identify the genetics underlying rare diseases not characterized to date, as well as 1 call for projects to develop mouse models and study further functional mechanisms involved in rare diseases. A total of 213 projects were received. A selective scientific process involving 150 experts led to the funding of 95 projects all over the national territory (77 NGS and 18 animal models) for a total of over €1.7 million. In parallel to its own sources of funding and call for proposals, the FFRD has also been involved in providing information to the French rare diseases research community on several other funding opportunities both at the French level (nationally and regionally) and at the EU level (such as IMI, COST, FP7, DG SANCO funding programmes for instance).

(2) Develop new treatments

Following a national workshop organised at the *College de France* in July 2013 to enable scientists to share knowledge and experiences in the field of molecular screening of drug candidates, the FFRD launched its first dedicated call for projects in October 2013. A total of 15 high-flying projects are currently under selection, in collaboration with 5 dedicated technology platforms. In parallel, the FFRD actively engaged in anticipating the R&D needs of innovative diagnostic and therapeutic approaches. This led to the detection of 66 promising candidates in 2013, including new molecules, repurposed drugs and innovative medical devices. Guidance is provided at each step of development together with dedicated partners (IP experts, national and EU regulatory agencies, pharma/biotech, investment funds aso). As an example, a total of 10 procedures of orphan designation have been initiated in 2013 with the support of OrphanDev, a national network dedicated to methodological support to clinical studies. Similarly, 5 public-private partnerships were proposed in order to accelerate the pre-clinical

<sup>253</sup> More than a European sound box: capitalising on the added value of the European perspective in cancer treatment. JM Borrás, J Prades, J-M Bréchet, S Faithfull, A Trama, P G Casali. In: Boosting Innovation and Cooperation in European Cancer Control – Key Findings from the European partnership for Action Against Cancer (EPAAC), ed Jose M Martin-Morena, Tit Albrecht, Sandra Rados Krnel, Ljubljana 2013, pp 117-139.

<sup>254</sup> <http://fondation-maladiesrares.org/>

and clinical development of academic proofs of concept opening the way to new therapeutic strategies. Finally, the FFMR initiated a think tank of pharmaceutical companies to start working on topics such as databases and registries from the perspective of private contributors, as well as orphan drug economics.

(3) Improve patients' care

As rare diseases scientific and clinical research is tightly linked to societal challenges, the FFRD has been actively promoting humanities and social sciences research. In December 2012, a first dedicated call for proposals was launched, in collaboration with the National Solidarity Fund for Autonomy ("*Caisse nationale de solidarité pour l'autonomie*" – CNSA) and the General Directorate for Health ("*Direction Générale de la Santé*" - DGS) to address three different areas: diagnostic pathway; ethical and societal impact of new technologies in the field of genetics; social, educational and professional integration of patients affected by a rare disease. FFRD regional coordinators supported connections between academic researchers, clinicians and patients' organisations. A total of 77 projects involving 188 research teams and 38 patients' organisations all over France were submitted to the assessment of 88 experts from both the rare diseases clinical and social/humanities fields. In 2013, €643 was allocated to 10 successful projects. The high demand encouraged renewing this call for proposals on an annual basis. At the end of 2013, a similar call for proposals was thus implemented and received 80 letters of intents (involving 257 research teams, 61 patients' organisations) that are currently under selection, with results expected for June 2014. Additionally, the FFRD has been initiating and driving boards of experts at the national levels in order to discuss essential updates, especially in the field of patients' protection and information, including a reflection on a consensus document for informed consent for genetic testing, whose results have been invited to be presented at the national "*Assises de Génétique*" congress, bringing together clinicians, geneticists and all involved learned societies for an update on the clinical genetics developments in January 2014.

In parallel, the FFRD has been actively participating in national and international public health and research policies and frameworks. One main objective is to participate in and promote international collaborations. This includes raising awareness for acquainted international research policies and rare diseases researchers' access to the resulting opportunities, such as dedicated funding lines included in the H2020 programme, as well as an active commitment within international consortia such as E-rare and IRDiRC thereafter described. The FFRD also initiated an innovative cooperation programme with The World Academy of Sciences in order to promote rare diseases research collaborations with emerging countries. This led to the launch of a first joint call for proposals, targeting scientists from the wider Mediterranean and Middle-Eastern areas in October 2013. A total of 90 teams from 17 countries were involved in the submission of 19 international collaborative proposals dedicated to bring together the rare diseases research and clinical communities on key issues. Projects are under international selection, with results expected for the beginning of 2014.

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which was launched at the beginning of 2013 (called "*Programme de recherche translationnelle en santé*" – PRTS, Programme for translational research in Health<sup>255</sup>). This call for proposals is not specifically for rare diseases. The first objective of this programme is to select and fund research projects at the interface between basic research projects currently funded by ANR and clinical research projects currently funded by PHRC.

In addition, some charities, private foundations or patient organisations provide funding for research, such as the AFM-Téléthon (French Muscular Dystrophy Association). In 2013, the AFM-Téléthon (which has been developing a variety of innovative therapeutic approaches over the past 25 years) and the *Fonds National d'Amorçage* (FNA) (which provides public funds towards innovative biotherapies and rare diseases thanks to the French "*Programme d'Investissements d'Avenir*") have moved closer to constitute the first seed fund dedicated to innovative biotherapies and rare diseases. This action forms part of an "*Environmental, Social and Governance*" process. With an initial endowment of €50 million, for a final target of €120 million, the fund aims to create a portfolio of 12 to 15 participants in companies at the seed stage. The amount invested will be between €3 and €10 million per company. The AFM-Téléthon has contributed to a budget of €30 million, and CDC Entreprise, via the FNA, has bestowed €20 million. The fund will target innovative SMEs with strong development potential that have been in existence for less than eight years. They must also follow standards that are consistent with the industrial development of therapies such as gene therapy, cell therapy,

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<sup>255</sup> [www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/](http://www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/)

pharmacological modulation of gene expression, monoclonal antibodies, therapeutic proteins and immunotherapies.

### **Participation in European projects**

French teams participate (have participated) in 151 FP7 rare disease related projects and are coordinating team for 49 projects.

In addition, the French National Cancer Institute participates in The International Rare Cancers Initiative (IRCI), which is a joint initiative between the National Institute for Health Research in the UK, the National Cancer Institute (NCI) in the US and the European Organization for Research and Treatment of Cancer (EORTC). Its objective is to facilitate the development of international clinical trials for patients with very rare cancers. The French National Cancer Institute joined the membership Committee in 2013<sup>256</sup>.

### **E-Rare**

The *GIS Maladies Rares* was the coordinating partner of the E-Rare for Research Programmes on Rare Diseases, and organised the first Joint Transnational Call in 2007<sup>257</sup> for research on rare diseases, with the participation of 6 countries and a total of 13 funded consortia (French research teams participated in each of these funded projects/consortia). France took part in the 2<sup>nd</sup> E-Rare Joint Transnational Call in 2009 and is represented in 11 of the 16 consortia selected for funding, with funding totalling around €2 million. France also took part in the 3<sup>rd</sup> Transnational Call launched at the start of 2011 in the context of E-Rare2: French research teams have been funded to participate in 13 of the projects selected for funding. France participated in the 4<sup>th</sup> Joint Transnational Call in 2012, with French teams participating in 7 out of the 11 consortia selected for funding. From April 2013, the French Foundation for Rare Diseases is in charge of the E-Rare 2 coordination on behalf of INSERM. France participated in the 5<sup>th</sup> Joint Transnational Call in 2013, with French teams participating in 9 out of the 12 consortia selected for funding. The E-Rare 2 consortium now brings together 18 ministries and funding national agencies from 15 countries to support projects in translational research on rare diseases across Europe and worldwide. In December 2013, the consortium launched its annual Joint Call 2014 on “innovative therapeutic approaches for rare diseases” with a budget of €13 million.

### **IRDIRC**

In 2013, the AFM-Téléthon (French Muscular Dystrophy Association), the French National Agency for Research (*Agence Nationale de la Recherche – ANR*), and *Lysogene* (all French-based organisations) were committed members of the International Rare Disease Research Consortium (IRDIRC). Since October 2012, the French Foundation for Rare Diseases has been actively involved, together with Orphanet, in the IRDiRC Scientific Secretariat<sup>258</sup>. At the end of 2013, French representatives were also involved in Scientific Committees: 2 members out of 11 were French in the Interdisciplinary Scientific Committee and 3 out of 17 in the Therapy Scientific Committee which was chaired by the French CEO of EURORDIS. In 2013, French scientists also took part in 10 of the 12 established IRDiRC Working Groups.

### **Orphan medicinal products<sup>259,260</sup>**

Four institutions are involved in the field of orphan medicinal products on the French market: the French National Agency for the Safety of Medicine and Health Products (ANSM, ex-AFSSAPS), the French National Authority for Health (HAS), the French Economic Committee for Health Products (*Comité Economique des Produits de Santé – CEPS*), and the Ministry of Health.

The LEEM (French Pharmaceutical Industry Association) is a constituted professional organisation that represents the pharmaceutical industry in France, i.e. the companies whose missions are research, development, manufacturing and marketing of medicinal products. Rare diseases became priority action in the LEEM's strategy in 2002: a rare disease working group made up of key stakeholders in the public and private sectors meets regularly to discuss: innovative therapies for rare diseases (and how to bring these therapies to patients), the provision of health care for rare disease patients, the communication of information on rare

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<sup>256</sup> <http://www.irci.info/>

<sup>257</sup> [http://www.e-rare.eu/images/stories/e-rare\\_final\\_list\\_of\\_funded\\_projects.pdf](http://www.e-rare.eu/images/stories/e-rare_final_list_of_funded_projects.pdf)

<sup>258</sup> In February 2014, the French Foundation for Rare Diseases joined the IRDiRC as a funder member and a member of the Executive Committee.

<sup>259</sup> This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

<sup>260</sup> This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (pp12-14)

diseases and treatment, ways to create the correct conditions for optimal and innovative clinical treatment and ways to support the national plan for rare diseases. The LEEM organises a workshop dedicated to orphan medicinal products every year. Since 2001 the LEEM evaluates the advances made in clinical research in France, including clinical research in the field of rare diseases. In its annual overview of therapeutic advances for 2012, a particular emphasis was put on new orphan drugs in relation to the development of personalised medicine<sup>261</sup>.

#### **Orphan medicinal product committee**

There is no orphan medicinal product committee currently in France, apart from the multistakeholder group at the LEEM (see above).

#### **Orphan medicinal product incentives**

Initiatives are in place to stimulate the development of orphan medicinal products: research support is provided through national funding programmes: the Hospital Clinical Research Programme (“PHRC”). As far as research support is concerned, the French Foundation for Rare Diseases also supported the identification of new molecules with opportunities to become new drugs, through the launch of a first high throughput molecular screening call in 2013 (results to be published mid-2014). It also brought support to research teams in the implementation of all relevant steps to move from a scientific hypothesis to a research protocol (orphan designation – in liaising with OrphanDev, study design, funding etc.).

During orphan medicinal product development, free scientific advice is available from the ANSM; and budgetary incentives (from 2001) are available in the form of a tax exemption. Other incentives measures, such as free early advice and fast track process of the assessment for reimbursement by the Transparency Committee (CT) are performed by the HAS.

Free scientific advice is available for medicines from the ANSM as well as CT and compassionate use authorisation (cohort ATU) from the ANSM. The HAS is performing early meetings at the national level, the European level (within the EUnetHTA network of Health technology agencies) on request of pharmaceutical industry or on its own request. These scientific meetings aim to let the marketing authorisation (MA) owner know what data the HTA bodies expect especially concerning the relative effectiveness assessment in usual care.

Sponsors of orphan medicinal products are exempted from taxes to be paid by companies:

- tax on the turnover of medicinal products if under €20 millions;
- tax on the promotion of medicinal products, based on their promotion costs if turnover under €30 millions;
- taxes paid in France by the companies on their sales (there is no turnover threshold for these taxes);
- the safeguard clause for medicinal products whose turnover is under €30 millions;
- tax on direct sales for medicine whose turnover is under 30€ millions;
- tax on the distribution of medicines for medicine whose turn over is under 30 € millions.

These are some of the initiatives aimed at stimulating research by the pharmaceutical industry into rare diseases in addition to the provisions of the European Regulation on Orphan Medicinal Products.

The public authorities decided in 2010 to abrogate the framework agreements which exempt orphan medicinal products from certain regulations, and recommended price cap for orphan medicinal products costing more than €50 000 per year and per patient. An obligation to treat all affected patients was also proposed.

A law adopted by Parliament on 22 March 2011 allows non-profit organisations to become pharmaceutical establishments and will give the status of medicine to gene-therapy products. As a direct result, the Généthon Bioprod non-profit laboratory, inaugurated in November 2010, will be able to produce products for gene-therapy for clinical trials.

#### **Orphan medicinal product pricing policy**

Before any pricing, all drugs including orphan medicinal products are assessed by the Transparency Committee of the French National Authority for Health (“HAS”) for reimbursement purpose. This committee provides the Ministry of Health and National Health Insurance with an opinion about the pertinence of reimbursement and the level of copayment, and specifies the added value of the drug, which is the basis for price definition. For innovative drugs (new therapeutic modality, presumably efficient and well tolerated, and covering an unmet medical need), often including orphan medicinal products, the Transparency Committee performs a fast track assessment before and delivers its opinion shortly after MA is granted. However, the official process starts

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<sup>261</sup><http://www.leem.org/les-essentiels-maladies-rares>

after marketing authorisation (MA). This fast track reduces the usual timelines, which is of 90 days after MA, to 15 days.

After that step, an Industry-government agreement via the French Economic Committee for Health Products (CEPS) is defined, which sets the rules for the pricing of reimbursed medicines in France.

HAS also provides early dialogues for medicines that are under development in order to answer questions that the sponsor wants to ask about the way the development should go to *in fine* provide most adequate evidence of clinical interest for the patient and the public health. This is particularly adapted to orphan drugs that usually bring innovation for a limited population in a situation where the need is not covered.

#### **Orphan medicinal product market availability situation**

According to the registry of the French National Agency for the Safety of Medicine and Health Products (ANSM) website, the availability of orphan medicinal products in France can be represented as follows:

- Orphan medicinal products with valid market authorisation and with mention of commercialisation: Adcetris, Aldurazyme<sup>262\*</sup>, Arzerra, Atriance, Bosulif, Bronchitol, Busilvex\*, Carbaglu, Cayston, Ceplene, Cystadane, Dacogen, Defitelio, Diacomit, Duodopa, Elaprase, Esbriet, Evoltra, Exjade, Fabrazyme\*, Firazyr, Firdapse, Flisint, Gliolan, Glivec, Iclusig, Imnovid, Increlex, Inovelon, Jakavi, Kalydeco, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Naglazyme, Nexavar, Nexobrid, Nplate, Orfadin, Orphacol, Pedeia, Prialt, Replagal\*, Revatio, Revlimid, Revolade, Savene, Signifor, Siklos, Soliris, Somavert\*, Sprycel, Tasigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Trisenox\*, Ventavis\*, Vidaza, Volibris, Votubia, Vpriv, Vyndaqel, Wilzin, Xagrid, Yondelis, Zavesca.
- Orphan medicinal products with valid market authorisation without mention of commercialisation: Glybera, Peyona, Plenadren, Procysbi, Revestive, Xaluprine.

#### **Orphan medicinal product reimbursement policy**

Orphan medicines can be dispensed in out-patient or in-patient settings through one of the two corresponding lists: list for medicines reimbursed by National Health Insurance and available in community pharmacies, and list for hospital pharmacies. Within the hospital list, the drugs are generally funded through GHS (*Groupes H*, a diagnostic-related group system established by the TZA (*tarification à l'activité*, Hospital Activity-Based Payment) policy. However, some expensive drugs used in hospitals are fully reimbursed to the hospitals by the National Health Insurance. These drugs are listed in a specific list (called *liste hors GHS*) established by the French Ministry of Health. Some of the drugs available in hospital pharmacies can be made available to outpatients (retrocession list) and paid for by the National Health Insurance. Within the 68 orphan medicinal products that have been granted MA in Europe, 3 have not requested reimbursement and within the 65 medicines remaining, all but two have been granted a positive advice for reimbursement in France.

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*<sup>263</sup>, "particular prescribing conditions are in place for: drugs for hospital use, drugs with hospital prescription, drugs with initial hospital prescription, drugs with prescription only by specialists, drugs with a particular follow up during the treatment." From 1 January 2010, the Ministry of Health and the French National Health Insurance made it mandatory for the first prescription of an orphan medicinal product to be validated by a relevant Reference Centre when available, or by the Competence Centre directly linked to the relevant Reference Centre.

#### **Other initiatives to improve access to orphan medicinal products**

Compassionate use for individual patients takes the form of either cohort use (cohort Temporary Authorisation for Use) or named patient supply (nominative Temporary Authorisation for Use) prior MA granted both by the ANSM. Patients can also be treated with drugs before these drugs have received MA through clinical trials or hospital preparations. Reimbursement measures are in place for compassionate use. Innovative drugs are eligible for an ATU (*Autorisation temporaire d'utilisation* - Temporary Authorisation for Use) from the ANSM if there is a public health need.

<sup>262</sup> In February 2014, the French Foundation for Rare Diseases joined the IRDiRC as a funder member and a member of the Executive Committee.

<sup>263</sup> Some drugs (\*) are no longer considered as orphan medicinal products because they are at the end of the ten-year period of commercial exclusivity.

This process was modified in 2012 following the law reinforcing the monitoring of safety of drugs and other healthcare products, published on 29 December 2011 (Law N° 2011-2012). The new law maintains the possibility of an ATU, in particular in the case of rare diseases. The drug must fulfil the following criteria: the treatment cannot be postponed; there is no alternative therapeutic to the drug; the efficacy and security of the drug are strongly presumed from the results of clinical trials (cohort ATU) or from scientific published data and knowledge (nominative ATU); the patient cannot be treated within a clinical trial. The ATU is given for a limited period, but renewable. A therapeutic protocol and data collection concerning safety and efficacy are mandatory for both cohort and nominative ATU.

This law also introduced the concept of “temporary recommendation of use” (“recommandation temporaire d’utilisation” - RTU) developed and published under the responsibility of the ANSM. The aim of RTU is to provide a framework for the prescription of a medicinal product beyond the indications of its MA when no other medicinal product with a MA or a cohort ATU is available for the considered indication. The development of RTU is possible when the ANSM considers the available data are sufficient to presume a favourable benefit risks ratio. Prospective data collection concerning safety and efficacy of the drug is mandatory when a RTU is published. In November 2012, the ANSM published a template<sup>264</sup> for the follow-up of patients and collection of data if RTU are available. In order to help the ANSM to prepare the development of RTUs for rare diseases, the Ministry of Health asked the Reference Centres in July 2012 to carry out an inventory of their prescriptions out of the MA of the medicinal products that could be eligible for RTU. The questionnaire was returned by 70% of the Reference Centres. The data were compiled by the ministerial authorities and sent in November 2012 to the ANSM which has used this data in 2013. No RTU were published by the ANSM in 2013.

In hospitals, Temporary Treatment Protocols (“*Protocoles temporaires de traitement*” - PTT) may also be used to extend the indication for a drug or device with reimbursement permitted. Temporary Treatment Protocols are limited to expensive drugs used only in hospitals and registered on a special list.

In 2006, the law for the financing in 2007 of French Social Security system planned a derogative pathway for exceptional coverage of off-label use of medicinal products and of non-covered medical devices or services by the National Health Insurance<sup>265</sup>. Orphan or non-orphan medicinal products used off-label, medical devices or services intended for rare diseases are in particular concerned. The complete reimbursement is allowed for a limited renewable period by the Ministry of Health after the HAS has given a positive opinion. Since the law of the 29 December 2011 reinforcing the monitoring of safety of drugs and other healthcare products, the ANSM must publish a RTU before the HAS is allowed to advise the complete reimbursement of a medicinal product used off-label.

The ANSM also established a national public register of clinical trials on medicines conducted in France, which is regularly updated.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Orphan devices**

No specific information reported.

#### **Specialised social services**

Respite care services are available for patients whose care is demanding temporary relief of their relatives: this is only partially reimbursed for some rare diseases. Therapeutic recreational programmes are available mostly within hospital organisations and patient organisations or local institutions, and are mostly fully reimbursed. Social assistance community centres (“*Centres communaux d’action sociale*” - CCAS), social assistants within hospital structures, and services provided by patient organisations all aim to assist the integration of patients with rare disease into daily life. These services are financed either by government or community budgets (through the “*Maisons départementales des personnes handicapées*”) or patients’ organisations. The AFM has a number of administrative, medical and social coordinators who assist families with their specific needs.

On 9 February 2010 an interministerial observatory was created to evaluate the accessibility of public buildings, housing, work places, transport and footpaths/roads to all persons.

On 31 May 2013, a Decree was published concerning the skills and qualifications required of those in charge of giving and coordinating therapeutic education of patients.

<sup>264</sup>

[http://www.legifrance.gouv.fr/jopdf/common/jo\\_pdf.jsp?numJO=0&dateJO=20121122&numTexte=13&pageDebut=18412&pageFin=18414](http://www.legifrance.gouv.fr/jopdf/common/jo_pdf.jsp?numJO=0&dateJO=20121122&numTexte=13&pageDebut=18412&pageFin=18414)

<sup>265</sup>

Article L162-17-2-1 of the Social Security Legal Code.

## RARE DISEASE ACTIVITIES IN FRANCE IN 2013

### National plan/strategy for rare diseases and related actions

#### **Second French National Plan for Rare Diseases 2011-2014**

The Steering Committee of the plan held two meetings in 2013 on 19 March and 19 November. These meetings concluded that significant progress has been made to date which is in line with the objectives of the Second French National Plan.

In the area of research, a significant development has been the setting up of a funding process to support Preclinical and Early Clinical Research. This is especially important as France provides sources of funding for basic research (from the “*Agence nationale de la recherche*” – ANR – “National Research Agency”, financed by the Ministry for Research) and for academic clinical research (from the “*Programme hospitalier de recherche Clinique*” – PHRC – “Hospital Clinical Research Programme” - financed by the Ministry of Health), but not for research projects that fall somewhere in between basic and clinical research. An annual call for proposals for translational research in health was announced and launched in 2013.

A total of 34 university hospitals received funds (€9.6 million over 2 years) to obtain necessary equipment to provide new generation sequencing services to speed up standard diagnosis. An in-depth reflexion has been in progress in 2013 to design one national NGS platform for complex diagnosis and research.

The initiative to establish a French national rare diseases databank (“*Banque nationale de données maladies rares*” - BNDMR<sup>266</sup>) in order to have a central data repository on rare disease patients from various existing sources, for health care planning and clinical research, began in 2011. The minimum dataset was approved during the Steering Committee meeting on 19 March 2013. A national interoperability framework was also defined in 2013. A specific steering committee was created in November 2013 to follow the implementation of the BNDMR.

In the area of health care delivery, improving the way Reference Centres are evaluated is one of the main objectives of the second plan, to ease the reporting carried out by the centres and to create the tools for an accurate assessment on which to base decision on the renewal of the designation and on the allocation of funds. An annual reporting system and a new external evaluation process were defined after 2 years of solid effort by working groups composed of representatives of Reference Centres, patients’ associations, French National Authority for Health (“HAS”), French Agency for the Evaluation of Research and Higher Education (“AERES”) and Ministry of Health. The new process will be ready to be launched in 2014.

Another main objective of the second plan is to reorganise Reference Centres and group them in a functional way that maximises collaboration and allows better and easier orientation of patients. These “national networks for rare diseases” (“*filiales de santé maladies rares*”) will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: Reference and Competence Centres, diagnostic and research laboratories, imaging, health and social care, professionals and patients’ associations etc. Preliminary work and surveys in 2012 identified 23 possible groupings of Reference Centres. The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres. At the end of the call, in November 2013, 32 projects have been received. The “Permanent Working Group”, planned to monitor the activity of Reference Centres and national networks, held a first meeting on 18 December 2013 and began to examine the submitted projects. The national networks will be designated by the Ministry of Health in early 2014.

In conclusion, the second French plan is well on the way and several initiatives delineated in the plan have been implemented. A new leader of the implementation of the plan was named in July 2013. The Steering Committee recognises that the final months of the plan will present challenges as the rare disease community will have to prepare for the future in the context of a constrained budget but also to build on all the improvements resulting from the two national plans.

#### **Second French National Plan for Cancers (including rare cancers) 2009-2013**

A second National Plan for Cancers<sup>267</sup> was launched on 2 November 2009 for the period 2009-2013. The final report concerning the implementation of the cancer plan, including a section on the actions in the field of rare cancers, was published in 2013<sup>268</sup>.

<sup>266</sup> <http://www.bndmr.fr/>

<sup>267</sup> [http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013\\_english.pdf](http://www.plan-cancer.gouv.fr/images/stories/fichiers/plancancer20092013_english.pdf)

<sup>268</sup> <http://www.plan-cancer.gouv.fr/accueil/actualites/43-actualites/1204-publication-du-rapport-final-au-president-de-la-republique-du-plan-cancer-2009-2013.html>



As for the preparation of the third French National Plan for Cancers (including rare cancers) 2014-2019: recommendations for a third plan for cancers<sup>269</sup> in the field were transmitted to the Minister of Health in autumn 2013. A third National Plan for Cancers was then prepared and published on 4 February 2014<sup>270</sup>. Organisation of care for adults with a complex cancer, improvement of the organisation of second opinion in pathology for rare cancers and organisation of care for very rare cancers in children are planned.

### **French National Plan for Rare Disabilities 2009-2013**

A fourth national resource centre for patients with rare disabilities and severe epilepsy was created in 2013. Inter-regional intermediary teams ("*equipes relais*") of these national centres were launched in 2013 with the aim of their complete deployment in 2014-2015. Cooperation between national resource centres and inter-regional teams for rare disabilities and Reference Centres for rare diseases is also underway. A leaflet<sup>271</sup> was published describing the national organisation of care in this area.

The Ministry of Social Affairs and Health has asked for an evaluation of the first plan and will announce a second one in 2014 based on various studies conducted during the first one, such as the expert report conducted by INSERM at the request of the CNSA entitled<sup>272</sup> "*Rare handicaps: context, purposes, perspectives*". It highlights the need to describe rare disabilities with the International Classification of Functioning, Disability and Health (ICF), the utility of creating national and international registries or databases, and suggests strengthening the organisation created by the first plan.

### **Other French national initiatives related to rare diseases**

On 2 May 2013, the third National Plan for Autism for the period 2013-2017 was published by the Ministry of Social Affairs and Health. This plan aimed at improving early diagnosis and early care, structuring healthcare, educational and social pathways for patients, supporting families, improving training for all the professionals in charge of patients, and strengthening research<sup>273</sup>.

On 25 January 2011 the Ministry of Higher Education and Research funded the RaDiCo ("*Rare Diseases Cohorts*") project for duration of 10 years and for a total of €10 million. The RaDiCo project showed accelerated development in 2013<sup>274</sup>, and prepared the launch its first call for rare diseases cohort proposals at the beginning of January 2014. The RaDiCo projet has developed very close links with the BNDMR.

### **Centres of expertise**

In 2013 major steps were made to coordinate individual Reference Centres and group them in a functional way that maximises collaboration across the country. The "*national networks for rare diseases*" ("*filières de santé maladies rares*") will be centered on a homogeneous group of rare diseases and gather all the relevant stakeholders: not only Reference and Competence Centres, but also diagnostic and research laboratories, imaging, health and social care, professionals and patients' associations etc. The designated networks will receive funds from the Ministry of Health for their coordination activity. A preliminary survey identified 23 possible groups gathering nearly all the 131 Reference Centres (some centres do not fall in any of these groups). The Ministry of Health published in July 2013 a call for proposals aiming to receive structured projects from Reference Centres: at the end of the call, in November, 32 projects have been received. The Permanent Working Group began to analyse these projects in December 2013. The result of this call is expected in early 2014<sup>275</sup>.

In July 2013, the Ministry of Health published a directive concerning the process for succession as coordinator of a Reference Centre, and for the creation or abrogation of a Competence Centre linked to a Reference Centre.

Three "*national resource centres*" for rare disabilities have been designated in 2011, and a fourth one in 2013 thanks to the French National Plan for Rare Disabilities 2009-2013<sup>276</sup>.

<sup>269</sup> <http://www.sante.gouv.fr/IMG/pdf/Recommandations-pour-le-3e-plan-cancer.pdf>

<sup>270</sup> <http://www.e-cancer.fr/publications> (english) <http://www.e-cancer.fr/le-plan-cancer?gclid=CKLYntPlyb4CFbShtAodTDoAcA>

<sup>271</sup> <http://www.cnsa.fr/IMG/pdf/Memos23-WEB.pdf>

<sup>272</sup> The expert report has been published in May 2013: <http://www.inserm.fr/actualites/rubriques/actualites-societe/handicaps-rares-contextes-enjeux-et-perspectives-une-expertise-collective-de-l-inserm>

<sup>273</sup> <http://www.social-sante.gouv.fr/actualite-presse,42/breves,2325/presentation-du-3eme-plan-autisme,15797.html>

<sup>274</sup> <http://www.radico.fr>

<sup>275</sup> The list of the first 15 accepted "*national networks for rare diseases*" was published on the website of the Ministry of Health on 28 February 2014. <http://www.sante.gouv.fr/les-filières-de-santé-maladies-rares.html>

<sup>276</sup> [http://www.cnsa.fr/IMG/pdf/CNSA\\_Schema-national-Handicap-rare-2.pdf](http://www.cnsa.fr/IMG/pdf/CNSA_Schema-national-Handicap-rare-2.pdf); [http://www.cnsa.fr/article.php3?id\\_article=726](http://www.cnsa.fr/article.php3?id_article=726)

## Registries

A National Rare Disease Registry Committee was created in October 2006 as part of objective 1 - "Improve knowledge of epidemiology of rare diseases" - of the first National Plan for Rare Diseases. In 2012, a reflection began on a possible evolution of the Committee's missions and the needs of the other registries and databases existing in France for support and evaluation and in April 2013 the committee was dissolved at the same time as the national committee created in 1996 for the evaluation of non-rare disease registries. The InVS, Inserm and INCa launched a call for experts in October 2013 in order to create a Registry Evaluation Committee which will consider, amongst others, rare disease registries. This committee will consist exclusively of experts of registries, epidemiology and public health.

The Second National Plan for Rare Diseases also has foreseen the creation of a National Rare Disease Database (BNDMR). A minimum data set (MDS) common to all rare disease centres of expertise and to all rare diseases was discussed and validated by the Steering Committee of the plan in March 2013. The MDS will be entered through an application called BaMaRa ("Banque Maladies Rares" – Rare Diseases Databank), either directly by the centres of expertise, or through their own application if appropriate. To enable data flows between French hospitals and the BaMaRa, a national interoperability framework was defined in 2013. It consists in setting the necessary compatibility elements such as patient identification, data elements and nomenclatures, technical data flows and security. It will help gathering data at the Reference and Competence Centre level and linking this information to biobank data and other national databases (medico-economic databases, national health insurance databases etc.). A data warehouse, the National Rare Disease Database (BNDMR), will host several types of de-identified national rare disease data sets in accordance with the Data Protection Act. A steering committee specific of the BNDMR was set up in 2013 including representatives from the concerned ministries and stakeholders, including patients' associations. In 2013, the BNDMR team also began to develop a specific application named LORD (Linking Open Rare Disease data) to help with rare disease diagnosis coding in hospital health information systems<sup>277</sup>. This application will be used at national level to help coding RD patients either in hospital information systems or registries.

## Genetic testing

Guidelines for good practices related to the examination of genetic characteristics in the medical context in order to assure quality of care were finalised in at the end of 2012, and published in the form of an official text on 2 June 2013<sup>278</sup>. These guidelines describe in particular information to be delivered to patients before and after performing genetic tests.

## Sources of information on rare diseases and national help lines

### *Orphanet activities in France*

In December 2009, Orphanet signed a partnership with the National Solidarity Fund for Autonomy (CNSA) and leads a project, in the framework of both the National Plan for Rare Disabilities and the National Plan for Rare Diseases, to develop and make available the information concerning the disabilities caused by rare diseases. The CNSA decided to maintain the cooperation for three more years in March 2013.

## Guidelines

During the first national plan up to December 2012, the Reference Centres produced, with the sustained help of the HAS, 50 national good practice guidelines ("PNDS") for diagnosis, treatment and follow-up of patients with rare disease. Only 2 new PNDS were published in 2013.

## Training and education initiatives

In 2013, the French Foundation for Rare Diseases organised 3 national workshops designed for rare diseases researchers. A total of 450 participants had the opportunity to meet up with technology platforms and scientific experts in the field of proteomics, animal models and molecular screening, with the objective to boost the development of cutting-edge research projects ahead of the launch of dedicated call for proposals by the FFRD. The FFRD also initiated a reflection on the first national academic training dedicated to rare diseases research. Partner universities have been contacted and details of the objectives, programme and access will be discussed over 2014 for a national implementation as early as 2015.

<sup>277</sup> This application was launched in early 2014: <http://enlord.bndmr.fr>

<sup>278</sup> [http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v\\_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id](http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=773056AA79FC0692CE1CA09922718E1D.tpdjo04v_1?cidTexte=JORFTEXT000027513617&dateTexte=&oldAction=rechJO&categorieLien=id)

### National rare disease events 2013

To mark the Rare Disease Day 2013 in France, a gathering took place at the Pont des Arts in Paris including the members of the Rare Disease Platform to raise hands in solidarity. Orphanet also marked the day with the launch of their mobile application. From 28 February to 2 March for the third year in a row, an awareness raising campaign was organised on several train lines to raise awareness of this issue amongst the passengers using the service. The Rare Disease Platform also held a press conference on 21 February.

On 12 March, a regional event was organised in Limoges by the Regional Health Agency (“Agence régionale de santé”) to bring together healthcare professionals, regional administrative officers and patients’ associations, for discussions concerning rare diseases and implementation of the plans in Limousin Region, with presentations from actors in the field and regional decision makers.

On 23 September, Orphanet and the French Rare Disease Alliance organised in Paris their annual forum for patient organisations on the theme of information and communication technologies. This forum has become, over the years, a major event for many patients’ organisations, and this year’s event was attended by over 100 attendees. The theme for 2013 was “ICT for the collection and sharing of information on rare diseases”. The first part was dedicated to the latest news of the French rare diseases community, and then the role of patients and patient organisations in registries and cohorts was discussed. The second part focused on how patients can play a role in data collection by highlighting the benefits and the risks they are exposed to.

On 16 September, a regional event was organised in Marseille by the Rare Diseases Alliance, bringing together more than 150 participants from patients’ organisations and from the clinics, research and medico and social care areas with the participation of French Ministry of Health representative.

On 17-18 October, the French Foundation for Rare Diseases supported the organisation of Orphan Drug and Rare Disease Seminar in Marseille organised by Eudipharm, F-CRIN and OrphanDev with the aim to raise awareness among clinical research stakeholders on drug development specificities in the rare diseases field.

On 21 November, a Rare Diseases Conference, organized by the Regional Health Agency, in partnership with the Rare Diseases Alliance and the French Foundation for Rare Diseases, was organised in Rennes in order to inform the public about the availability of regional care, medical resources and technical facilities dedicated to rare diseases patients. This meeting also aimed at bridging teams and dedicated platforms at national and regional levels, raising awareness on latest developments of research as well as addressing social and ethical implications associated with rare diseases.

On 28-29 November, the third edition of the “Rare Conferences”, Rare2013<sup>279</sup>, was organised by Eurobiomed in Montpellier with over 300 participants attending the presentations and roundtables to hear about advances in the field of rare diseases.

Each year in December, an annual *Téléthon* is organised by the AFM-Téléthon (“Association française contre les myopathies” - French Muscular Dystrophy Association) over 30 hours to raise funds. The funds raised go towards rare disease research, information services (including the French Rare Disease Platform), awareness campaigns, patient care and patient organisations. In 2013, the 27<sup>th</sup> edition of the *Téléthon* took place on 6-7 December, raising over 78 million Euros. On the same weekend, the 14<sup>th</sup> Rare Disease March took place in Paris, organised by the Rare Disease Alliance, bringing together 2000 participants.

### Hosted events in 2013

Amongst the events hosted by France in the field of rare diseases were: the European Society of Human Genetics (Paris, 8-12 June 2013), Orphan Drug & Rare Disease Seminar “Accelerating access to therapeutic innovation” (17-18 October 2013, Marseille), 16th International Conference on Behçet's Disease (18-20 September 2013, Paris), 2nd International Symposium on Hypothalamic Hamartomas (20-21 September 2013, Marseille), 2nd International Expert Meeting on Congenital Melanocytic Nevi and Neurocutaneous Melanocytosis (28-30 September 2013, Marseille), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France), Myasthenia 2013 (1-2 July 2013, Paris), European Human Genetics Conference 2013 (8-11 June 2013, Paris), Fifth BHD Symposium and Second HLRCC Symposium (28-29 June 2013, Paris, France).

The French National Cancer Institute, associated partner of EPAAC (European partnership action against cancer) work package 7 (WP7) organised a workshop on rare cancers in July 2013. The purpose of this workshop was to explore the feasibility and relevance to harmonize clinical practice guidelines at European level in the context of rare cancers (with sarcoma as an example), taking into account the results of the survey

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<sup>279</sup> <http://www.rare2013.com/>

which has been conducted in the frame of EPAAC WP7 on existing rare cancer networks and patients groups in Europe. A report of this workshop was presented in Open Forum EPAAC in Slovenia in November 2013<sup>280</sup>.

## Research activities and E-Rare partnership

### **National research activities**

Flagship of the Second National Plan, the French Foundation for Rare Diseases (FFRD) has been actively promoting rare diseases research since its launch in February 2012. The unique cooperative framework is proving to be an efficient design to implement the main objective to accelerate rare diseases research, and more specifically, to bridge all rare diseases stakeholders in order to:

(4) Understand rare diseases

The French Foundation for Rare Diseases carefully selected 7 technology platforms, both public and private, with whom it initiated partnerships in order to fulfil key needs in the area of rare diseases research: by the end of 2013, the FFRD had launched 4 calls for projects to facilitate researchers' access to NGS technologies and identify the genetics underlying rare diseases not characterized to date, as well as 1 call for projects to develop mouse models and study further functional mechanisms involved in rare diseases. A total of 213 projects were received. A selective scientific process involving 150 experts led to the funding of 95 projects all over the national territory (77 NGS and 18 animal models) for a total of over €1.7 million. In parallel to its own sources of funding and call for proposals, the FFRD has also been involved in providing information to the French rare diseases research community on several other funding opportunities both at the French level (nationally and regionally) and at the EU level (such as IMI, COST, FP7, DG SANCO funding programmes for instance).

(5) Develop new treatments

Following a national workshop organised at the *College de France* in July 2013 to enable scientists to share knowledge and experiences in the field of molecular screening of drug candidates, the FFRD launched its first dedicated call for projects in October 2013. A total of 15 high-flying projects are currently under selection, in collaboration with 5 dedicated technology platforms. In parallel, the FFRD actively engaged in anticipating the R&D needs of innovative diagnostic and therapeutic approaches. This led to the detection of 66 promising candidates in 2013, including new molecules, repurposed drugs and innovative medical devices. Guidance is provided at each step of development together with dedicated partners (IP experts, national and EU regulatory agencies, pharma/biotech, investment funds etc). As an example, a total of 10 procedures of orphan designation have been initiated in 2013 with the support of OrphanDev, a national network dedicated to methodological support to clinical studies. Similarly, 5 public-private partnerships were proposed in order to accelerate the pre-clinical and clinical development of academic proofs of concept opening the way to new therapeutic strategies. Finally, the FFRD initiated a think tank of pharmaceutical companies to start working on topics such as databases and registries from the perspective of private contributors, as well as orphan drug economics.

(6) Improve patients' care

As rare diseases scientific and clinical research is tightly linked to societal challenges, the FFRD has been actively promoting humanities and social sciences research. In December 2012, a first dedicated call for proposals was launched, in collaboration with the National Solidarity Fund for Autonomy ("*Caisse nationale de solidarité pour l'autonomie*" – CNSA) and the General Directorate for Health ("*Direction Générale de la Santé*" - DGS) to address three different areas: diagnostic pathway; ethical and societal impact of new technologies in the field of genetics; social, educational and professional integration of patients affected by a rare disease. FFRD regional coordinators supported connections between academic researchers, clinicians and patients' organisations. A total of 77 projects involving 188 research teams and 38 patients' organisations all over France were submitted to the assessment of 88 experts from both the rare diseases clinical and social/humanities fields. In 2013, €643 was allocated to 10 successful projects. The high demand encouraged renewing this call for proposals on an annual basis. At the end of 2013, a similar call for proposals was thus implemented and received 80 letters of intents (involving 257 research teams, 61 patients' organisations) that are currently under selection, with results expected for June 2014. Additionally, the FFRD has been initiating and driving boards of experts at the national levels in order to discuss essential updates, especially in the field of

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<sup>280</sup> More than a European sound box: capitalising on the added value of the European perspective in cancer treatment. JM Borrás, J Prades, J-M Bréchet, S Faithfull, A Trama, P G Casali. In: Boosting Innovation and Cooperation in European Cancer Control – Key Findings from the European partnership for Action Against Cancer (EPAAC), ed Jose M Martin-Morena, Tit Albrecht, Sandra Rados Krnel, Ljubljana 2013, pp 117-139.

patients' protection and information, including a reflection on a consensus document for informed consent for genetic testing, whose results have been invited to be presented at the national "*Assises de Génétique*" congress, bringing together clinicians, geneticists and all involved learned societies for an update on the clinical genetics developments in January 2014.

In parallel, the FFRD has been actively participating in national and international public health and research policies and frameworks. One main objective is to participate in and promote international collaborations. This includes raising awareness for acquainted international research policies and rare diseases researchers' access to the resulting opportunities, such as dedicated funding lines included in the H2020 programme, as well as an active commitment within international consortia such as E-rare and IRDiRC thereafter described. The FFRD also initiated an innovative cooperation programme with The World Academy of Sciences in order to promote rare diseases research collaborations with emerging countries. This led to the launch of a first joint call for proposals, targeting scientists from the wider Mediterranean and Middle-Eastern areas in October 2013. A total of 90 teams from 17 countries were involved in the submission of 19 international collaborative proposals dedicated to bring together the rare diseases research and clinical communities on key issues. Projects are under international selection, with results expected for the beginning of 2014.

In 2012, the ANR and the DGOS prepared a common call for proposals in translational research, which was launched at the beginning of 2013 (called "*Programme de recherche translationnelle en santé*" – PRTS, Programme for translational research in Health<sup>281</sup>). This call for proposals is not specifically for rare diseases. The first objective of this programme is to select and fund research projects at the interface between basic research projects currently funded by ANR and clinical research projects currently funded by PHRC.

In addition, some charities, private foundations or patient organisations provide funding for research, such as the AFM-Téléthon (French Muscular Dystrophy Association). In 2013, the AFM-Téléthon (which has been developing a variety of innovative therapeutic approaches over the past 25 years) and the *Fonds National d'Amorçage* (FNA) (which provides public funds towards innovative biotherapies and rare diseases thanks to the French "*Programme d'Investissements d'Avenir*") have moved closer to constitute the first seed fund dedicated to innovative biotherapies and rare diseases. This action forms part of an "*Environmental, Social and Governance*" process. With an initial endowment of €50 million, for a final target of €120 million, the fund aims to create a portfolio of 12 to 15 participants in companies at the seed stage. The amount invested will be between €3 and €10 million per company. The AFM-Téléthon has contributed to a budget of €30 million, and CDC Entreprise, via the FNA, has bestowed €20 million. The fund will target innovative SMEs with strong development potential that have been in existence for less than eight years. They must also follow standards that are consistent with the industrial development of therapies such as gene therapy, cell therapy, pharmacological modulation of gene expression, monoclonal antibodies, therapeutic proteins and immunotherapies.

### **E-Rare**

From April 2013, the French Foundation for Rare Diseases is in charge of the E-Rare 2 coordination on behalf of INSERM. France participated in the 5<sup>th</sup> Joint Transnational Call in 2013, with French teams participating in 9 out of the 12 consortia selected for funding. The E-Rare 2 consortium now brings together 18 ministries and funding national agencies from 15 countries to support projects in translational research on rare diseases across Europe and worldwide. In December 2013, the consortium launched its annual Joint Call 2014 on "innovative therapeutic approaches for rare diseases" with a budget of €13 million.

### **IRDiRC**

In 2013, the AFM-Téléthon (French Muscular Dystrophy Association), the French National Agency for Research (*Agence Nationale de la Recherche – ANR*), and *Lysogene* (all French-based organisations) were committed members of the International Rare Disease Research Consortium (IRDiRC). Since October 2012, the French Foundation for Rare Diseases has been actively involved, together with Orphanet, in the IRDiRC Scientific Secretariat<sup>282</sup>. At the end of 2013, French representatives were also involved in Scientific Committees: 2 members out of 11 were French in the Interdisciplinary Scientific Committee and 3 out of 17 in the Therapy Scientific Committee which was chaired by the French CEO of EURORDIS. In 2013, French scientists also took part in 10 of the 12 established IRDiRC Working Groups.

<sup>281</sup> [www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/](http://www.agence-nationale-recherche.fr/programmes-de-recherche/appel-detail/programme-de-recherche-translationnelle-en-sante-prts-2013/)

<sup>282</sup> In February 2014, the French Foundation for Rare Diseases joined them in IRDiRC as a funder member and a member of the Executive Committee.

## Orphan medicinal products<sup>283,284</sup>

### Orphan medicinal product incentives

Initiatives are in place to stimulate the development of orphan medicinal products: research support is provided through national funding programmes: the Hospital Clinical Research Programme (“PHRC”). As far as research support is concerned, the French Foundation for Rare Diseases also supported the identification of new molecules with opportunities to become new drugs, through the launch of a first high throughput molecular screening call in 2013 (results to be published mid-2014). It also brought support to research teams in the implementation of all relevant steps to move from a scientific hypothesis to a research protocol (orphan designation – in liaising with OrphanDev, study design, funding etc.).

### Specialised social services

On 31 May 2013, a Decree was published concerning the skills and qualifications required of those in charge of giving and coordinating therapeutic education of patients.

## 1.11. GERMANY<sup>285</sup>

### Definition of a rare disease

Stakeholders in Germany accept the European Regulation on Orphan Medicinal Products definition of a prevalence of not more than 5 in 10 000 individuals.

### National Plan of Action for People with Rare Diseases

In the German health care system every patient is entitled to complete health care coverage consisting of preventive, diagnostic, therapeutic and rehabilitative measures. The medical care of patients is generally of high quality and the access to medical doctors and specialists is on a high international standard.

In 2009, the German Federal Ministry of Health (BMG) published a research report entitled “Measures to improve health in people with rare diseases.” The goal of this study was, first, to analyse the care currently offered to persons with rare diseases in Germany and, second, to develop ways and means as well as concrete suggestions and solutions for improving their lot. The results of this research report pointed clearly to the need to improve the pluralistic health care system in Germany to include the prevention, diagnosis and therapy of rare diseases. In the process, the priority fields of action in the areas of the general care situation, specialised forms of care, diagnosis, therapy, exchange of information and experience as well as research, were identified. The report suggested that improvements would only be possible through the concerted efforts of existing initiatives and the establishment of common, coordinated and targeted actions of all involved.

To this end, in order to create this crucial prerequisite for improving the health situation in the area of rare diseases, on 8 March 2010 the National Action League for People with Rare Diseases (*Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen* (NAMSE)<sup>286</sup>) was founded at the behest of the German Federal Ministry of Health. Together with the German Federal Ministry for Education and Research (BMBF) and the Alliance of Chronic Rare Diseases (Allianz Chronischer Seltener Erkrankungen, ACHSE e.V.), NAMSE became a national council - a co-ordination and communication platform comprising all key bodies and organisations - responsible for coordinating and publishing the common efforts. The primary goal of NAMSE was to prepare suggestions for establishing a National Plan of Action for People with Rare Diseases by 2013 as well as supporting the establishment of national centres of expertise. All essential partners from the health care system involved with rare diseases (both central and umbrella organizations) were and still are

<sup>283</sup> This section has been written using the KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp45-49)

<sup>284</sup> This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (pp12-14)

<sup>285</sup> The German Federal Ministry of Health can only verify the information and data which concern federal responsibilities. The information provided here is illustrative and not exhaustive, and that it is validated by the ECEGRD/EUCERD Member State representative to the best of their knowledge.

<sup>286</sup> <http://namse.de/>

participants in the National Action League: the Federal Ministry of Health, the Federal Ministry of Education and Research, the Federal Ministry of Labour and Social Affairs, the Federal Ministry for Family Affairs, Senior Citizens, Women and Youth, the 16 Federal *Laender* (federal states), health insurance funds (sickness funds), associations of panel doctors, hospital associations, the Federal Joint Committee, medical societies, scientific societies, patient representatives, including the National Alliance for Rare Diseases “ACHSE”. NAMSE is coordinated in a joint effort by the Ministry of Health, the Ministry of Education and Research and ACHSE. By accepting the common declaration all members of NAMSE have reinforced their will to establish the necessary prerequisites to ensure a long-term and effective improvement in the health situation of persons with rare diseases. NAMSE consists of a Steering Committee. The Steering Committee in turn consists of the representatives from the 28 member partners of NAMSE. This committee sets the goals and defines the methods in accordance with the results of the research report. Thus, for the drafting of the National Plan of Action the four workgroups were founded to implement the four major action fields “information management,” “diagnostics,” “care/centres/networks” and “research.” Members of these workgroups were high-ranking experts from the respective fields.

One established goal is to contribute to implementing the Recommendation of the Council of the European Union. This includes the drafting of a National Action Plan for Rare Diseases and its implementation and monitoring, the coordination of measures for improving the health situation of persons with rare diseases, supporting the establishment of centres of expertise, initiating pilot projects and further action in the field of rare diseases, and assembling initiatives and making all actors involved cooperate in a coordinated and goal-orientated manner to put patients’ care first.

At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, the German National Plan of Action for People with Rare Diseases<sup>287</sup> was adopted in August 2013. A total of 52 policy proposals have been included in this plan covering 7 action fields. This publication of these policy proposals concludes the first phase of the National Plan of Action for People with Rare Diseases. Now begins the implementation and monitoring phase of the suggested proposals.

### Centres of expertise

The implementation of national centres of expertise in Germany is challenged by the decentralised, federal structure of the German health care system, since the provision of sufficient structural resources for health care is a matter solely concerning the *Laender* (federal states). German legislation provides the basis for the *Ambulante Spezialfachärztliche Versorgung* (highly specialised outpatient care) for a limited number of diseases (see below), some of which are rare. In order to improve further the care of complex diseases – in particular rare diseases – new opportunities were opened by the Act on Care Structures in the Statutory Health Insurance System (*GKV-Versorgungsstrukturgesetz – GKV-VStG*) that entered into force on 1 January 2012. It provides for the gradual establishment of a new specialist care sector aimed to achieve seamless care provision between outpatient and inpatient settings. Specifically, highly specialised outpatient care can now be provided by both hospitals and non-hospital doctors (office-based specialists) on a high level and at the same conditions in terms of quality and remuneration (Social Code V, Section 116b).

Highly specialised out-patient care comprises the diagnosis and management of complex, hard-to-treat diseases that require special qualifications, interdisciplinary co-operation and appropriate equipment. They include rare diseases and conditions with correspondingly low case numbers such as:

- tuberculosis
- cystic fibrosis
- haemophilia
- malformations, congenital skeletal abnormalities and neuromuscular conditions
- serious immunological disorders
- biliary cirrhosis
- primary sclerosing cholangitis
- Wilson's disease
- transsexualism
- caring for children with congenital metabolic disorders
- Marfan's syndrome
- pulmonary hypertension
- short bowel syndrome

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<sup>287</sup> <http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf>

- caring for pre- and post-transplant patients and for living organ donors

The sector of highly specialised outpatient care is organised by the Federal Joint Committee (*Gemeinsamer Bundesausschuss, G-BA*) that fleshes out the relevant legal provisions through binding guidelines. This includes, particularly, the specification of diseases, scope of treatment, technical resources and staff required for service provision as well as referral requirements and quality assurance measures. The Federal Joint Committee (*G-BA*) also can extend this list of diseases which has been stipulated by law (Social Code V, Section 116b).

The Federal Joint Committee (*G-BA*) is the supreme decision-making body of the so-called self-governing system of service providers and health insurance funds in Germany<sup>288</sup>. In the field of outpatient care for rare diseases provided by hospitals according to Social Code Book V, Section 116b, the Federal Joint Committee (*G-BA*) has to regulate both the structural and personnel resources needed for outpatient care provided by both hospitals and office-based specialists. Consequently, all of these service providers are subject to the same staffing, equipment and regulatory/contractual requirements as well as special measures for quality assurance. Basically, access is free for service providers that prove compliance with the applicable requirements.

From now on, the Federal Joint Committee (*G-BA*) will be able to broaden the catalogue of services and diseases in response to an application from one of its member organisations or the organisations on the Federal level that champion the interests of patients, also the self-help organisations of chronically ill and disabled persons. In addition to the so-called 'Section 116b centres', other centres like social-paediatric centres (Social Code V, Section 119) or university clinics for outpatient care (Social Code V, Section 117) may also be involved in the treatment of rare disease patients. This applies also to specialised ambulatory care offered by authorized physicians in hospitals.

Several self-appointed centres for rare diseases already exist in Germany<sup>289</sup>. However, these do not share a nation-wide concept and are not reviewed in respect of any specific quality criteria for rare diseases. NAMSE recommends the establishment of centres for rare diseases at three different, cross-linked levels of specialisation. These levels are not to differ in the quality of the care they provide, but only in the spectrum of services they offer. They are to be embedded in the local healthcare structures in both primary and specialist care. Some centres of expertise have a special role to play since, as reference centres, they are a fundamental component of a Europe-wide reference network for rare diseases, as called for in Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.

To facilitate the implementation of the three-tiered model of centres for rare diseases two actions were proposed by NAMSE. First existing funding options are to be used to ensure funding for the three-tiered structure of the centres for rare diseases. Once questions of funding and implementation have been resolved, it is recommended that the care providers implement the three-tiered model of NAMSE. Secondly a working group has been established in NAMSE by the steering committee to prepare the designation process for the three-tiered model of centres for rare diseases, taking into account the commonly agreed upon criteria published in the National Plan of Action. By now, a transparent preliminary procedure to designate the centres is under development by NAMSE.

The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner). The group decided in 2013 to continue the state-wide cooperation of these centres; to share the experiences of the centres, with particular emphasis on their coordinating functions in both the framework of the medical faculties and the administration of the university hospitals ; to share efforts to attain sustainability; to help patients with rare and very rare diseases, and their responsible physicians/experts or clinical departments, to find and use the best expertise available; to coordinate an application for financial support for clinical research; to share information on the participation of National or European institutions for research and clinical care in the field of rare diseases.

## Registries

In Germany there is presently no central coordinated registration of patients with rare diseases. Patient

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<sup>288</sup> Physicians, dentists, hospitals and health insurance funds are represented in the *G-BA*. Since 2004 national groups representing patients were given the right to file applications and to participate in the consultations of the *G-BA*. The *G-BA* issues the directives/binding guidelines that are necessary for safeguarding medical service provisions. The latter aims to ensure that medical services for persons ensured under the statutory health insurance in Germany are adequate, appropriate and efficient. The *G-BA* issues directives and thus determines the benefit package of the statutory health insurance (*gesetzliche Krankenversicherung, GKV*) covering about 70 million people. The *G-BA* is responsible for reimbursement decisions in the statutory health insurance (*GKV*).

<sup>289</sup> Listed in <http://www.orpha.net/national/DE-DE/index/zentren-für-se/>



registries for specific rare diseases are also seldom. Those that do exist often do not cover large geographic areas and are not uniform in their data structure or data safety.

NAMSE recommends to set up a web-portal of registries concerning rare diseases in Germany. This facilitates access to existing registries, for example, through a webportal – a “telephone book” of such registries as it were. This webportal could represent in the future the national interface to communicate with the European registry platform of the EU-Commission Joint Research Centre in Ispra. Further NAMSE recommends to develop a prototypical registry for a “Disease-Specific Registries of Rare Diseases”. This prototype – or individual software modules contained therein – should be adaptable for existing registries. A standardization of all existing registries is desirable.

Further NAMSE recommends a uniform coding scheme for all patients with rare diseases employing the Orpha diagnostic coding system in conjunction with ICD-10 GM and in anticipation of the publication of ICD-11. The German Federal Ministry of health supports a project to include Orphacodes into the current coding system of the ICD-10 GM to ensure that rare diseases are coded in health information systems.

There is no public central clinical trial registry dedicated solely to rare diseases. However the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) which is funded by the Federal Ministry of Education and Research (BMBF) aims at registering all trials performed in Germany, including those for rare diseases. All federal states are obliged to register cancers, including rare cancers, in existing population based cancer registries. An analysis based on the Orphanet database identifies about 80 registries, most of them belonging to academic institutions. Some of these registries are implicated in international networks or covers the whole European region.

German teams contribute to European registries such as CompERA-XL, CWS-SoTISaR, DOSAK, CEDATA-GPGE, EUROCAT, TREAT-NMD, EBAR, ENETS, EPICURE, EU-RHAB, EurIPFreg, EUROFA-EFACT, EHDN, EIMD, EurIPFnet, E-IMD, EURIPEDES, European Alport registry, EuroDSD, EUROSCA-R, EUTOS, Kids Lung Register, KINDLERNET, NCL-Registry, PODONET, Register for rare myeloproliferative neoplasms, RetDis Database, and RegiSCAR, and generally to clinicaltrials.eu.

### **Genetic testing and Newborn Screening Policy**

The Genetic Diagnosis Act (Gendiagnostikgesetz – GenDG) establishes the prerequisites for genetic testing, and genetic analysis conducted in the framework of genetic testing and stipulates requirements for the use of genetic samples and data. It applies to genetic testing and genetic analysis on born human beings as well as on embryos and fetuses during pregnancy and to the handling of the genetic samples and genetic data obtained in the process for medical purposes, to clarify parentage as well as the insurance sector and working life. It does not, however, apply to genetic testing and analysis and the handling of genetic samples and data inter alia for research purposes. The GenDG seeks to prevent discrimination based on genetic characteristics, to protect human dignity and the right to informational self-determination and aims at providing binding standards for good genetic testing practice.

Since 2005 there has been a mandatory legalised screening program covering fourteen conditions: phenylketonuria, biotinidase deficiency, galactosaemia, MCAD deficiency, VLCAD deficiency, LCHAD deficiency, CPT1, CPT2, CAT deficiencies, maple syrup urine disease, glutaric aciduria type 1, isovaleric acidemia, congenital adrenal hyperplasia and congenital hypothyroidism.

Newborn screening is a genetic test as defined in the GenDG. As such, it is subject to the exclusive right of medical professionals to practise medicine as well as the requirements for informed and written consent. The Federal Joint Committee - as the joint self-administration body representing health insurance funds, the medical profession and hospitals - specifies in a binding guideline the conduct of newborn screening and the diseases and conditions the screening for which is eligible for reimbursement by the statutory health insurance system.

Diagnostic tests are registered as available in Germany for 1880 genes and an estimated 2074 diseases in the Orphanet database<sup>290</sup>.

### **National alliances of patient organisations and patient representation**

In Germany, the German National Alliance for Chronic Rare Diseases (ACHSE) is a network of more than 100 patient organisations of people living with a specific rare disease. Through ACHSE, rare disease patient organisations support each other, exchanging know-how so as to strengthen their influence in the political

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<sup>290</sup> Information extracted from the Orphanet database (January 2014): this information is not verified by the German Federal Ministry of Health.

arena and improve the quality and duration of life of people living with a rare disease. ACHSE is an active member of EURORDIS and a member of its Council of National Alliances.

In Germany, health-related self-help groups and organisations are eligible for financial support from the statutory health insurance funds. A legislative reform (1 January 2009) has made access to funding easier and the distribution of the funding ear-marked by the statutory health insurance funds is guaranteed: this meant about €40 million in 2011.

The Ministry of Health currently supports different projects concerning the participation of patients with rare diseases at the Charité Berlin. One of these projects (2009 – 2011) dealt with the “Contribution of self-help groups/ patient organisations to the organisation of interfaces within the health care system”, aimed at improving patient participation and orientation. The Ministry of Health also supports other activities in the field of rare diseases such as conferences, brochures, workshops.

An important role is played in the regulation of the medical services of the German health care system by self-governing bodies such as patient associations: since 2004, national groups representing patients participate in the consultations of the Federal Joint Committee.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Germany***

The Orphanet portal on rare diseases is available in German<sup>291</sup> and is widely used as a major information source on rare diseases in Germany. Since 2001 there is a dedicated Orphanet team in Germany, currently hosted by the Human Genetics department of the Hannover Medical School (MHH). This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was officially designated as the Orphanet national team for Germany by the Federal Ministry of Health in 2010. In 2010, the Orphanet-Germany national website was launched<sup>292</sup>. This German language page is maintained by the Orphanet-Germany team and features information, news and events specific to field of rare diseases in Germany. Users can access the main Orphanet site in any of the five available languages, as usual, from this page.

Further, NAMSE recommends to set up a central and integrated information portal for rare diseases on the Internet with the focus on quality-assured knowledge for patients, their relatives and experts. An interactive map of all care-giving structures (se-atlas) is being developed as one part of the portal. The different care offers should be presented by the map and additional information on contact details of the professionals and institutions for the respective disease. [www.se-atlas.de](http://www.se-atlas.de)

#### ***Official information centre for rare diseases***

There is no official information centre on rare diseases in Germany.

#### ***Help line***

There is currently no official help line for rare diseases in Germany. NAMSE maintains that a hotline can become an important, low-threshold part of an internet-based information portal on rare diseases. NAMSE recommends setting up a pilot project to determine which target groups would make best use of such a hotline, what types of questions would most often be posed and what answers can best be delivered to these questions. This information would serve to determine the probable frequency and type of questions and how to plan to best meet these demands. A project (ZIPSE) funded by the Federal Ministry of Health concerning an information portal for rare diseases is going to examine the need for such a service. However, ACHSE offers a privately funded help line for people living with a rare disease since 2006 and answers about 600 to 800 requests per year. The help line is also open for professionals, but not often addressed by them. The help line is financed solely with donations and through charity events.

#### ***Other sources of information on rare diseases***

All medicinal products, including orphan medicinal products, are included in a database called PharmNet, run by the German Institute of Medical Documentation and Information (DIMDI) ensuring public access to package leaflet, summary of product characteristics (Fachinformation in German) and the assessment report (publicly accessible version).

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<sup>291</sup> [www.orphanet.de](http://www.orphanet.de)

<sup>292</sup> <http://www.orpha.net/national/DE-DE/index/startseite/>

On the first of January 2011 Section 42b AMG (Arzneimittelgesetz, Medicinal Products Law) came into force stipulating pharmaceutical companies and sponsors of clinical trials to report results of clinical trials to the federal higher authorities for purposes of publication in the public database PharmNet.Bund run by DIMDI<sup>293</sup>.

The ACHSE website<sup>294</sup> provides a platform for information on rare diseases. This platform is a validated and patient-orientated source of information. It encourages patient organisations to improve their information continuously. ACHSE has also established a help line to inform patients and their families in particular those without a diagnosis or an established patient organisation.

The KINDERNETZWERK<sup>295</sup> offers a service line for patients with rare diseases together with patient oriented online diseases descriptions. The KINDERNETZWERK additionally holds a database for registering parents with children suffering of rare diseases. Information on patient groups can also be found at the NAKOS website<sup>296</sup> (The National Clearing House for the Encouragement and Support of Self-Help Groups). Other non-rare disease specific help lines are available to help patients understand the health care system.

Beside the above mentioned internet information sources for rare diseases there exist several informational websites for rare diseases run by e.g. patient organisations, learned societies and university institutions. Some (genetic) diagnostic labs also offer information about tested diseases in detail. Several other internet databases are offering information on common diseases which imply also information on rare diseases: DermIS (www.dermis.net) an internet based information system for dermatology (recently public funded by the Federal Ministry of Education and Research, now private funding by Bayer Health Care), ONKODIN (www.onkodin.de) with focus on hematological diseases, public funding, www.patienten-information.de (www.patienten-informationen.de) of the ÄZQ (Agency for Quality in Medicine) – an initiative of the Bundesärztekammer (German Medical Association) and the Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians) and others. The University Rostock, Albrecht-Kossel-Institut for Neurodegeneration is hosting the data-base www.selteneerkrankungen.de, mainly focusing on rare neurogenerative diseases and the laboratories that are apparently qualified for diagnosis (Funding is unclear). There is also the Rare Metabolic Diseases Database which receives public funding from the German Federal Ministry of Education and Research, and is hosted by the Bielefeld University, Bioinformatics Department. It also represents a patient registry for rare metabolic diseases.

### Guidelines

For some rare diseases there exist practice clinical guidelines (i.e. cystic fibrosis, diagnostic of myopathy, congenital adrenal hyperplasia) from the AWMF (Association of the Scientific Medical Societies, *Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften*). In 2011 the Institute for Quality and Efficiency in Health Care (IQWiG) published a rapid report (V 10-01) concerning the question “What type of evidence is currently being considered in the development of clinical practice guidelines for rare diseases?”<sup>297</sup>.

### Training and education initiatives

Germany is elaborating a national catalogue of learning objectives for medicine for medical students. In this process criteria are being developed to integrate rare diseases in this catalogue to better incorporate them in basic medical training.

The Centre for Rare Diseases Tuebingen (University Hospital Tuebingen) provides continued education for physicians since April 2011. The program is called the German Academy for Further Medical Training on Rare Diseases (FAKSE). The goals of the academy were: to educate practice-based physicians and clinicians on the matter of rare diseases in an interdisciplinary and illustrative fashion; to raise awareness for these disorders and provide physicians with methodologies and “Red Flags” for better recognition of RD; and to bring physicians in contact with relevant experts and patient organisations. Throughout its first year, FAKSE organised four training courses and has already trained 250 physicians. Before and beside this programme there exist also other possibilities for continued education for physicians concerning rare diseases.

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<sup>293</sup> Protocol related data from clinical trials (<http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>), result related in the near future (<http://www.pharmnet-bund.de/dynamic/de/ergebnisberichte/index.htm>).

<sup>294</sup> [www.achse.info](http://www.achse.info)

<sup>295</sup> [www.Kindernetzwerk.de](http://www.Kindernetzwerk.de)

<sup>296</sup> [www.nakos.de](http://www.nakos.de)

<sup>297</sup> [https://www.iqwig.de/download/V10-01\\_Executive\\_Summary\\_Evidence\\_for\\_guidelines\\_on\\_rare\\_diseases.pdf](https://www.iqwig.de/download/V10-01_Executive_Summary_Evidence_for_guidelines_on_rare_diseases.pdf)

### **National rare disease events in 2013**

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

To mark Rare Disease Day 2013 a number of events were held across Germany to raise awareness of rare diseases in Berlin, Bielefeld, Dessau, Essen, Flensburg, Hamburg, Cologne, Münster, Nuremberg and Würzburg. The events included information stands and fairs, press conferences and balloon campaigns. Hospitals, medical professionals, health insurers and celebrities joined the cause to raise public awareness of rare diseases. In addition, the annual Eva Luise Köhler Research Prize for Rare Diseases was awarded in Berlin.

The ACHSE-Central Prize for Patient-Centered Care (ACHSE-Central Versorgungspreis) was awarded in Düsseldorf on 26 June 2013.

The Innovation-Congress “Rare heroes – Orphan Drugs and Rare Diseases in Germany” (Innovationskongress “Seltene Helden – Orphan Drugs und Seltene Erkrankungen in Deutschland) was held on 13 October 2013 by the Institute for Health and Social Research - IGES, Berlin

The Workshop “Registries for patients with undiagnosed Rare Diseases” was held on 21 November 2013 by Reseach for Rare (Research Networks sponsored by BMBF), TMF e.V. and ACHSE e.V.

### **Hosted rare disease events in 2013**

Amongst the events hosted in Germany and announced in *OrphaNews Europe* was the LeukoTreat Final Public Conference (3-6 July 2013, Berlin).

### **Research activities and E-Rare partnership**

#### ***National research activities***

In 2003, the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) funded ten networks of national academic groups, clinical centres, specialised laboratories and patients organisations for basic and clinical research for an initial three years. After a successful interim evaluation, nine of the networks for rare diseases were funded for another two years. The budget of this rare disease research programme was €31 million.

In 2007, the BMBF opened a new funding programme on rare diseases research with a substantial increase in budget to €24 million for the first 3 year period and a possible extension of the maximum funding duration of 3 times renewable 3 year periods for new networks. Starting in October 2008, 16 networks were funded for 3 years. In 2010, the networks have been granted €6 million additional funds for investments in shared research equipment, most notably next generation sequencing. In September 2010, a new call for proposals for the possible extension of previously funded networks and the creation of new networks was published. After the evaluation of 39 proposals by a review board of international rare disease experts, the BMBF is currently funding 12 research consortia since 2012 with more than €23million for three years.

Additional funding of rare disease research is ongoing in other funding initiatives of the BMBF such as the National Genome Research Network (NGFN), Innovative Therapies, Regenerative Medicine, Molecular Diagnostics, Clinical Trials and others with about €20 million in 2013. All these activities are funded within the framework programme “Health research”. In co-operation with the Federal Ministry of Health, the BMBF assumes responsibility for the programme which is financed with funds from the BMBF. The support of RD research continues to be an important topic within this framework programme.

In 2013, the BMBF has commissioned a survey to collect information on funded research projects in Germany. The results are expected for summer 2014 and will be taken into account for the strategic development of future RD research funding.

The *Eva Luise und Horst Köhler Stiftung für Menschen mit Seltenen Erkrankungen*, a foundation of the former First Lady and the former president of the Federal Republic of Germany, is dedicated to patients with rare diseases and supports research projects into rare diseases annually since 2006.

Regional sources of funding are also available.

#### ***Participation in European research projects***

Teams in Germany participate/have participated in 182 projects related to rare diseases and coordinated 57 projects.

### **E-Rare**

Germany is a partner of the E-Rare project, represented by the *BMBF* and the Project Management Agency of the German Aerospace Centre (*PT-DLR*). Germany participated in the E-Rare joint transnational calls in 2007, 2009, 2011 and 2012 and funds the participating German research groups of 45 transnational research projects with a total of about €13 million. Germany participated in the 5<sup>th</sup> Joint Transnational Call in 2013 with German research groups participating in 8 of the 12 projects selected for funding with about € 2.8 million.

### **IRDiRC**

The Federal Ministry of Education and Research (*BMBF*) is a committed member of IRDiRC.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

No specific information reported.

#### ***Orphan medicinal product market availability situation***

No specific information reported.

#### ***Orphan medicinal product pricing policy***

All orphan medicinal products are reimbursed directly after market authorisation. As the German maximum reimbursement prices scheme (*Festbeträge*) normally does not cover orphan medicinal products. Only generic products and those considered to belong to the same pharmacological or therapeutic group can be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, for every new drug with a new active substance a binding ex-factory price based on the added value of the drug has to be negotiated on Federal Level. This is carried out by the Federal Association of Sickness Funds and the manufacturer. If no agreement can be achieved, the price is set by arbitrage committee, in which both contract parties are represented. For the first 12 months following marketing authorisation each new drug is still reimbursed at the full price set by the manufacturer. Mandatory Price Negotiations have been introduced by the Act for the New Order for the Drug Market in Social Health Insurance (*AMNOG*). According to this law, previous to price negotiations the value of the drug is evaluated. The manufacturer issues a Dossier when they enter the market. It is assessed by the German Institute for Quality and Efficiency in Health Care (*IQWiG*). The Federal Joint Committee (*G-BA*) appraises and decides on the added value of the drug compared to standard therapy. Orphan medicinal products authorised by EMA under EU-regulation 141/2000 with an annual turnover below €50 million are exempted from the benefit assessment, because the benefit is taken as granted. Still, price negotiations are mandatory also for these drugs.

#### ***Orphan medicinal product reimbursement policy***

Once authorised at European level, all orphan medicinal products are fully reimbursed by the statutory health insurance (*GKV*). Until 31 December 2010, all newly authorised drugs could be put on the marketplace without any restrictions on reimbursed prices. Only generic products and those considered to belong to the same pharmacological or therapeutic group could be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, the act on new regulations for the drug-market (*AMNOG*) is mandating that all drugs with patented substances are subject to a cost/benefit analysis followed by a price negotiation. However, while this procedure that is limited to 12 months following marketing authorisation, is running, the product is still reimbursed at the price set by the manufacturer.

#### ***Other initiatives to improve access to orphan medicinal products***

Irrespective of the prevalence of the disease, the off-label use of drugs is reimbursed by the statutory health insurance (*GKV*) on the following conditions: the drug will be used to treat a life-threatening or fatal disease; there is an absence of pharmaceutical therapy with a marketing authorisation in Germany; and there is scientific evidence of positive therapeutic effects<sup>298</sup>.

In Germany, as in many other European countries, it has been basically possible to administer promising medicinal products for severely ill patients before authorisation in case no alternatives exist. In 2005, on the basis of Art. 83 of the Regulation (EC) No 726/2004 the German government implemented general rules providing such medicinal products in form of so-called Compassionate Use Programmes in Section 21 sub-section 2 no. 6 of the German Medicinal Products Act. In 2009 it was added that the provision of a medicinal

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<sup>298</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011)

product in such cases has to be free of charge. An ordinance, coming into force 2010, contains special regulations for the proper procedure of Compassionate Use Programmes. An overview on Compassionate Use Programmes confirmed by the Federal Institute for Drugs and Medical Devices (BfArM) is available on the website<sup>299</sup>. Once authorised, all orphan medicinal products are fully reimbursed by statutory health insurance.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Orphan devices**

No specific information reported.

#### **Specialised social services**

No specific activity reported.

## **RARE DISEASE ACTIVITIES IN 2013 IN GERMANY**

### **National Plan of Action for People with Rare Diseases**

At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, the German National Plan of Action for People with Rare Diseases<sup>300</sup> was adopted in August 2013. A total of 52 policy proposals have been included in this plan covering 7 action fields. This publication of these policy proposals concludes the first phase of the National Plan of Action for People with Rare Diseases. Now begins the implementation and monitoring phase of the suggested proposals.

### **Centres of expertise**

To facilitate the implementation of the three-tiered model of centres for rare diseases two actions were proposed by NAMSE. First existing funding options are to be used to ensure funding for the three-tiered structure of the centres for rare diseases. Once questions of funding and implementation have been resolved, it is recommended that the care providers implement the three-tiered model of NAMSE. Secondly a working group has been established in NAMSE by the steering committee to prepare the designation process for the three-tiered model of centres for rare diseases, taking into account the commonly agreed upon criteria published in the National Plan of Action. By now, a transparent preliminary procedure to designate the centres is under development by NAMSE.

The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner). The group decided in 2013 to continue the state-wide cooperation of these centres; to share the experiences of the centres, with particular emphasis on their coordinating functions in both the framework of the medical faculties and the administration of the university hospitals ; to share efforts to attain sustainability; to help patients with rare and very rare diseases, and their responsible physicians/experts or clinical departments, to find and use the best expertise available; to coordinate an application for financial support for clinical research; to share information on the participation of National or European institutions for research and clinical care in the field of rare diseases.

### **Registries**

NAMSE recommends to set up a web-portal of registries concerning rare diseases in Germany. This facilitates access to existing registries, for example, through a webportal – a “telephone book” of such registries as it were. This webportal could represent in the future the national interface to communicate with the European registry platform of the EU-Commission Joint Research Centre in Ispra. Further NAMSE recommends to develop a prototypical registry for a “Disease-Specific Registries of Rare Diseases”. This prototype – or individual software modules contained therein – should be adaptable for existing registries. A standardization of all existing registries is desirable.

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<sup>299</sup> [www.bfarm.de](http://www.bfarm.de)

<sup>300</sup> <http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf>

Further NAMSE recommends a uniform coding scheme for all patients with rare diseases employing the Orpha diagnostic coding system in conjunction with ICD-10 GM and in anticipation of the publication of ICD-11. The German Federal Ministry of health supports a project to include Orphacodes into the current coding system of the ICD-10 GM to ensure that rare diseases are coded in health information systems.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Germany***

NAMSE recommends to set up a central and integrated information portal for rare diseases on the Internet with the focus on quality-assured knowledge for patients, their relatives and experts. An interactive map of all care-giving structures (se-atlas) is being developed as one part of the portal. The different care offers should be presented by the map and additional information on contact details of the professionals and institutions for the respective disease. [www.se-atlas.de](http://www.se-atlas.de)

#### ***Help line***

NAMSE maintains that a hotline can become an important, low-threshold part of an internet-based information portal on rare diseases. NAMSE recommends setting up a pilot project to determine which target groups would make best use of such a hotline, what types of questions would most often be posed and what answers can best be delivered to these questions. This information would serve to determine the probable frequency and type of questions and how to plan to best meet these demands. A project (ZIPSE) funded by the Federal Ministry of Health concerning an information portal for rare diseases is going to examine the need for such a service.

### **Training and education initiatives**

Germany is elaborating a national catalogue of learning objectives for medicine for medical students. In this process criteria are being developed to integrate rare diseases in this catalogue to better incorporate them in basic medical training.

### **National rare disease events in 2013**

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

To mark Rare Disease Day 2013 a number of events were held across Germany to raise awareness of rare diseases in Berlin, Bielefeld, Dessau, Essen, Flensburg, Hamburg, Cologne, Münster, Nuremberg and Würzburg. The events included information stands and fairs, press conferences and balloon campaigns. Hospitals, medical professionals, health insurers and celebrities joined the cause to raise public awareness of rare diseases. In addition, the annual Eva Luise Köhler Research Prize for Rare Diseases was awarded in Berlin.

The ACHSE-Central Prize for Patient-Centered Care (ACHSE-Central Versorgungspreis) was awarded in Düsseldorf on 26 June 2013.

The Innovation-Congress “Rare heroes – Orphan Drugs and Rare Diseases in Germany” (Innovationskongress “Seltene Helden – Orphan Drugs und Seltene Erkrankungen in Deutschland) was held on 13 October 2013 by the Institute for Health and Social Research - IGES, Berlin

The Workshop “Registries for patients with undiagnosed Rare Diseases” was held on 21 November 2013 by Reseach for Rare (Research Networks sponsored by BMBF), TMF e.V. and ACHSE e.V.

### **Hosted rare disease events in 2013**

Amongst the events hosted in Germany and announced in *OrphaNews Europe* was the LeukoTreat Final Public Conference (3-6 July 2013, Berlin).

### **Research activities and E-Rare partnership**

#### ***National research activities***

Additional funding of rare disease research is ongoing in other funding initiatives of the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) such as the National Genome Research Network (NGFN), Innovative Therapies, Regenerative Medicine, Molecular Diagnostics, Clinical Trials

and others with about €20 million in 2013. All these activities are funded within the framework programme “Health research”. In co-operation with the Federal Ministry of Health, the *BMBF* assumes responsibility for the programme which is financed with funds from the *BMBF*. The support of RD research continues to be an important topic within this framework programme.

In 2013, the *BMBF* has commissioned a survey to collect information on funded research projects in Germany. The results are expected for summer 2014 and will be taken into account for the strategic development of future RD research funding.

#### **E-Rare**

Germany participated in the 5<sup>th</sup> Joint Transnational Call in 2013 with German research groups participating in 8 of the 12 projects selected for funding with about € 2.8 million.

## **1.12. GREECE**

### **Definition of a rare disease**

The definition of a rare disease in Greece is that of the EU Regulation on Orphan Medicinal Products (i.e. a disease is considered to be rare when it affects no more than 1 person per 2 000).

### **National plan/strategy for rare diseases and related actions**

A commission composed of government officials, health professionals and patient representatives was formed in 2007 following requests by the Greek Alliance for Rare Diseases (PESPA) to help draft the Greek National Plan for Rare Diseases. PESPA members presented a draft to the Committee, which was then modified by officials of the Greek Ministry of Health to the format of the current Plan. An outline for this National Plan of Action for Rare Diseases (to run over the period 2008-2012<sup>301</sup>) was presented by the Greek Minister for Health in February 2008: this document identified and outlined eight strategic priorities:

- Acknowledgement of the specificity of rare diseases (registration on the list of chronic long-term disorders),
- Increase the knowledge of the epidemiology of rare diseases and establish a National Registry of Rare Disorders,
- Develop information for patients, health professionals and the general public concerning rare diseases,
- Upgrade services for diagnosis, therapy and rehabilitation of rare diseases patients (training for health care professionals to improve diagnosis and access to quality health care),
- Organise screening and access to diagnostic tests,
- Promote research and innovation regarding rare diseases and specifically effective new therapies,
- Respond to the specific needs of people living with rare diseases,
- Generation of an integrated platform for action in the field of rare diseases at a national level and the development of European partnerships.

The provisions of the Greek National Plan for Rare Diseases (2008-2012) were discussed in detail during the Greek National Conference on Rare Diseases<sup>302</sup> co-organised by the Greek Alliance for Rare Diseases (PESPA) and EURORDIS, - in Athens (26-27 November 2010) in the framework of the Europlan project. The priorities listed during the conference included: the need for a legal framework of the National plan and a steering committee, the need for a policy to establish centres of expertise, the need to complete the map of diagnostic laboratories, the need to establish universal access to orphan medicinal products, the need to officially recognise the specialty of Clinical and Laboratory Genetics, the need to fully reimburse diagnostic tests (including molecular diagnosis), the need for therapy and rehabilitation, the need for price adjustment of orphan medicinal products in order to continue to be available in the Greek market, the need for funding of rare disease research and the need for more information on rare diseases in Greek.

<sup>301</sup> [http://www.ygeianet.gov.gr/HealthMapUploads/Files/SPANIES\\_PATHISEIS\\_TELIKO\\_LOW.pdf](http://www.ygeianet.gov.gr/HealthMapUploads/Files/SPANIES_PATHISEIS_TELIKO_LOW.pdf)

<sup>302</sup> [http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/FINAL%20Report%20Greece%20EUROPLAN%202010.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report%20Greece%20EUROPLAN%202010.pdf) (accessed 05/06/2014)



Although an initial estimate for the budget required was made, no funding has been officially allocated to the National Plan of Action for Rare Diseases, and none of the eight strategic priority actions have yet started. As of yet, there is no legal framework for the Plan so no progress has been made.

In fact, most of the objectives of the proposed nation plan of action for RD are or could be incorporated in the existing structure and function of Greek national health system (GNHS). Implementation of strategic priorities for RD is coordinated by the Ministry of Health and mainly by the Hellenic Centre of Disease Control and Prevention (KEELPNO) - alongside their official role in surveying and prevention of common and rare diseases.

In 2010 the Advisory Scientific Committee for Rare Diseases appointed by KEELPNO together with the office for RD of KEELPNO started to implement the main priorities of national plan for RD defined in the scope of the Europlan project that are incorporated in the Greek NHS. The program started in 2011 with two main objectives: i) to develop a national registry of rare diseases and ii) to identify the expertise centres (CEs) involved in the care of patients with rare diseases, within the Greek National Health System (NHS).

The Second EUROPLAN Conference<sup>303</sup>, organised by the Greek Alliance for Rare Diseases, on 1 December 2012, was met with great success, with the acceptance and active participation of all the involved stakeholders, as well as an impressive attendance by patients from all over the country. The conference was organised by PESPA with the support of EURORDIS, and was held under the auspices of His Excellency, the President of the Hellenic Republic, Mr. Karolos Papoulias. During the Conference, four working groups were created, in which various stakeholders from EOF, KEELPNO, IFET, SFEE, as well as patients, participated. The principle subjects worked upon were predetermined by the EUROPLAN program: Patients' Access to their Diagnosis and Medical/Pharmaceutical Care; Social Security Rights for Patients with Rare Diseases; Reference Centres for Rare Disease; and Rare Diseases Registries in Greece. The results of the working groups focused on present-day problems for Greek patients with rare diseases, changes that need to be made, as well as new suggestions, shaping a complete plan of action for rare diseases, which will form the basis of the final report that will be sent from Greece to the European Parliament.

In November 2012 a Steering Committee for Rare Diseases was appointed by the General Secretary of the Ministry of Health to review and supplement the plan proposed during the Europlan meeting in 2010 and submit it to the Ministry for discussion, adoption and implementation. This Committee was recently replaced by another one which has not yet started work.

To place these developments in context, health services already provided by Greek National Health System (NHS) can be classified in two main types. The first covers children and adolescents aged 0-19 years old and the second adults and older patients (over 20 years old). In the first type, primary health care is provided by family pediatricians and in the second by internists and physicians with basic specialties in Internal Medicine. For patients with life threatening disease and chronic debilitating diseases, such as rare diseases, hospital care is provided in two levels: for children and adolescents in paediatric clinics of rural hospitals for common and non severe diseases and University Departments of Paediatrics and Children Hospitals operating divisions of pediatric specialties, subspecialties, special reference units and basic and research laboratories. For adults and older patients' hospital care is provided in general regional hospitals and in University Hospitals and Referral General Hospitals with departments, divisions and special referral units, supported by routine and specialised research laboratories.

In both branches of Greece's NHS the care of patients with rare diseases is multidisciplinary and homogeneous to that of patients with relative common diseases of similar pathogenesis.

Special units in Research Institutes and private laboratories contribute to pre- and post- natal diagnosis for a number of rare diseases.

Other national actions related to rare diseases include:

- The National Programme for haemoglobinopathies (covering thalassaemia and sickle cell diseases) which includes carrier detection, prenatal diagnosis, patient diagnosis and therapy. This Programme is split into two areas, a prevention programme organised in the late 1970s and implemented in the 1980s, and a treatment programme implemented gradually in the 1970s
- The National Neonatal Screening Program that covers approximately 98% of the neonates born in Greece ,is provided for free by the Institute of Child Health and covers four diseases, namely: PKU,G6PD,Galactosemia and congenital Hypothyroidism

<sup>303</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-greece.pdf>

### Centres of expertise

Within the national health system special units providing expert services for groups of a limited number of diseases including specific rare diseases/groups of rare diseases have been organised during the past few decades. The Hellenic Centre for Disease Control and Prevention (KEELPNO) started to collect data on the nature and activities of these units and aimed to complete collection in 2012. Greece is working to provide better access to treatment for rare disorders, including the accreditation and creation of centres of expertise for rare disorders.

By the end of the 2011 the multidisciplinary centres of expertise (basically day care clinics) for the management of thalassemia, cystic fibrosis, neuromuscular disorders, hereditary bleeding diseases and primary immunodeficiencies were properly identified as follows:

- Thalassemia: 15 centres
- Cystic Fibrosis: 3 centres
- Neuromuscular Diseases: 6 centres
- Hereditary Bleeding disorders: 4 centres
- Primary immunodeficiency: 2 centres

These centres of expertise collaborate with the following expert laboratories and centres such as:

- The Laboratory of Medical Genetics of the University of Athens, "Agia Sophia" Children Hospital, for the molecular pre and post natal diagnosis of thalassemia, cystic fibrosis, and neuromuscular diseases; it also serves as national reference laboratory for a number of genetic diseases.
- The Units of Neurogenetics and Muscle Pathology of the 1<sup>st</sup> Department of Neurology, Athens University serving also as a National Reference Laboratory.
- The Institute of Child Health (Athens) for the laboratory diagnosis of Inborn Errors of Metabolism
- National Thalassemia Centre covering 60-70% of prenatal diagnosis of thalassemia. This was nominated (2012) as a Reference Centre for the Prevention of Thalassemia and Sickle Cell Disease" (Laikon General Hospital, Athens).
- The Melanoma Reference Centre, Department of Plastic Surgery (Gennimatas General Hospital of Athens – 2012).

(According to the National Health System (ESY) Act, one or more Public Hospitals in the country can be nominated as "Specialised Centres" involved in the provision of specific care in special areas of medicine and nursing, According to the procedure the Central Council of Health (KESY) reviews the applications and forwards a proposal to The Minister of Health. The terms and conditions governing the operation of such centres are established by case, and the existing framework is very general and vague. The criteria that should be employed in the recognition of such centres are not specified; nonetheless a number of "Specialised Reference Centres" have been nominated as such .

However, a number of clinics/laboratories in Greece, despite the fact that they may not have an "official status" as "Reference Centres", offer highly specialised services in the field of rare diseases. Therefore, in fact they act as "Reference Centres" for their respective activities (see above listing).

### Registries

There is currently no national registry for rare diseases in Greece. One of the main tasks of the KEELPNO and the new steering committee for rare diseases is to set up a national registry, according to the international standards. A pilot registry which started in 2011 is in progress. Creation of a registry for Registries to collect all available RD registries in Greece was discussed at the second Europlan conference in 2012. KEELPNO proposed to undertake this task.

In the absence of a national registry for rare diseases, scientific societies covering rare diseases, appointed working groups which, in collaboration with respective centres of expertise and patients organisations, have created "registries" for a number of rare diseases. These registries do not receive national financing. Greek teams contribute to the European registries EUROCARE CF, EIMD AND EUROGLYCANET.

### Neonatal screening policy

Neonatal screening covering around 98% of neonates in Greece and is provided by the Institute of Child Health, Athens, for congenital hypothyroidism, phenylketonuria, G6PD deficiency and galactosaemia. Recently, the neonatal screening is expanding in the private sector covering a number of inborn errors of metabolism, cystic fibrosis, adrenal hyperplasia and biotin deficiency, as well as screening for the early diagnosis and treatment of congenital deafness. Data on the extended neonatal screening program in regard to efficacy and neonatal

population coverage are not yet available. A Ministerial Decision for the standardisation of the process of Development of Implementation of the NBS was released in 2012.

### **Genetic testing**

Genetic testing is carried out in several laboratories specialising in the diagnosis of different rare diseases. There are neither official reference laboratories nor guidelines. Tests are reimbursed through insurance (public and private) schemes; genetic testing is possible abroad as well. Genetic tests provided by special laboratories of the Greek NHS fulfil European guidelines.

Diagnostic tests are registered as available in Greece for 125 genes and for an estimated number of 201 diseases in the Orphanet database<sup>304</sup>.

### **National alliances of patient organisations and patient representation**

PESPA is an umbrella non-profit organisation established in 2003, by health professionals and presidents of 20 rare disease patient associations (national or regional) with the help of EURORDIS. PESPA organises events for Rare Disease Day.

In 2012 PESPA organised the Europlan 2 conference and created a "Medical Support Fund for financially frail patients with Rare Diseases" to support in the current economic context families when they cannot receive support from their insurer.

In Greece, numerous national ("Pan-Hellenic") patient organisations exist mainly for the more prevalent rare diseases. They have their own websites and are members of the relevant International and European federations. The Hellenic Thalassaemia Federation, the Association of Patients with Haemophilia, the MDA Hellas and the Society of Cystic Fibrosis, ARTEMIS Association on Histiocytosis, Gaucher and other Lysosomal Diseases Association are some examples. In addition to national, there is also a considerable number of patients and parent/patient associations for rare diseases that autonomously organise their activities and conferences.

Alliances of friends of patients with rare diseases or group of rare diseases also exist. Few of them as the association of Friends of Children with Cancer "Elpida" and "Floga", MDA Hellas, Friends Association of Children with Chronic Rheumatoid Diseases are amongst the organisations which provide funding for the organisation and functioning of centres of expertise. Elpida run the donation of "The Paediatric Oncology Unit Marianna Vardinoyiannis –Elpida to the "Aghia Sophia" Children's Hospital. This modern and well-equipped wing, for the multidisciplinary care of children and adolescents with cancer has a capacity of 126 beds and started operating in 2011.

There are currently no public funding schemes to officially support RD patient organisations activities in Greece. However, in Greece, like most other NGO organisations, many RD, patients and parents clubs may receive several types of funding.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Greece***

Since 2004 there is a dedicated Orphanet team in Greece, currently hosted by the Institute of Child Health (Departments of Genetics (2009) and Enzymology/Cellular Function (2012). The team was designated as the Greek national Orphanet team by the Ministry for Health in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in the country for entry into the Orphanet database. A translation of Orphanet abstracts into Greek was initiated in 2013. Greece participates in the Orphanet Joint Action. The Orphanet Greece national website in Greek was launched in 2011<sup>305</sup>.

In 2013 Orphanet became the official database and contact point for rare diseases, operating as the National Contact Point foreseen in the implementation of the EU Cross-Border Healthcare Directive.

#### ***Official information centre for rare diseases***

There is no other official information centre for rare diseases in Greece apart from Orphanet

<sup>304</sup> Information extracted from the Orphanet database January 2014.

<sup>305</sup> <http://www.orpha.net/national/GR-EL/index/%CE%B1%CF%81%CF%87%CE%B9%CE%BA%CE%AE-%CF%83%CE%B5%CE%BB%CE%AF%CE%B4%CE%B1/>

### **Help line**

There is no official government-supported help line for rare disease information in Greece; some services, mainly voluntarily are offered by PESPA's members who provide psychological support and a wide range of general information to patients and families.

### **Other sources of information**

The websites of PESPA, Institute of Child Health, KEELPNO, ORPHANET, scientific and patient societies and associations for RDs offer information on rare diseases and a list of some rare diseases in Greek. Every specialised unit produces information leaflets for the disease(s) of its expertise. Some units and physicians with special interests in rare/orphan diseases use to distribute leaflets in foreign languages issued by relevant overseas organisations.

### **Guidelines**

Some scientific societies have published or renewed guidelines for specific rare diseases in local professional journals. All centres with expertise in rare diseases follow the international guidelines. There are national guidelines for thalassaemia.

### **Training and education initiatives**

Rare diseases is a topic included in the general curriculum of undergraduate and postgraduate studies of Medical Schools in Greece and is basically addressed in the training for specialities and sub-specialities in Paediatrics and Internal Medicine. Scientific societies also organise courses and workshops in order to educate physicians, nurses and students on specific rare diseases.

### **National rare disease events in 2013**

The Greek Alliance for Rare Diseases (PESPA) organised a series of events to mark Rare Disease Day 2013 including a series of speeches regarding the subject: "Rare Disorders Without Borders", at the Eugenides Foundation, from selected scientists and patients, the distribution of printed material in various focal points, the creation and screening of a TV advert on a variety of TV stations, throughout February 2013, culminating on Rare Disease Day (28 February 2013) with the organisation of various events including the events organised by the patient association members of PESPA, an event with PESPA members at the Acropolis Museum, an event with patient organisations at Zapeio, and press releases. KEELPNO organised a one day event entitled: "Rare Diseases: the Greek reality" in order to inform scientists, health professionals and patients on the initiatives regarding rare diseases in the country

### **Hosted rare disease events in 2013**

No events reported.

### **Research activities and E-Rare partnership**

#### **National research activities**

The GSRT / General Secretariat for Research and Technology (currently supervised by the Ministry of Education) has been funding research projects coping with all aspects of rare diseases (rare cancers included) in the framework of "biomedical research" in the past. However, there are no specific programmes for rare disease research and thus, it is not easy to determine funding allocated to rare diseases research only.

#### **Participation in European research projects**

Teams from Greece have participated/participate in 19 FP7 projects related to rare diseases and are coordinating team for two such projects.

#### **E-Rare**

Greece, through GSRT, participated in the 2<sup>nd</sup> Joint Transnational Call of E-Rare-1. In this context, one project coordinated by a Greek team (with a total funding of around €262,000) was approved following peer-review evaluation and it is in progress. Greece currently participates in E-Rare-2, and is represented by two institutions namely GSRT and KEELPNO. GSRT participated in the 3<sup>rd</sup> Joint Transnational Call launched in 2011 with the amount of €200 000: two Greek teams were approved for funding after evaluation of the call. Greece did not participate in the 4<sup>th</sup> Joint Transnational Call (2012) nor in the 5<sup>th</sup> Joint Transnational Call (2013).

### **IRDiRC**

The GSRT as a member of the E-Rare group of funders joined the IRDiRC in 2012.

### **Orphan medicinal products**

The Greek National Organisation for Medicines (EOF<sup>306</sup>) ensures the public health and safety of all medicinal products, including orphan medicinal products. Orphan medicinal products that are not marketed in Greece are imported by the Greek Institute of Pharmaceutical Research and Technology (IFET), and transferred to the patients requiring these drugs. A procedure for the compassionate use of orphan medicinal products (OMP) is in place.

### **Orphan medicinal product committee**

No specific committee exists on orphan products at the moment.

### **Orphan medicinal product incentives**

No specific information reported.

### **Orphan medicinal product market availability situation**

Access to orphan medicinal products for patients with rare diseases is ensured by the State.

Orphan medicinal products authorised by the EMA are officially certified by the EOF (National Organisation for Medicines), before launched on the market after the blue box is issued by EOF. Orphan medicinal products authorised by the EMA or FDA but not launched in Greece (not included in price bulletin) can be imported through IFET (Institute of Pharmaceutical Research and Technology) if prescribed by a doctor and approved by EOF. This process provides access to any medicinal product orphan or not, for any individual patient according to doctor's prescription.

The following orphan medicinal products are available in the market of Greece being authorized /priced by EOF: Adcetrin, Arzerra, Atriance, Bosulif, Dacogen, Cyaston, Elprase, Evoltra, Exjade, Firazyf, Gliolan, Increlex, Inovelon, Jakavi, Lysodren, Mepact, Mozobil, Myozyme, Nexavar, Nplate, Peyona, Prialt, Revatio, Revestive, Revlimid, Savene, Signifor, Siklos, Sprycel, Tassigna, Thalidomide/Celge, Tobi Rodhaler, Torisel, Tracleer, Vidaza, Volibris, Votubia, Vpriv, Vyndaqel, Xagrid, Yondelis, Zavesca.

The following orphan medicinal products being authorized as such by FDA or EMA and officially certified by EOF but not included in the price bulletin are distributed via IFET: Adagen, Alkeran (for injection), Ammonul, Cafcit, Carbaglu, Cometriq, Cyanokit, Cystadane, Cystagon, Diacomit, Depocyt, Desmopressin Acetate, Digibind, Elmiron, Espbriet, Firdapsi, Flolan, Folutyn, Galsulfase, Galzin, Iclusig, Kalydeco, Kuvan, Litak, Leukine, Lidoderm Patch, Lioresal Intrathecal, Litak, Mycobutin, Mylotarg, Naglazyme, Oncaspar, Ontak, Orfadin, Para-amino salicylic acid, Paser Granules, Pedeia, Prolastin, Riastap, Rifadin I.V., Soliris, Sulfamylon Solution, Syprine, Tepadine, Thiola, Treanda, Vumon For Injection, Wilzin, Xenazine, Zolinza

The following medicinal products are also available for the treatment of rare diseases although not currently carrying the orphan status: Aldurazyme, Busilvex, Cerezyme, Fabrazyme, Glivec, Replagal, Revolade, Somavert, Sutent, Trisenox, Ventavis

There is currently a concern and anxiety of patients with rare diseases for the delay to the access to new medicines after authorisation because the pricing procedure after a medicine is given orphan drug status follows the same way with all other medicines without prioritisation.

### **Orphan medicinal product pricing policy**

No specific information reported.

### **Orphan medicinal product reimbursement policy**

Practically, all orphan drugs are completely reimbursed by the state/public insurance system. However, there is a general claim that bureaucracy accompanying all relevant procedure should become more flexible.

### **Other initiatives to improve access to orphan medicinal products**

There are currently no programmes to facilitate access to Orphan medicinal products. The Greek Alliance PESPA has put in place some awareness raising campaigns concerning orphan medicinal products.

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<sup>306</sup> <http://www.eof.gr>

### **Other therapies for rare diseases**

Bone Marrow Transplantation is available in several centres mainly at the paediatric Oncology Unit, Marianna Vardinoyiannis “ELPIDA”, Aghia Sophia Children’s Hospital, Athens. BMT Units for adults also exist. Special dietary products for patients with inborn errors of metabolism are available.

### **Orphan devices**

No specific information reported.

### **Specialised social services**

Patients have limited access to respite care services, but these are not specifically for rare disease patients. The patients sometimes have to financially contribute to these services which are run by national institutions, patient associations and non-governmental organisations. A few therapeutic recreational programmes are available, organised by the same types of organisations, and the patient must also financially contribute to this. Limited help with household chores, psychological support, help with shopping and mobility assistance can be sought by patients with special needs (suffering from rare diseases or not), provided by local authorities or NGOs. PESPA provides some psychological support (with the help of professionals who are voluntary) to patients/families with rare diseases.

## **RARE DISEASE ACTIVITIES IN 2013 IN GREECE**

### **National plan/strategy for rare diseases and related actions**

In November 2012 a Steering Committee for Rare Diseases was appointed by the General Secretary of the Ministry of Health to review and supplement the plan proposed during the Europlan meeting in 2010 and submit it to the Ministry for discussion, adoption and implementation. This Committee was recently replaced by another one which has not yet started work.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Greece***

A translation of Orphanet abstracts into Greek was initiated in 2013.

In 2013 Orphanet became the official database and contact point for rare diseases, operating as the National Contact Point foreseen in the implementation of the EU Cross-Border Healthcare Directive.

### **National rare disease events in 2013**

The Greek Alliance for Rare Diseases (PESPA) organised a series of events to mark Rare Disease Day 2013 including a series of speeches regarding the subject: “Rare Disorders Without Borders”, at the Eugenides Foundation, from selected scientists and patients, the distribution of printed material in various focal points, the creation and screening of a TV advert on a variety of TV stations, throughout February 2013, culminating on Rare Disease Day (28 February 2013) with the organisation of various events including the events organised by the patient association members of PESPA, an event with PESPA members at the Acropolis Museum, an event with patient organisations at Zapeio, and press releases. KEELPNO organised a one day event entitled: “Rare Diseases: the Greek reality” in order to inform scientists, health professionals and patients on the initiatives regarding rare diseases in the country

## **1.13. HUNGARY**

### **Definition of a rare disease**

Stakeholders in Hungary accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### **National plan/strategy for rare diseases and related actions**

A decree of the Ministry of Health established the National Rare Disease Centre (NRDC) in Hungary on 11 November 2008 as a part of the National Centre for Healthcare Audit and Inspection (OSZMK) by modifying its foundation deed. The National Centre for Healthcare Audit and Inspection was a part of the National Public Health Institute, and was empowered to investigate quality related issues in health care, public health consequences of health care operation, and to initiate interventions if needed. Due to the restructuring of the national public health institutions, OSZMK was disbanded on 30 April 2011. The National Institute for Health Development (OEFI) became the new host organisation, which is subordinated to the Chief Medical Officer and is a part of the central public health institutions. The continuation of the NRDC operation has been ensured by the modification of the foundation deed of OEFI.

The NRDC participates in preparation of recommendations for Governmental Health Authorities in the following ways:

- It elaborates its own data collecting technology and co-operates with other stakeholders in order to obtain rare diseases related data and to prepare indicators;
- It defines public health indicators for rare diseases;
- It initiates the elaboration of rare disease guidelines and carries out the audit projects;
- It maintains the national database of rare diseases specialised health care providers;
- It contributes to the assignment of national centres of expertise and their participation in European networks;
- It facilitates the establishment and operation of the quality management programs for the Hungarian rare diseases laboratories;
- It facilitates the application of e-health in rare disease related care;
- It initiates the rare diseases teaching programs launching in the universities;
- It participates in the work of national agencies responsible for orphan medicinal product and orphan medical device legislation;
- It supports the improvement of the availability of special social services for rare disease patients;
- It supports the effective primary preventive program;
- It evaluates the effectiveness of the rare diseases screening programs;
- It facilitates rare disease research projects, both national and the international co-operations;
- It contributes to the development of collaboration between governmental bodies, health care providers and patient organisations;
- It supports the Hungarian participation in the European rare diseases projects;
- It initiates programs, which contribute to the improvement of the perception of rare diseases among the general public;
- It co-ordinates the elaboration and monitoring of national policy on rare diseases;
- It reports on the Hungarian achievements regularly.

The NRDC is supported by an advisory group; the member experts were appointed by the Chief Medical Officer. Its members are from the four medical universities (the Hungarian Medical Universities' representatives to the national advisory group are nominated by the deans), governmental institutions, and patient organisations. This group has a key advisory function of strategic planning, but does not have influence and control on the implementation of the decisions made.

The NRDC established a National Plan Organising Committee by supplementing the current expert committee with representatives of sectors such as government and industry and the patient groups. The Ministry is in the designation process of a competent, responsible Head of the expert committee, authorised to make decisions, to lead the development of the National Plan for Rare Diseases. However, currently there is no appointed Organising Committee, state or governing body to coordinate or implement the Plan.

The former IT centre facilities of OSZMK are under reconstruction for the systematic analysis of the hospital and outpatient discharge records of rare diseases patients (for rare diseases which have their own ICD10 code), as well as laboratories, research programmes and patient groups. This investigation constrained to the rare diseases with distinct ICD10 codes tries to demonstrate the usefulness of rare disease specific indicators both for quality management and for public health purposes. On the basis of the results of these analyses, a project was initiated to introduce the orphan codes into the discharge records of hospitals and outpatient services.

The NRDC also works with the National Rare Disease Research Coordination Centre established in 2009 under the umbrella of OSZMK (host institution of NRDC) and the University of Pecs. This unit operates under the monetary support of the University of Pecs.

The NRDC cooperates with the National Ministerial Board for Clinical Genetics and with the officials responsible for rare diseases policy at the Ministry of Health, and at the National Institute for Quality and Organisational Development in Healthcare and Medicines (GYEMSZI). Project based collaboration has been established with universities' rare disease coordination units, sociological centres (for studying sociological characteristics of the patient groups), the National Centre for Statistics (for studying the mortality trends of rare diseases), and the Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS).

At the Europlan Hungarian national conference on rare diseases<sup>307</sup>, organised by HUFERDIS on 18-19 October 2010 in Budapest, it was suggested that the issue of rare diseases should be adapted into the present, on-going reorganisation of the health care and social care system.

At the end of 2011, the main content of the plan was finalised and an expert meeting was held to finalise the chapters. Expert opinion was sought on the plan in March 2012. The third Hungarian Europlan Conference on Rare Diseases<sup>308</sup> (16-17 November 2012) was organised by HUFERDIS, together with the Ministry of National Resources, in Budapest. All stakeholders were present during the two day conference aimed at defining further concrete steps to develop a National Plan for Rare Diseases.

By the end of 2012 the National Plan for Rare Diseases was submitted to the Ministry of Health. The fourth Hungarian Europlan conference on 25-26 October 2013, organised with the participation of the Ministry of Health, examined the document and the budgetary question: the conference was a lively one thanks to the signing of National Plan for Rare Diseases by the Minister of Human Resources. The National Plan for Rare Diseases has now been approved (at the end of 2013)<sup>309</sup> and there is an elaborated budgetary plan for the 7 year strategy. The approval of the budget proposal is expected in 2014 in order to finalise the plan. The National Plan for Rare Diseases covers widely the needs of RD patients, extending all important areas and in harmony with the EU recommendations. All stakeholder groups supported the implementation of National Plan for Rare Diseases, including the allocation of a dedicated budget. The implementation of National Plan for Rare Diseases is jeopardized by some uncertainty caused by the prospective MP election, therefore the enhancement of national and international advocacy work is continuously necessary. Beside the National Plan for Rare Diseases the Ministry plans rare disease specific communications in project "Development of public health communication" supported by Cohesion Fund.

In 2012 an expert group was also established at the Ministry of Health to identify the technical specification for a pilot study concerning the introduction of Orphacodes into hospital and healthcare centre records and the study started in 2013.

Hungary also has a National Cancer Plan where the rare cancers are covered.

The formation of a RD help line system, together with the development of rare disease emergency cards was also discussed in the 4<sup>th</sup> Europlan conference. However, no steps have been made yet.

### Centres of expertise

There are currently no officially approved centres of expertise in Hungary, although eight are informally recognised. There are four university centres with expertise in the field of rare diseases and diagnostic and therapeutic facilities: Budapest, Szeged, Pecs and Debrecen. In Hungary, a committee on the treatment of rare conditions has been set up within the Scientific Health Council (*Egészségügyi Tudományos Tanács*). It ensures, *inter alia*, that people suffering from such conditions receive adequate care in all cases. People suffering from rare conditions in Hungary are registered at the treatment centres.

The much of the designation criteria for centres of expertise (objectives, scope, task, indicators, etc.) have already defined on the basis of the EUCERD Recommendations in this area) in the National Plan for Rare Diseases. Two main factors are to be considered for the designation of Hungarian national centres of expertise: the presence of equipment for diagnosis, and personal expertise of the medical professionals in the centre. In Hungary, the need for 5 rare disease centres playing a coordinating role has been identified. The 4 existing medical universities could play this role, but it has to be assured that the adequate expertise is provided in these centres. Healthcare pathways will be considered as will interdisciplinary, which should be a key feature of the designation. In the National Plan for Rare Diseases, therefore, the strategy will be to designate the four medical universities as centres of expertise due to the existing structure of the health system by speciality and the prominence and reputation of the medical university in terms of research, amongst other disciplines. There

<sup>307</sup> [http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/final\\_report\\_%20hungary\\_europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_%20hungary_europlan.pdf)

<sup>308</sup> <http://europlan.rirosz.hu/>

<sup>309</sup> [http://ec.europa.eu/health/rare\\_diseases/docs/national\\_hungary\\_en.pdf](http://ec.europa.eu/health/rare_diseases/docs/national_hungary_en.pdf)



are expert groups outside of the medical universities who respect the criteria, but the ways of involving these groups into the existing structures need further examination.

NRDC initiated a collaboration with the National Health Insurance Fund for the listing and transparent accreditation of centres of expertise, hospitals, and laboratories working in the field of rare diseases taking into account existing resources and their concentration, as well as eliminating parallelism and formalising existing informal relations and determining patients' pathways. The research project final report is expected to be published in 2014.

The NRDC has also initiated an open registry concerning the activities of centres of care and expertise, including the activities of consultants and laboratories requiring accreditation.

The legal base for establishing rare diseases expert centres had been set up at the end of 2013 by the Ministry of Health. The details of the designation process are to be elaborated.

### **Registries**

The National Register of Congenital Anomalies (VRONY) operates countrywide according to the EUROCAT protocol. The former case definition of VRONY (congenital anomalies diagnosed from conception to the end of the first year of the newborn) has been extended by eliminating the age limit. Consequently, all the diagnosed congenital anomalies are to be reported from 2013 in an obligatory manner. The NRDC has initiated the establishment of an overall register for rare diseases. Currently, the clinical centres of rare diseases maintain registries of cared patients: these registries do not report their cases to a national data collecting system, and their registration methodology is developed according to the local need of care management and to the research requirements. All of these registries are in line with the Hungarian laws on genetic data handling and on the personal data protection. Hungary contributes to European Registries such as TREAT-NMD, EUROCAT, SCNIR and EUROCARE CF.

### **Neonatal screening policy**

A compulsory, government-financed newborn screening program covering the whole country has been running since 1975, and after introduction of tandem mass spectrometry screening in 2007, now includes 26 diseases, amongst which phenylketonuria, hypothyroidism, galactosaemia and biotinidase deficiency which belong to the classic core. Two centres are responsible for the operation of this nationwide network.

A HURO-euro programme started in May 2011 on the "Newborn screening and molecular genetic diagnosis of rare diseases: developing a Euro-regional infrastructure and cooperation". The University of Szeged is the project leader, and the Clinic de Urgență pentru Copii "Luis Țurcanu", (Timișoara) and Universitatea de Vest "Vasile Goldis" (Arad) are the Romanian partner institutions. The cooperation was active in 2012.

### **Genetic testing**

The Genetic Professional College established in 2004 a protocol adopted by the Ministry of Healthcare entitled *Genetic Consultation*, which defines the conditions necessary for supplying the laboratory background, the infrastructure and the personal/operational costs for genetic diagnosis. Around 20% of laboratories have at least one diagnostic test validated by an external quality control scheme. The National Centre for Healthcare Audit and Inspection has also initiated an open registry including laboratories requiring accreditation.

Genetic diagnostic testing abroad is available through an application process to the National Health Insurance Fund and in many instances the Fund reimburses the costs.

Diagnostic tests are registered as available in Hungary for 57 genes and an estimated 77 diseases in the Orphanet database<sup>310</sup>.

### **National alliances of patient organisations and patient representation**

The Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS) is the national alliance of 42 rare disease patient organisations in Hungary, affiliated with EURORDIS. HUFERDIS is currently encouraging the creation of a Hungarian Rehabilitation Centre for Rare Disease Patients which has got into the priority list of Norwegian grant of Hungary. HUFERDIS represents rare diseases patients in the Hungarian Expert Committee of Rare Diseases (which was the base of the forming National Plan Organising Committee), the Council of National Alliances (CNA) of EURORDIS, and at the EUCERD.

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<sup>310</sup> Information extracted from the Orphanet database (January 2014): an update has been provided to the coordinating team which is being entered into the database.

Patient organisations provide information and act as contact points for rare disease patients and organise conferences. HUFERDIS organised an Expert Committee to help the National Plan Organising Committee in the development of National Plan for Rare Diseases, and participates in the accreditation of centres of expertise, the determination of guidelines, and in the therapeutic education and care programs, medical and social care training etc.

Non-medical services for rare disease patients are currently available at local level or by non-profit organisations. Patient organisations are partly supported by the '1% Law' which allows taxpayers to transfer 1% of their previous year's taxable income to a non-profit organisation (which may be a patient organisation), without loss of income. Grants from the new National Fund of Cooperation are also available to patient organisations. There is no regular, direct governmental support for rare disease self-help groups, but there are many indirect governmental financing mechanisms: 25% of the civil budget is from governmental sources. HUFERDIS does not receive nominative state support such as that received by other umbrella patient organisations in Hungary.

Following previous collaboration established between HUFERDIS, NRDC and the Hungarian Orphanet team, new projects were not carried out because of the reorganisation of NRDC. However a new system was established at the National Health Insurance Fund for the evaluation of high valued medicines and care, and the representatives of HUFERDIS were invited to this expert committee. HUFERDIS takes part in several international projects including Europlan, POLKA, BURQOL-RD, Rare Disease Days, EUPATI. To foster the opinion of patient representatives on future European policies for rare diseases, or to collect their views on existing ones, HUFERDIS participated on the European POLKA project coordinated by EURORDIS. HUFERDIS started new cooperation with other international organisations as well, including DIA, EPF, EPHA, ECOP, ISOQOL.

During 2013 HUFERDIS played an important role in of the establishment of Hungarian National Patient Forum, resulting in the election of its president as the Coordinator of the Forum. The federation was also a funder member of the new Hungarian Alliance of Patient Organisations (HAPO).

#### **Sources of information on rare diseases and national help lines**

##### ***Orphanet activities in Hungary***

Since 2004 there is a dedicated Orphanet team in Hungary, initially hosted by the University of Pecs. After its establishment, the NRDC was designated as the official Orphanet team for Hungary in 2010 by the Ministry of Health. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The Orphanet website is widely used by professionals. There is an Orphanet national website launched in 2012, in the Hungarian language<sup>311</sup>.

##### ***Official information centre for rare diseases***

There is currently no official information centre for rare diseases in Hungary apart from Orphanet.

##### ***Helpline***

There is currently no rare disease specific helpline in Hungary. Many patient organisations provide support by telephone. HUFERDIS started a process to establish the necessary help line system, by applying for a Norwegian grant.

##### ***Other sources of information***

Some websites, maintained by the government ([www.gyemszi.hu](http://www.gyemszi.hu), [www.oefi.hu/aboutus.htm](http://www.oefi.hu/aboutus.htm)), have limited information concerning rare diseases. Scientific societies ([www.mhgt.hu](http://www.mhgt.hu)), non-governmental expert groups ([www.betegmagzat.hu](http://www.betegmagzat.hu)) and market-based organisations ([www.webdoki.hu](http://www.webdoki.hu)) have web based services for patients. The only other significant rare disease-specific website is the homepage of HUFERDIS ([www.rirosz.hu](http://www.rirosz.hu)). Several member associations of HUFERDIS have also detailed specific websites for a given rare disease.

##### **Guidelines**

Guidelines related to rare diseases had been produced by the Ministry of Health and are available including: autism spectrum, cystic fibrosis, diagnosis of the inherited metabolic diseases, genetic counselling, haemophilia, investigation of familial clustering of anomalies, investigation of multiple congenital anomalies, Legg-Calve-Perthes disease (Perthes disease), multiple sclerosis, myasthenia gravis, Osgood-Schlatter disease,

<sup>311</sup> <http://www.orpha.net/national/HU-HU/index/honlap/>

prenatal screening of Down syndrome, Scheuermann disease, systemic lupus erythematosus, Tibial hemimelia, clubfoot. Hungary supports the participation of local experts in the development of international guidelines that should help diagnosis and care of rare diseases patients at national level. Some guidelines have been developed in collaboration with patient organisations and specialised clinics, in line with the new European guidelines (e.g. Williams syndrome). One of the missing guidelines in the field of rare diseases was a national protocol for the communication of a diagnosis: another expert team of HUFERDIS has thus developed a new rare disease protocol to properly communicate a diagnosis. The reformulation of the expired guidelines is the dedicated task of a governmental institution (GYEMSZI subordinated to the Ministry of Health).

### **Training and education initiatives**

The education provided to health professionals currently includes information about the existence of rare diseases and the resources available for their care. This includes medical training in fields relevant to the diagnosis of rare diseases (genetics, oncology, immunology, neurology, paediatrics), further education for young doctors and scientists working in the field of rare diseases, and exchange and sharing of expertise between centres of expertise in the country.

Annual courses on rare diseases for graduates and postgraduates have been held at the Debrecen University, Department of Rare Diseases, since 2003 (with 40-100 participants). Rare diseases are also discussed at the Days of Internal Medicine of Debrecen (100-150 participants) which have been held seven times to date. The Department of Medical Genetics at the University of Pécs has organised since 2009 3-day clinical genetics course covering among others the diagnosis and management of selected rare diseases; the meeting is intended for specialists in the field as well as for family practitioners. The course in October 2012 aimed to show the interdisciplinary participation of various disciplines in the diagnosis and care of rare disease patients. The institutions and clinics participating in rare disease care constitute a Rare Disease Network of the University of Pécs established in February 2012. The Hungarian Clinical Neurogenetic Society organises annual meetings, which focuses on inherited neurological and neuromuscular disorders. The Semmelweis University also organises courses even for patients such as the “Molecular Medicine for Everybody”. Regular conferences are organised on the area of rare diseases by the Hungarian Society of Personalised Medicine or by Industry, like the Personalised Healthcare Days of Roche.

The Epidemiology of Rare Diseases has been accepted as research area by the Health Sciences Doctoral School of University of Debrecen. The students are involved in the folic acid supplementation, prenatal screening, patient pathway and diagnostic delay investigations.

### **National rare disease events in 2013**

HUFERDIS, the Hungarian rare disease alliance, organised a number of events to mark Rare Disease Day in Hungary in both Budapest and Pécs.

In the central event, there were parallel professional meetings in Budapest. A professional conference brought together patient associations, healthcare professionals, pharmacists, technical diagnostic support specialists and also decision makers to share their opinions and ideas on how to act in the field. There was a roundtable discussion about the National Plan for Rare Diseases, updating the authorisation procedures concerning rare diseases. An overview of diagnostic opportunities and new horizons was given, summarising the experiences and finished projects from last year's efforts. There were several useful programmes for families as well, including patient organisation presentation booths, poster sessions, a press conference, play ground, crafts and entertainment. HUFERDIS also organised a Rare Beauties exhibition to mark the Day in an artistic fashion. A Solidarity Walk of 1,7 km through the City Park was also organised bringing together patients and those supporting them.

As a joint effort of the Department of Medical Genetics of the University of Pécs, the Éltés Mátyás School for Children with Special Needs, and the Pécs Gallery at the Zsolnay Cultural Center, an information day for all rare disease patients in the region was held on 23 February 2013. The Zsolnay Cultural Centre, located on the site of the famous Zsolnay porcelain factory in Pécs, proved to be an attractive location for the patients, families, caregivers, and local people interested in rare diseases. The backbone of the program consisted of musical performances by the students of the Éltés Mátyás School, many of whom are affected by rare diseases themselves, and information stands of various Hungarian rare disease patient organisations and caregivers from the region. Speeches given by the Dean of the Medical Faculty, the Director of the Clinical Centre, and the Vice Rector of the University, stressed the role of the University and its academic resources in the region's rare disease care and research.

As previously mentioned, the fourth Hungarian Europlan Conference on Rare Diseases was organised by HUFERDIS on 25 October 2013, when the Hungarian National Plan for Rare Diseases was publicly presented for the first time. It is a strategy of health policy from 2014-2020 for RD.

### **Hosted rare disease events in 2013**

No reported events.

### **Research activities and E-Rare partnership**

#### ***National research activities***

Governmental research funds for rare diseases are available from the Hungarian Scientific Research Fund. The Ministry of Health announces its health related research grants through the Scientific Health Council (ETT), Department of Research Coordination every three years. In the last evaluated period (2009-2011) 166 research grants were supported from 495 applications<sup>312</sup>. In these programs, rare diseases were not one of the priority areas, but many rare diseases related grants were financed (e.g. governmental supported the project on the periconceptional folate status and on attitude towards different supplementation programs).

A multidisciplinary centre had been established in the Semmelweis University (Budapest) on rare disorders. The centre organises its work according to the principals published in the Communication from the European Commission on Rare Diseases. The centre has a patient registry, a diagnostic department, a multidisciplinary care providing network, research projects, and a teaching program<sup>313</sup>. The coordinator of this Rare Disease Centrum is the Institute of Genomic Medicine and Rare Disorders<sup>314</sup>.

To ensure the scientific expertise for NRDC, the general director of the National Centre for Healthcare Audit and Improvement, the rector of Pecs University, and the head of the Department of Medical Genetics signed the detailed agreement which established the National Rare Disease Research Coordinating Centre on the 21 April 2009; this Centre is still embedded into the Department of Medical Genetics of University of Pecs. The Medical Faculty, Faculty of Health Sciences and the Faculty of Special Pedagogy are involved in this cooperative project. The experts employed by these faculties come from the fields of medicine, paramedicine, social services and education. This working environment is expected to improve the Hungarian teams' ability to contribute to the work of European organisations.

All Hungarian Medical Faculties have started to establish their own coordinating centres to harmonise their rare diseases related activities, including research.

#### ***Participation in European research projects***

Teams from Hungary participate/participated in 9 FP7 rare disease related projects.

#### ***E-Rare***

Hungary is full partner of E-Rare-2 via the National Rare Disease Research Coordinating Centre at University of Pécs. Hungary did not participate in the 4<sup>th</sup> Joint Transnational Call in 2012, but it did participate in the 5<sup>th</sup> Joint Transnational Call in 2013 although no Hungarian teams participate in the selected projects.

#### ***IRDiRC***

Hungarian funding agencies have not currently committed funding to the IRDiRC, but as part of the E-Rare group of funders there is the possibility for Hungary to participate in the IRDiRC through the University of Pecs.

#### ***Orphan medicinal products***<sup>315</sup>

The holders of marketing authorisations for orphan medicinal products (or their representatives in Hungary) cooperate with the medical profession and the OEP (The National Health Insurance Fund - *Országos Egészségbiztosítási Pénztár*).

#### ***Orphan medicinal product committee***

There is no committee for orphan medicinal products in Hungary, but there is a new committee for the evaluation of reimbursement inclusion decisions in case of highly expensive medicines and care. A new system was established at the National Health Insurance Fund for the evaluation of high valued medicines and care,

<sup>312</sup> The summary report of the 2009-2011 program evaluation is available here: [http://www.ett.hu/palyazat/tam\\_09\\_11.pdf](http://www.ett.hu/palyazat/tam_09_11.pdf)

<sup>313</sup> <http://www.molneur.eoldal.hu/cikkek/english>

<sup>314</sup> <http://semmelweis-egyetem.hu/genomikai-medicina/>

<sup>315</sup> This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)

besides professionals caring for patients with rare diseases where high valued therapy is available, the representatives of HUFERDIS were invited to this expert committee. The committee has issued guidelines on the diagnosis, treatment and care of various rare diseases where therapy is available, those guidelines serve as a basis for the individual decision on the reimbursement of high valued orphan drugs to Hungarian rare disease patients.

#### **Orphan medicinal product incentives**

No specific activity reported.

#### **Orphan medicinal product market availability situation**

At the beginning of 2011 in Hungary, 69 of the 74 orphan medicinal products were available according to the Department of Rare Diseases in University of Debrecen. This institution implemented in Hungary the survey of the Rare Disease National Alliances & EURORDIS on Patients' Access to Orphan Medicinal Products in Europe. Most of orphan medicinal products are available via centres assigned by the National Health Insurance Fund.

The orphan medicinal products on the market in Hungary are: Afinitor™ (Everolimus), Aldurazyme™ (Laronidase), Arzerra™ (Ofatumumab), Atriance™ (Nelarabine), Busilvex™ (Busulfan (Intravenous use), Carbaglu™ (N-carbamyl-L-glutamic acid), Cayston™ (Aztreonam lysinate inhalation use), Ceplene (Histamine dihydrochloride), Cystadane™ (Betaine anhydrous), Diacomit™ (Stiripentol), Dudopa™ (Levodopa/Carbidopa gastrointestinal use), Elapraxe™ (Iduronate-2-sulfatase) , Evoltra™ (Clofarabine), Exjade™ (Deferasirox), Fabrazyme™ (α-Galactosidase A), Firazyr™ (Icatibant acetate), Firdapse™ (Amifampridine), Gliolan™ (INN-5-aminolevulinic acid hydrochloride), Glivec™ (Imatinib mesilate), Ilaris™, Increlex™ (Mecasermin rinfabate), Inovelon™ (Rufinamid), Ixiaro™, Kuvan™ (Sapropterin dihydrochloride), Litak™ (Cladribine), Lysodren™ (Mitotane) , Mepact™ (Muramil Tripeptid Foszfatidil Etanolamin), Mozobil™ (Plerixafor), Myozyme™ (Recombinant human acid α-glucosidase), Naglazyme™ (N-acetyl galactosamine 4-sulfatase), Nexavar™ (Sorafenib tosylate), Nexavar™ (Sorafenib tosylate) , Nplate™, Nymusa™ (Caffeine citrate), Onsenal™ (Celecoxib) , Orfadin™ (Nitisinone), Pedeax™ (Ibuprofen), Photobarr™ (Porfimerum for photodynamic therapy), Prialt™ (α-Galactosidase A), Replagal™ (α-Galactosidase A), Revatio™ (Sildenafil citrate), Revlimid™ (Lenalidomid), Revolade™ (Eltrombopag olamin), Savene™ (Dexrazoxane), Siklos™ (Hydroxyurea), Soliris™ (Eculizumab), Somavert™ (Pegvisomant), Sprycel™ (Dasatinib), Tassigna™ (Nilotinib), Tassigna™ (Nilotinib), Tepadina™ (Thiotepa), Thalidomide Celgene™ (Thalidomide), Thelin™ (Sitaxentan), Torisel™ (Temsirrolimus), Tracleer™ (Bosentan), Trisenox™ (Arsenic trioxide), Ventavis™ (Iloprost), Vidaza™ (Azacitidine) , Vidaza™ (Azacitidine), Volibris™ (Ambrisentan), Votrient (Patorma)™ (Pazopanib hydrochloride), Wilzin™ (Zinc acetate dihydrate), Xagrid™ (Anagrelide Hydrochloride), Yondelis™ (Ecteinascidin 743), Yondelis™ (Trabectedin), Zavesca™ (Miglustate).

#### **Orphan medicinal product pricing policy**

The OEP does not have a direct impact on pricing.

#### **Orphan medicinal product reimbursement policy**

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal product*<sup>316</sup>, "the Hungarian Government promotes the use of orphan medicinal products for specific patients by means of special financial arrangements".

"Some rare conditions (such as Fabry disease or adult-type chronic myeloid leukaemia - CML), the National Health Insurance Fund (OEP) provides standard price-support for the medicinal products in a predetermined manner. In this case the patient's contribution is negligible or 0%. In other cases, support for the orphan medicinal products imported for patients' treatment can be provided on application under a special equity procedure laid down by law. The OEP pays the price-support for the necessary medicinal products from earmarked resources in the outpatients' equity fund"<sup>317</sup>. In most cases, support is only available via discretionary claims. There is a yearly budget for such claims managed by the OEP. The discretionary procedure takes into account the financial situation of the claimant. In 2009, 289 patients had their discretionary claims accepted. Around 13 rare diseases receive support within the framework of discretionary claims. 33 orphan medicinal products are 100% reimbursed in Hungary. The re-regulation of pharmaceutical reimbursement inclusion decisions started in 2011. The National Health Insurance Fund established the above mentioned advisory group

<sup>316</sup> Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)

<sup>317</sup> Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision (p15)

to evaluate the applications for expensive medical treatments. The operation rules for this committee have been elaborated. A significant proportion of applications are submitted by rare disease patients' physicians.

#### **Other initiatives to improve access to orphan medicinal products**

Off-label use is possible, provided that the benefits of the drugs for a certain disease are certified, but the process is highly bureaucratic.

#### **Other therapies for rare diseases**

No specific activity reported.

#### **Orphan devices**

No specific activity reported

#### **Specialised social services**

There are good and high quality programs in the field of early development and respite care which support patients and their families. However, these programmes do not cover the whole country. Legislation exists on care, training, integration, work help for special needs children (i.e. extra home care), however these initiatives are not available to all rare disease patients. The change of this legislation has started in favour of rare disease patients. There are measures in place to support patients who need to travel inland to access health care through an assessment of needs by the Health Insurance Fund.

The Ministry of Human Resources started to work together with HUFERDIS for a project establishing the National Habilitation, Development and Service Centre of Rare Disorders to help the social integration of rare disease patients. Several health care institutions started to change care profile during the reorganisation within the Semmelweis Plan. Some of them will be able to offer more rehabilitation and social care.

HUFERDIS joined the therapeutic recreational programs of a member association (Hungarian Williams Syndrome Association) and organised programmes for capacity building and training, networking, awareness raising, exchange of information and best practices, during a special development family camp and after. HUFERDIS is also participating in the EUCERD Joint Action activities concerning Specialised Social Services.

## **RARE DISEASE ACTIVITIES IN 2013 IN HUNGARY**

#### **National plan/strategy for rare diseases and related actions**

By the end of 2012 the National Plan for Rare Diseases was submitted to the Ministry of Health. The fourth Hungarian Europlan conference on 25-26 October 2013, organised by with the participation of the Ministry of Health, examined the document and the budgetary question: the conference was a lively one thanks to the signing of National Plan for Rare Diseases by the Minister of Human Resources. The National Plan for Rare Diseases has now been approved (at the end of 2013)<sup>318</sup> and there is an elaborated budgetary plan for the 7 year strategy. The approval of the budget proposal is expected in 2014 in order to finalise the plan. The National Plan for Rare Diseases covers widely the needs of RD patients, extending all important areas and in harmony with the EU recommendations. All stakeholder groups supported the implementation of National Plan for Rare Diseases, including the allocation of a dedicated budget. The implementation of National Plan for Rare Diseases is jeopardized by some uncertainty caused by the prospective MP election, therefore the enhancement of national and international advocacy work is continuously necessary. Beside the National Plan for Rare Diseases the Ministry plans rare disease specific communications in project "Development of public health communication" supported by Cohesion Fund.

In 2012 an expert group was also established at the Ministry of Health to identify the technical specification for a pilot study concerning the introduction of Orphacodes into hospital and healthcare centre records and the study started in 2013.

<sup>318</sup> [http://ec.europa.eu/health/rare\\_diseases/docs/national\\_hungary\\_en.pdf](http://ec.europa.eu/health/rare_diseases/docs/national_hungary_en.pdf)

The formation of a RD help line system, together with the development of rare disease emergency cards was also discussed in the 4<sup>th</sup> Europlan conference. However, no steps have been made yet.

### **Centres of expertise**

NRDC initiated a collaboration with the National Health Insurance Fund for the listing and transparent accreditation of centres of expertise, hospitals, and laboratories working in the field of rare diseases taking into account existing resources and their concentration, as well as eliminating parallelism and formalising existing informal relations and determining patients' pathways. The research project final report is expected to be published in 2014.

The legal base for establishing rare diseases expert centres had been set up at the end of 2013 by the Ministry of Health. The details of the designation process are to be elaborated.

### **Registries**

The National Register of Congenital Anomalies (VRONY) operates countrywide according to the EUROCAT protocol. The former case definition of VRONY (congenital anomalies diagnosed from conception to the end of the first year of the newborn) has been extended by eliminating the age limit. Consequently, all the diagnosed congenital anomalies are to be reported from 2013 in an obligatory manner. The NRDC has initiated the establishment of an overall register for rare diseases.

### **National alliances of patient organisations and patient representation**

During 2013 HUFERDIS played an important role in of the establishment of Hungarian National Patient Forum, resulting in the election of its president as the Coordinator of the Forum. The federation was also a funder member of the new Hungarian Alliance of Patient Organisations (HAPO).

### **Sources of information on rare diseases and national help lines**

#### **Helpline**

HUFERDIS started a process to establish the necessary help line system, by applying for a Norwegian grant.

### **National rare disease events in 2013**

HUFERDIS, the Hungarian rare disease alliance, organised a number of events to mark Rare Disease Day in Hungary in both Budapest and Pecs.

In the central event, there were parallel professional meetings in Budapest. A professional conference brought together patient associations, healthcare professionals, pharmacists, technical diagnostic support specialists and also decision makers to share their opinions and ideas on how to act in the field. There was a roundtable discussion about the National Plan for Rare Diseases, updating the authorisation procedures concerning rare diseases. An overview of diagnostic opportunities and new horizons was given, summarising the experiences and finished projects from last year's efforts. There were several useful programmes for families as well, including patient organisation presentation booths, poster sessions, a press conference, play ground, crafts and entertainment. HUFERDIS also organised a Rare Beauties exhibition to mark the Day in an artistic fashion. A Solidarity Walk of 1,7 km through the City Park was also organised bringing together patients and those supporting them.

As a joint effort of the Department of Medical Genetics of the University of Pécs, the Éltes Mátyás School for Children with Special Needs, and the Pécs Gallery at the Zsolnay Cultural Center, an information day for all rare disease patients in the region was held on 23 February 2013. The Zsolnay Cultural Centre, located on the site of the famous Zsolnay porcelain factory in Pécs, proved to be an attractive location for the patients, families, caregivers, and local people interested in rare diseases. The backbone of the program consisted of musical performances by the students of the Éltes Mátyás School, many of whom are affected by rare diseases themselves, and information stands of various Hungarian rare disease patient organisations and caregivers from the region. Speeches given by the Dean of the Medical Faculty, the Director of the Clinical Centre, and the Vice Rector of the University, stressed the role of the University and its academic resources in the region's rare disease care and research.

As previously mentioned, the fourth Hungarian Conference on Rare Diseases was organised by HUFERDIS on 25 October 2013 as part of the Europlan initiative, when the Hungarian National Plan for Rare Diseases was publicly presented for the first time. It is a strategy of health policy from 2014-2020 for RD.

## Research activities and E-Rare partnership

### E-Rare

Hungary participated in the 5<sup>th</sup> Joint Transnational Call in 2013 although no Hungarian teams participate in the selected projects.

## 1.14. IRELAND

### Definition of a rare disease

Stakeholders in Ireland accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10'000 individuals.

### National plan/strategy for rare diseases and related actions

There is currently no national plan/strategy for rare diseases in Ireland, but the development of a plan is underway. The Health Service Executive National Advocacy Unit is supporting the Department of Health in its initiative to develop a national rare disease plan. The patient-centred policy framework will encompass actions targeting the prevention, detection and treatment of rare diseases based on the principles of quality care and equity. The policy will operate over a five-year period and define priority actions, subject to resource availability, in the areas of centres of expertise, orphan drugs and technologies, research and information and patient empowerment and support.

A National Steering Group of stakeholders was established (Spring 2011) under the aegis of the Department of Health and Children to work on the development of a five-year national plan, starting with a mapping exercise and focusing on the structure, governance and monitoring of a national strategy. The Minister for Health appointed four patient representatives from GRDO, IPPOSI and MRCG to the Steering Group: the Steering Group held their first meeting in April 2011 and meets every 1-2 months.

On 7 March 2012 a motion<sup>319</sup> was heard in the Seanad Éireann (Senate) on the subject of rare diseases: the Minister for Health, Dr. James Reilly, announced the intention of the Health Service Executive to develop a Clinical Care Programme for Rare Diseases. A Clinical Lead in Rare Diseases in the Health Service Executive was recruited in 2013 to guide the implementation of the plan.

The National Steering Group invited stakeholders to participate in a consultation process designed to gather views concerning the plan's various components; a National Consultation Day event was held on 11 June 2012<sup>320</sup>. This was followed by an online consultation process which received almost 500 valid responses.

The Institute of Public Health, which is providing support for the development of the Plan, is preparing a report on both aspects of the consultation process which it intends to publish alongside the Plan itself. The Plan was finalised in 2013 and should be published in 2014 once a budget has been determined for the foreseen actions.

### Centres of expertise

Currently the Department (Ministry) of Health has no specific list of national centres of expertise nor does it set standards for centres to be considered "national". However the Department does recognise that particular centres have particular expertise and would give specific funds to support those specialist services. The Health Service Executive (HSE) is responsible for these services and supports centres of expertise and laboratories, including 8 cancer centres; the National Centre for Medical Genetics at Crumlin Children's Hospital which provides a service for patients (both adults and children) affected by or at risk of a genetic disorder; the National Centre for Inherited Metabolic Disorders, a tertiary care referral centre for the investigation and treatment of patients suspected of having a metabolic genetic disease, linked to the newborn screening programme; and the National Centre for Hereditary Coagulation Disorders at St. James' hospital which is a centre of expertise for rare blood disorders, principally haemophilia. There are also 15 centres for the management of Cystic Fibrosis in Ireland – both paediatric and adult centres (Ireland has the highest incidence of CF in the world). Patients with a rare disease are generally directed towards one of the major children or adult hospitals in Ireland, but for many rare diseases there is not a dedicated multi-disciplinary team to treat such diseases. Some people with a rare disease are directed for shared care to hospitals in the UK.

<sup>319</sup> <http://debates.oireachtas.ie/seanad/2012/03/07/00008.asp>

<sup>320</sup> <http://www.dohc.ie/press/releases/2012/20120614d.html>



A policy concerning centres of expertise is under development as part of the national plan for rare diseases.

### Registries

There is no designation process for rare disease registries currently in Ireland. There is no national committee or policy statement in relation to any patient registry in Ireland with the exception of the Cancer Registry which is established by Statute. Patient groups, in particular the Medical Research Charities Group (MRCG) and IPPOSI, have called for the establishment of a coordinating body and plan for all patient registries in Ireland, including those with a rare disease. Governance issues in relation to patient registries are being included in a forthcoming Health Information Bill. However financial support or planning for registries will not be included in the legislation.

The Cancer Registry is funded by government. Some registries received some support from Government and others did not. The Medical Research Charities Group (MRCG) created a Steering Group in 2008 involving the MRCG, Health Services Executive (HSE), Health Research Board (HRB) and the Health, Information and Quality Authority (HIQA) to oversee research into the area of patient registries in Ireland. The aim was to identify existing patient registries in Ireland, to describe these in detail (functions, methodologies, standards, funding mechanisms) and also to identify best practice and guidelines for quality standards in this area. The research was presented at an IPPOSI/MRCG run event in October 2011. The outcome report from that event entitled "Towards a National Strategy for Patient Registries in Ireland, considerations for Government"<sup>321</sup> was launched in 2011. Part of a national strategy on Patient Registries in Ireland is the mainstreaming of the role and work of registries into existing and forthcoming policy. The immediate priority is the inclusion of a stronger focus on Patient Registries in: the programme of work of the Quality and Clinical Care Directorate of the HSE, including the development of clinical standards in specific areas of policy and the appointment of clinical leads in particular areas of policy; the work of the Health Information and Quality Authority; and the Health Information Bill. The Health Identifiers Bill was published in 2013 and provides a legislative framework for the implementation of unique identifiers for individuals, healthcare professionals and healthcare organisations and will make provision for the establishment and maintenance of registers. A subsequent health information bill which will address ethical and legal issues concerning data collection and sharing patient data is in progress but does not currently have a publication date. IPPOSI facilitated a roundtable discussion in June 2014 with the Secretary General of the Department of Health on the Health Information-related legislation. An outcome report from that meeting will be made available in July 2014.

There are 11 patient registries for rare diseases registered with Orphanet: 5 of these contribute to the EUROCAT registry. Ireland also contributes to other European registries, such as EURO CARE CF and SCNIR.

### Neonatal screening policy

Neonatal screening is in place for galactosaemia, hypothyroidism, phenylketonuria, homocystinuria, maple syrup urine disease and cystic fibrosis<sup>322</sup>. Concomitant with the addition of CF, the entire governance of the newborn screening programme was reviewed and revised in 2011. The revised programme included the launch of an enhanced information process for all parents and guardians and the introduction of signed consent on individual blood-spot cards.

All cards from 1984 onwards have been archived, but the Office of the Data Protection Commissioner, following a complaint in 2009, indicated that newborn screening cards currently stored without explicit consent should be disposed. The Minister for Health requested the HSE to conduct a review of the decision to destroy these cards following receipt of representations from a number of people and organisations, who pointed out their potential value for research. The review examined both the legal and ethical basis for retention of newborn screening cards and the potential use of the existing cards for research purposes. The report and recommendations of the review group were submitted in January 2012. The review re-affirmed the original decision reached in 2010, i.e. that in order to meet both ethical and legal obligations, newborn screening cards older than ten years should be destroyed. Following careful consideration this recommendation was accepted. The Review Group also explored how the cards could be made available to the research community in a way which is compatible with ethical and legal obligations. In the interests of facilitating research, the HSE launched a public information campaign on 8 January 2013. This campaign offering members of the public the opportunity to have their screening card returned to them, prior to any destruction of the cards taking place,

<sup>321</sup> <http://ipposi.ie/index.php/information-centre/patient-registries/179-towards-a-national-strategy-for-patients-registries-report>

<sup>322</sup> <http://www.hse.ie/eng/services/healthpromotion/newbornscreening/>

ended on 31 March 2013. The HSE has received approximately 40,000 requests from people seeking to have cards returned to them.

The Minister has sought advices from the Attorney General on how the remaining New Born Screening Cards can be retained in compliance with Irish and EU data protection legislation. The Minister has also requested that no destruction of the cards begins before an expert group has had an opportunity to consider the matter further.

### **Genetic testing**

Genetic testing in the Republic of Ireland is available through the National Centre for Medical Genetics (NCMG)<sup>323</sup>, Our Lady's Children's Hospital, Crumlin, which processes approximately 13,000 cytogenetic and molecular genetic tests annually. The cytogenetic and molecular genetics laboratories are externally accredited by CPA (UK). The National Centre for Medical Genetics is publicly funded via the Irish Health Service Executive. When a genetic test is not available from a laboratory in Ireland, and is clinically indicated, DNA samples are sent to specialised laboratories abroad.

Diagnostic tests are registered as available in Ireland for 23 genes and an estimated 47 diseases in the Orphanet database<sup>324</sup>.

The Disability Act Part IV, passed by the Oireachtas and signed into law in 2005 states that genetic testing shall not be carried out unless the consent of the person has been obtained. In addition, genetic tests cannot be used in relation to employment, insurance, pensions or mortgages.

A small amount of genetic testing is also available in private clinics.

### **National alliances of patient organisations and patient representation**

#### ***The Rare Disease Taskforce***

The Rare Diseases Towards 2013 Taskforce was set up in 2011 by the Medical Research Charities Group (MRCG), the Genetic and Rare Disorders Organisation (GRDO) and the Irish Platform for Patients' Organisations, Science and Industry (IPPOSI). The Taskforce brings the three umbrella organisations together to work collaboratively to ensure that the needs of the Rare Diseases stakeholders are represented in the National Strategy for Rare Diseases.

The Minister for Health has established a National Steering Group which is tasked with developing a five year national plan and which will deal with the diagnosis, prevention, management, treatment and research of rare diseases in Ireland. The Rare Disease Taskforce will support this National Steering group and provide input from the appropriate stakeholders. The aim of the Taskforce was the delivery by the State of a comprehensive, targeted and achievable National Strategy for Rare Diseases by 2013.

#### ***Genetic and Rare Diseases Organisation (GRDO)***

The Genetic and Rare Disorders Organisation (GRDO) is a non-governmental organisation created in 1988 which acts as an umbrella group for rare disease patient organisations. GRDO was initially founded with a view to lobbying for the establishment a National Centre for Medical Genetics. In 1992 this Centre was established by Government. Until October 2011, the organisation was run by volunteers and has since 1988 acted as an advocate for the voluntary sector concerned with genetics. This has been achieved by creating awareness and providing information on genetic disorders to policy makers and health officials in order to achieve a high quality of services for those directly affected by genetic conditions and their families. GRDO also acts as a watchdog in relation to legislation concerning disability to ensure that the rights of people with genetic conditions are protected: the organisation was involved in the consultation process for the Disability Act, 2005 resulting in the inclusion in the Act of provisions regarding genetic tests. Since October 2011, a part-time employee has been hired by GRDO to facilitate the development of the organisation.

At the end of 2011 GRDO launched a survey to gather information relating to patient support and advocacy organisations operating in Ireland for people with rare conditions. This information is being used to assist the Taskforce to engage with the Rare Diseases Steering Committee of the Department of Health. The results of this survey were published on Rare Disease Day 2012, which highlighted the urgent need for development of co-ordinated healthcare pathways and a central information point on rare conditions.

The results also reveal significant difficulties in the areas of access to diagnosis, information and to treatment, as well as a lack of coordination in delivery of services. 13.3% of respondents report waiting more than 10 years for diagnosis and 37.2% report receiving an incorrect diagnosis before the correct one. 73.1% of

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<sup>323</sup> <http://www.genetics.ie/>

<sup>324</sup> Information extracted from the Orphanet database (January 2014).

those surveyed report attending more than one hospital consultant or other medical professional for treatment yet 44.8% report not having a specific point of contact to go to with questions about their condition. 62.5% of respondents list the Internet as their main source of information. The establishment of a National Rare Disease Office in Ireland and the development of co-ordinated healthcare pathways are the two changes to the healthcare system that respondents would most like to see (82%), followed by more information about their conditions (73%). A national office would act as a focal point for the development of a national registry of rare conditions, and a vitally needed information portal for patients and medical professionals. It would help patients to access Centres of Expertise, whether in Ireland or abroad, and ensure the best model of care for patients with faster diagnosis and access to treatment. It would also be cost efficient.

In the context of developing a National Rare Disease Plan and the EU Directive on the Application of Patients' Rights in Cross-border Healthcare, GRDO is working to establish a cross border working group with their equivalent organisation in Northern Ireland, the Northern Ireland Rare Disease Partnership.

#### ***The Irish Platform for Patients' Organisations, Science and Industry (IPPOSI)***

IPPOSI has a special interest in the rare disease area given that one of its strategic objectives is to address together with key stakeholders (patients' organisations, scientists and industry (and where possible with State Agencies) policy, legislation and regulation around the development of new medicines, products, devices and diagnostics for unmet medical needs. As a non-lobbying organisation, a unique partnership of patient groups/medical charities, science and industry, IPPOSI works to smooth the path in Ireland for new medicines and therapies to move from basic science in laboratories to the patients who need them. This is achieved through expertise, dialogue, consensus building, networking etc. Since its establishment in 2001 the organisation has been involved in a number of conferences relating directly and indirectly to the rare disease area and to therapy development for unmet medical need including Orphan Medicinal Products Regulation of the EU; the Commercialisation of Health Research, the EU Clinical Trials Directive, Clinical Research Infrastructure in Ireland, Access to Medicines and New Medical Technologies in the Era of Health Technology Assessments in Ireland, Patient Registries in Ireland etc. IPPOSI have a place on the Ministry for Health Steering Group developing a strategy for Rare Diseases in Ireland and are members of the National Rare Disease Taskforce.

#### ***The Medical Research Charities Group (MRCG)***

MRCG was formed in 1998 to inform and support charities in Ireland in the development of their medical research. As an alliance promoting medical research, the MRCG works to raise the profile of medical research, increase funding, and ultimately alleviate suffering and mortality caused by illness. The MRCG work to identify the barriers to patient led research (both for rare disease and common disease) and strives to remove those barriers through dialogue and collaboration with key research stakeholders. Since 2006 the MRCG charities have been co-funding research projects with the Health Research Board (HRB). This is made possible by an allocation of funding to the HRB from the Department of Health and Children. While the scheme does not focus solely on rare diseases a number of research projects in the area have been funded. Since the Scheme was put into action in 2006, 89 projects (covering rare and non-rare conditions/diseases) have been supported. In this joint funding scheme the Department of Health and Children provides an on-going annual allocation of €900,000 to the HRB which is matched by the research charities. Total investment through this scheme since 2006 has been €16 million of which €8 million has been provided by the Department of Health.

The MRCG are represented on the Ministry for Health Steering Group developing a strategy for Rare Diseases in Ireland and are members of the National Rare Disease Taskforce.

#### **Sources of information on rare diseases and national help lines**

##### ***Orphanet activities in Ireland***

There has been an Orphanet national coordinator based in Ireland since 2004. However, the funding for an operational team finished in March 2011. Since then the Orphanet UK team, hosted by the University of Manchester in the UK, has been taking care of the Orphanet Ireland activities on a voluntary basis. The main activities are the data collection and validation. This team is in charge of collecting data on rare disease related services (expert centres, specialised clinics, medical laboratories, ongoing research, registries and databases, clinical trials, networks of excellence and patient organisations), the annual update of information, regular data quality controls, the point of contact of Orphanet Ireland and the management of the national Irish website<sup>325</sup>,

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<sup>325</sup> [www.orphanet.ie](http://www.orphanet.ie)

launched in April 2011. It is the intention that the National Plan currently being developed will recommend that the running of the Orphanet for Ireland will be relocated to Ireland.

#### **Official information centre for rare diseases**

There is no official information centre for rare diseases in Ireland other than Orphanet. However, GRDO operates as a conduit to information on rare diseases and it is hoped that the National Plan for Rare Diseases currently in development will prioritise the establishment of a national information centre for rare diseases.

#### **Help line**

There is currently no help line dedicated to rare diseases in general, but some disease specific help lines exist and are funded through public/private partnerships.

#### **Other information on rare diseases**

Patient groups are currently providing a significant level of information on particular diseases. However where a rare disease does not have a patient group, the level of information can be minimal/very patchy. The Rare Disease Task Force (GRDO/IPPOSI/MRCG) has highlighted the need for more comprehensive information on rare diseases to be provided by Government under the national plan.

Public information about rare diseases is also provided by patient organisations and GRDO.. Irish Platform for Patients' Organisations, Science and Industry (IPPOSI)-provides web-based information and policy support to patient groups. IPPOSI are funded partly by the government and membership fees.

In 2008 a report entitled *An investigation into the social support needs of families who experience rare disorders on the island of Ireland* published by Rehab Care, a unit of the independent non-profit organisation Rehab Group<sup>326</sup> and funded by Ireland's Health Research Board discovered an urgent need for information and support resources for both patients and medical professionals encountering rare disease patients in their practice. The report recommended developing a centre of excellence in Ireland dedicated to rare diseases that could support health professionals and also provide materials suitable for patients and their families. The authors recommend that Orphanet, as a freely-accessible information resource for professionals and patients, receive a high profile in Ireland, along with UK charity Contact a Family<sup>327</sup>.

#### **Guidelines**

Clinical guidelines exist for certain rare diseases. The need for an overall Clinical Programme for Rare Diseases has been accepted by the Minister for Health and the appointment of a National Clinical Lead in Rare Diseases in the Health Service Executive took place in late 2013. It is anticipated that one of the roles of the person appointed to this position will be to instigate the development of clinical guidelines.

#### **Training and education initiatives**

In 2011 IPPOSI and the School of Medicine and Medical Sciences (SMMS) at University College Dublin launched a Rare Disease Module for 3rd year medical students. IPPOSI/UCD planned the first module of its kind in Ireland to focus exclusively on rare diseases and the impact on patients. The module is entitled Rare Genetic Disorders and the Medical Healthcare Professional. The lecturers on this module are scientists, clinicians and patients describing their own condition to students. The plan is to role this out to other medical schools in Ireland and Europe to bring patients and their patient organisations into the classroom.

#### **National rare disease events in 2013**

To mark Rare Disease Day 2013 an all Ireland meeting of patients' organisations, science and industry was organised and the Irish Presidency of the Council of the European Union was held in the City Hall in Dublin<sup>328</sup>. The conference was organised by The Rare Disease Taskforce in Ireland which brings together the Genetic and Rare Disorders Organisation (GRDO), Irish Platform for Patient's, Science and Industry (IPPOSI) and the Medical Research Charities Group (MRCG) along with the Northern Ireland Rare Disease Partnership (NIRDP) and Rare Disease UK.

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<sup>326</sup> <http://www.rehab.ie/index.aspx>

<sup>327</sup> <http://www.cafamily.org.uk/index.php?section=861>

<sup>328</sup> <http://vimeo.com/channels/rdwb13>

### **Hosted rare disease events in 2013**

The following events were hosted in Ireland: International Rare Diseases Research Consortium Conference 2013 (16-17 April 2013, Dublin), 10th HHT Scientific Conference (12-15 June 2013, Cork), 9th European Cytogenetics Conference (29 June - 2 July 2013, Dublin).

### **Research activities and E-Rare partnership**

#### ***National research activities***

The Medical Research Charities Group (MRCG) was formed in 1998 to inform and support charities in Ireland in the development of their medical research. As an alliance promoting medical research, the MRCG works to raise the profile of medical research, increase funding, and ultimately alleviate suffering and mortality caused by illness. Since 2006 the MRCG charities have been co-funding research projects with the Health Research Board (HRB). This is made possible by an allocation to the HRB from the Department of Health and Children. While the scheme does not focus solely on rare diseases a number of research projects in the area have been funded. Since the Scheme was put into action in 2006, over 89 projects (covering rare and non rare conditions/diseases) have been supported. In this joint funding scheme the Department of Health and Children provides an ongoing annual allocation of €900,000 to the HRB which is matched by the research charities. Total investment through this scheme since 2006 has been €16 million of which €8 million has been provided by the Department of Health.

On 26 March 2012 a workshop hosted by the Health Research Board on behalf of the National Steering Group for Rare Diseases, brought together national and international speakers and Irish researchers. This meeting was intended to provide an opportunity to input to planning for the future of rare disease research in Ireland and inform deliberations in the area of research for the forthcoming Irish National Plan for Rare Diseases. This event outlined how Ireland can move forward in the area of rare disease research and participate at an international level. Keynote presentations on the elements involved in successful research in the area of rare disease were followed by a panel discussion on the barriers, solutions and opportunities in rare disease research.

#### ***Participation in European research projects***

Teams in Ireland participate/have participated in 9 FP7 rare disease related projects and also coordinate 4 such projects.

#### ***E-Rare***

Ireland is not currently a partner of the E-Rare project.

#### ***IRDiRC***

Irish funding agencies have not currently committed funding to the IRDiRC.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

This will be addressed as part of the work of the Steering Group for the National Rare Disease Plan at the Department of Health. Protocols for access to orphan medicinal products are under development.

#### ***Orphan medicinal product incentives***

This will be covered in the National Rare Disease Plan. The approval of Kalydeco for use in Ireland for patients with cystic fibrosis with at least one copy of the G551D gene alteration is likely to be an indirect incentive to support the development of orphan medicinal products. Ireland, through cystic fibrosis centres, played a key role in supporting the phase three clinical trials for this groundbreaking gene modification therapy.

#### ***Orphan medicinal product market availability situation***

This will be covered in the National Rare Disease Plan.

#### ***Orphan medicinal product pricing policy***

This will be covered in the National Rare Disease Plan. Orphan medicinal product pricing is decided by the Corporate Pharmaceutical Unit in the Health Service Executive (HSE) and the Health Technology Assessment is conducted by the National Centre for Pharmaco-Economics (NCPE). The appraisal pathway for orphan drugs is

the same as for other drugs<sup>329</sup>. In the IPPOSI HTA meeting in October 2012, patient organisations articulated a willingness to get involved in the HTA process at the earliest stage. The Director of the NCPE agreed that this was an area the NCPE are interested in pursuing and indicated that IPPOSI would be an ideal partner in linking his team with relevant patient groups as new applications arrive in to the NCPE office. This type of engagement happened recently with the cystic fibrosis example mentioned above.

#### **Orphan medicinal product reimbursement policy**

This will be covered in the National Rare Disease Plan. The reimbursement of medicines in general is provided for through a number of “Community Drug Schemes” and “National High Tech Drug Schemes”. As a result of the 2012 Industry-Department of Health recent supply terms and pricing agreement, a budget for innovative and new treatments was created and it is the view that emerging high cost drugs will fall into this budget.

#### **Other initiatives to improve access to orphan medicinal products**

This will be covered in the National Rare Disease Plan. There is no system at present which deals with pricing and reimbursement of orphan medicinal products. The process is the same for all new therapies and treatments in Ireland, all of which undergo a rapid HTA and may then undergo a full HTA. There is no special criteria for orphan medicinal products.

No formal derogation from these general reimbursement schemes exists but individual hospitals may decide to supply a patient with an expensive orphan medicinal product neither reimbursed under the community drugs schemes nor accessible via other schemes. Companies sometimes provide orphan medicinal products to patients free of charge on a compassionate use basis<sup>330</sup>.

There has been compassionate use of some orphan drugs, for example, in relation to Kalydeco prior to its approval by the Irish government for reimbursement.

#### **Other therapies for rare diseases**

This will be covered in the National Rare Disease Plan.

#### **Orphan devices**

This will be covered in the National Rare Disease Plan.

#### **Specialised social services**

Some non-rare disease specific social services exist in Ireland, such as those provided by the Centre for Independent Living and Personal Assistants Scheme. Other support services and respite care are provided by specific rare disease patient organisations.

## **DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 IN IRELAND**

### **National plan/strategy for rare diseases and related actions**

The Health Service Executive National Advocacy Unit is supporting the Department of Health in its initiative to develop a national rare disease plan. The patient-centred policy framework will encompass actions targeting the prevention, detection and treatment of rare diseases based on the principles of quality care and equity. The policy will operate over a five-year period and define priority actions, subject to resource availability, in the areas of centres of expertise, orphan drugs and technologies, research and information and patient empowerment and support.

The Institute of Public Health, which is providing support for the development of the Plan, is preparing a report on both aspects of the consultation process (completed in 2012) which it intends to publish alongside the Plan itself. The Plan was finalised in 2013 and should be published in 2014 once a budget has been determined for the foreseen actions.

A Clinical Lead in Rare Diseases in the Health Service Executive was recruited in 2013 to guide the implementation of the plan.

<sup>329</sup> Also see the Industry-Department of Health 2012 Pricing Agreement which is relevant to all Medicinal Products.

<sup>330</sup> EMINET: Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner, May 2011 (pp52-53).

### **Centres of expertise**

A policy concerning centres of expertise is under development as part of the national plan for rare diseases.

### **Registries**

Part of a national strategy on Patient Registries in Ireland is the mainstreaming of the role and work of registries into existing and forthcoming policy. The immediate priority is the inclusion of a stronger focus on Patient Registries in: the programme of work of the Quality and Clinical Care Directorate of the HSE, including the development of clinical standards in specific areas of policy and the appointment of clinical leads in particular areas of policy; the work of the Health Information and Quality Authority; and the Health Information Bill. The Health Information Bill was published in 2013 and addresses ethical and legal issues concerning data collection and sharing patient data.

### **Neonatal screening policy**

All cards from 1984 onwards have been archived, but the Office of the Data Protection Commissioner, following a complaint in 2009, indicated that newborn screening cards currently stored without explicit consent should be disposed. The Minister for Health requested the HSE to conduct a review of the decision to destroy these cards following receipt of representations from a number of people and organisations, who pointed out their potential value for research. The review examined both the legal and ethical basis for retention of newborn screening cards and the potential use of the existing cards for research purposes. The report and recommendations of the review group were submitted in January 2012. The review re-affirmed the original decision reached in 2010, i.e. that in order to meet both ethical and legal obligations, newborn screening cards older than ten years should be destroyed. Following careful consideration this recommendation was accepted. The Review Group also explored how the cards could be made available to the research community in a way which is compatible with ethical and legal obligations. In the interests of facilitating research, the HSE launched a public information campaign on 8 January 2013. This campaign offering members of the public the opportunity to have their screening card returned to them, prior to any destruction of the cards taking place, ended on 31 March 2013. The HSE has received approximately 40,000 requests from people seeking to have cards returned to them.

The Minister has sought advices from the Attorney General on how the remaining New Born Screening Cards can be retained in compliance with Irish and EU data protection legislation. The Minister has also requested that no destruction of the cards begins before an expert group has had an opportunity to consider the matter further.

### **Guidelines**

Clinical guidelines exist for certain rare diseases. The need for an overall Clinical Programme for Rare Diseases has been accepted by the Minister for Health and the appointment of a National Clinical Lead in Rare Diseases in the Health Service Executive took place in late 2013. It is anticipated that one of the roles of the person appointed to this position will be to instigate the development of clinical guidelines.

### **National rare disease events in 2013**

To mark Rare Disease Day 2013 an all Ireland meeting of patients' organisations, science and industry was organised and the Irish Presidency of the Council of the European Union was held in the City Hall in Dublin<sup>331</sup>. The conference was organised by The Rare Disease Taskforce in Ireland which brings together the Genetic and Rare Disorders Organisation (GRDO), Irish Platform for Patient's, Science and Industry (IPPOSI) and the Medical Research Charities Group (MRCG) along with the Northern Ireland Rare Disease Partnership (NIRDP) and Rare Disease UK.

### **Hosted rare disease events in 2013**

The following events were hosted in Ireland: International Rare Diseases Research Consortium Conference 2013 (16-17 April 2013, Dublin), 10th HHT Scientific Conference (12-15 June 2013, Cork), 9<sup>th</sup> European Cytogenetics Conference (29 June - 2 July 2013, Dublin).

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<sup>331</sup> <http://vimeo.com/channels/rdwb13>

## 1.15. ITALY

### Definition of a rare disease

Stakeholders in Italy accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

Although there is no specific national plan/strategy for rare diseases in Italy, they have been designated since 1998 as a health care priority in the context of the 3-year national health plans, which are intended by the national government as directions for actions at a national level, whilst the responsibility for actual implementation of measures is attributed to the regional governments. A coordinated and comprehensive framework of actions has been set up by the Ministry of Health Decree 279/2001, which established a national network for prevention, surveillance, diagnosis and treatment of rare diseases, a National Registry of Rare Diseases, a waiver for medical care cost, a diagnostic work-up and therapy for patients with a suspicion or diagnosis of one of the rare diseases included in an identified list. The Ministerial Decree 279/2001 established an inventory (*Livelli Essenziali di Assistenza - LEA*) of rare conditions (284 single rare diseases and 47 groups of diseases), which receive specific cost exemption. These diseases are assessed as being chronic, debilitating and requiring a high cost treatment. The LEA lists services provided by the National Health System (NHS) to citizens representing the “essential” services, granted to all Italian citizens or foreigners legally resident in Italy, and they are currently provided after paying a prescription charge as “co-payment”. In accordance with Decree 279/2001, all LEA services are free for citizens affected by a rare disease in the list. A major problem is that only a few hundred of rare diseases and some groups of diseases are included in this inventory, which has not been updated since 2001, denying cost exemption for diseases not included in the list. The act that updates the LEAs, drawn up by the Ministry of Health, has not yet come into force, because the Ministry of Finance is still assessing its feasibility and LEAs remain as first defined in 2001. When effective, the act will allow progress in quality, appropriateness and efficiency, because it includes not only a new list of 110 additional diseases, but also a list of procedures (for example, laboratory assays for the diagnosis of metabolic diseases). Following repeated requests to the Ministry of Health to add specific rare conditions to the list, stakeholders have joined together and circulated in 2012 a petition demanding that diseases not included under the current scheme should be added. Many of these are conditions identified in the most recent years following advancement of scientific and medical knowledge. While certain Regions of the country have recognised and extended care to some diseases not included under the Decree 279/2001, rare disease patients in other Regions remain without exemption for co-payment for diagnostics, treatment and care. The Europe-wide petition was launched to bring attention to this issue. On December 2012, the Minister of Health, Prof. Renato Balduzzi, has approved the new list of 110 additional single/group of rare diseases and send it for final endorsement to the Ministry of Economy.

A Committee ensures the interregional coordination for rare diseases between the Ministry of Health, the *Istituto Superiore di Sanità* (ISS – the National Institute for Health - NIH), and all Italian Regions. This Committee has several aims, which include harmonisation of the regional service networks for rare diseases, implementation of the National Registry for rare diseases and management of the list of rare diseases for which patients can obtain free diagnosis and treatment. Rare diseases’ costs are included in the general national health care budget, but €20 million of the total National Health Fund are assigned to rare diseases (art. 1, par. 34 and 34bis, Law dated 23 December 1996, n. 662 and the Agreement between the Government, Regions and the Provinces of Trento and Bolzano, concerning guidelines for the correct use of bound resources by the special statute Regions and Provinces). Until 2010, dedicated funds were available for the implementation of specific projects aimed at strengthening the regional service networks (€30 million for 2008 and €5 million for the following years).

In 2008 the National Centre for Rare Diseases (CNMR) was established at ISS, with the mission of promoting and developing scientific research and public health actions, as well as providing technical expertise and information on rare diseases and orphan medicinal products, aimed at the prevention, treatment and surveillance of these diseases. The CNMR took over the activities carried out for many years by a specific unit within the ISS to tackle rare diseases<sup>332</sup>.

<sup>332</sup> [www.iss.it/cnrmr](http://www.iss.it/cnrmr)



In 2009, following an agreement between the Ministry of Health, the NIH and the Italian Regions, €8 million were allocated to research projects on rare diseases: €5 million from Ministry of Health and Welfare and €3 million from AIFA (the Italian Drug Medicines Agency).

On 11-13 November 2010, the Italian Federation for Rare Diseases (UNIAMO FIMR Onlus), in collaboration with EURORDIS, organised a national conference on rare diseases<sup>333</sup> in Florence in the context of the EUROPLAN project. All stakeholders showed great interest in the sessions and worked together to draw up a final report, whose results were presented during a final plenary session open to the public. The aim was to develop an integrated, global and long term strategy for rare diseases in Italy, with the active involvement of all stakeholders to share common European guidelines. Several drafts of laws focusing on the incentives for research and access to therapies for rare diseases and the production of orphan medicinal products have been presented to the Italian Parliament over the last few years. Their approval lies outside the direct domain of the Ministry of Health.

In 2011, a working group was established at the Ministry of Health in Rome to thoroughly analyse the issues related to the National Plan for Rare Diseases and to draft the preliminary document. On 23 February 2012, a conference was organised at the Chamber of Deputies, and a white paper presented, with the aim of encouraging the government to put in place the rare diseases plan. Between March and April 2012 both Orphanet and UNIAMO organised public consultation on rare diseases with the aim of providing input from stakeholders into the process. The working group of the Ministry of Health preparing the draft of the national plan concluded in June 2012, and the document was sent by the Ministry of Health to AIFA for comments, and subsequently again to the Ministry of Health for final assessment. The document was presented in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step was for the document to be implemented by the stakeholders, from January to February 2013. Their comments were evaluated and included in the document in March 2013 by the Ministry of Health and sent for approval by the permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano.

In January 2013, UNIAMO FIMR organized in Rome a meeting with patients' representatives focused on the discussion of the Draft Plan for Rare Diseases. The contributions were forwarded to the Ministry of Health.

In April, UNIAMO FIMR started organizing the second EUROPLAN Conference 2012-2015, by setting the Steering Committee and activating the thematic working groups through face to face meetings and a virtual web platform set up *ad hoc*. The working groups included a broad representation of the key stakeholders.

On 25 May 2011, the Permanent Conference for relations between State, Regions and Autonomous Provinces of Trento and Bolzano, ratified an agreement, formalising the engagement of health authorities in guaranteeing, through concrete actions, the global, continuous and homogeneous nationwide management of patients affected by neuromuscular diseases. This goal was achieved via the intensive work carried out by the Ministerial Conference for Neuromuscular Diseases.

### **Rare Diseases Interregional Board**

In 2006, the Health Commission, constituted by the Health Representatives of all Italian Regions, has established a permanent Interregional Board on Rare Diseases. Members are experts officially appointed by every Regional Government.

The Board meets regularly, at least 6 times per year, in order to share best practices and promote a progressive harmonisation of the health policies for RD patients, which, in the decentralized Italian scenario, have been developed so far by the Regional Governments. In these years, among others, the following issues were addressed: methods adopted for the identification of Centres of expertise at regional/interregional level, set-up and maintenance of regional-interregional RD registries, access to therapies for RD patients, shared care pathways and diagnostic-therapeutic protocols for RD patients, innovative tools for patients' management (i.e. telemedicine).

The Board officially represented the Regional Governments' position in the first Italian Europlan Conference and in the context of several RD-related events promoted by patients' associations.

Since its establishment, the Board has produced, in collaboration with the Health Ministry and the ISS, a proposal of a list of RD to be added to the national list issued in 2001, and has worked on the elaboration of formal agreements between the State and the Regions leading to the definition of a common minimum data set to be transferred from regional/interregional Registries to the national Registry, Other documents

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<sup>333</sup>[http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/final\\_report\\_italy\\_europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf)

produced by the Board were focused on the regional/interregional governance of the RD care networks and on the position of the Regions with respect to the laws' proposals on rare diseases under discussion at the Italian Parliament.

In particular, in 2013, the Board has carried out an inventory of all the Centres for rare diseases, officially labelled at regional-interregional level since 2001. The inventory aimed, in particular, at exploring the RD Centres' compliance with the criteria adopted by Eucerd. Following this activity and the experience of the "A Community for RD" project, promoted by UNIAMO, a collaboration with Age.na.s (the Agency for the Regional Health Systems) has started. The aim is to analyse the methods used for the identification of RD Centres, in particular those developed by some Regions, based on the integrated analysis both of patterns of hospitalization of RD patients and regional Registries' data.

In 2013, the Interregional RD Board has produced an inventory of all the patients' organizations dealing with rare diseases active at national, interregional, regional and local level. For each association updated information regarding diseases followed, number of patients represented, officially appointed representatives, ongoing projects, territorial diffusion and contact details, has been collected and shared.

In 2013, the Health Commission officially adopted two other documents elaborated by the RD Interregional Board: one dealing with the identification of common regional modalities and pathways for the delivery of home cared therapies to RD patients; another one, addressed in particular to AIFA, containing the Regions' proposals regarding the main open issues in the field of the drug provision to RD patients. The contents of both these documents have been shared with the Interregional Pharmaceutical Board, in which all Regional Pharmaceutical Services are represented. Furthermore, the collaboration with the Pharmaceutical Interregional Board has led to the production of a list of off-label drugs and drugs marketed abroad for rare diseases, partially refundable by AIFA to Regions, which normally cover with their budget these costs.

In 2013, two working groups have been established in the context of the Interregional Board on RD. They will conclude their mandate in early 2014 with the approval of two documents representing the state of the art and the Regions' position and proposals on the following two issues: expanded newborn screening and telemedicine. Both these documents will be submitted in 2014 for final approval to the Health Commission.

### **Centres of expertise**

In 2001, the Ministerial Decree 279/2001 foresaw the establishment of a national network for rare diseases (*Rete Nazionale delle Malattie Rare*), made up of hospitals and referral centres, for around 500 rare diseases (covering around 5000 entities) included in the aforementioned list (LEA). Soon after the delivery of the Ministerial Decree, the Italian Constitution was changed, and health programmes and their organisation were assigned to the Regions. Because of their autonomy, the 20 Regions used different criteria to identify centres for rare diseases and adopted different models to organise their networks. In the years, there has been an effort towards progressive harmonization. Some Regions have shared a common methodology to identify Centres, based on the combined analysis of patterns of hospitalization of RD patients and on regional registries' data. Furthermore, formal agreements between Regions have led to the creation of interregional networks of Centres, working in collaboration for the definition of common diagnostic and therapeutic protocols. Around 215 centres (*Presidi*) have been identified.

According to the n. 279/2001 decree, each patient suspected to be affected by a rare disease is addressed to designated hospitals where a free of charge diagnosis can be achieved and, if the disease is confirmed, free treatment is offered by any hospital or outpatient facility within the NHS. Coordination centres have been created at regional level in order to manage the activities of referral centres, to exchange information between them, and to provide expertise and data to the regional rare disease registries, to provide information on RD to patients and health professionals and to collaborate with patients' organisations.

In 2011, UNIAMO FIMR<sup>334</sup> developed the project "A Community for Rare Diseases", aimed at defining a model to assess the quality of expertise centres for rare diseases in Italy. The project gathered all relevant stakeholders who reached a common definition of a Centre of Expertise. In December, Age.Na.s, the National Agency for Regional Health Services, together with UNIAMO FIMR visited in Milan five Centres (*Presidi*) to assess the validity of this model.

### **Registries**

The Italian National Registry for Rare Diseases, was established at ISS in 2001 in agreement with article 3 of the Ministerial Decree 279/2001. It is located at Italian CNMR- ISS and it is supported by public funds. The general objectives are epidemiological surveillance of rare diseases and national and regional planning of measures to

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<sup>334</sup> <http://www.uniamo.org/>

assist rare disease patients. Specific objectives include the following: estimation of incidence and prevalence; temporal and geographical distribution of cases and diseases at national level; diagnostic delay. The legal provisions envisage the Registry as a tool to support scientific research in the clinical, biomedical and epidemiological fields. The National Registry collects a minimum set of data from Regional registries, according to an Agreement between the State and the Regions, signed in 2007. Since 2001, each Italian Region established its own registry for rare diseases. These registries collect epidemiological information provided by accredited Centres for rare diseases (*Presidi*) and, in many cases, by other sources of data (i.e. territorial network of services, pharmaceutical services), and every year they send the agreed common minimum data set to the National Registry. The Regional Registries differ in their internal organisation, aims and collected information. Some of them have mainly epidemiological and public health purposes to support regional planning, while some are aimed at evaluating health services and diagnostic procedures, while others are information systems developed to support the delivery of services to RD patients, collecting at the same time epidemiologic as well as clinical data on registered patients. Agreements were established between regional administrations in order to create some interregional registries. Each interregional system has its informatics infrastructure, acting as a network connecting different centres and health professionals involved in the management of patients with rare diseases. Piedmont has developed a system shared with Aosta Valley Region, covering an area of about 4.5 million inhabitants. Veneto Region has developed since 2001 an information system, currently adopted by other 8 Italian Regions (Autonomous Provinces of Bolzano and Trento, Emilia-Romagna, Liguria, Umbria, Campania, Apulia and Sardinia – this last one under implementation), globally reaching a covered area of about 25 million inhabitants. Other Regions have developed their own system for collecting data (i.e. Lombardy, Tuscany, Marche, Friuli Venezia Giulia, Sicily and Lazio). The remaining Regions (Molise, Abruzzo, Calabria, Basilicata, for a total of about 2.5 million inhabitants) currently use the software developed by the National Registry at ISS.

In November 2011, the CNMR-ISS published the first Report on “National Registry and Regional/Interregional Registries for rare diseases<sup>335</sup>”, describing the surveillance system for rare diseases in Italy. In addition to a background of European initiatives on rare diseases, this report also provides detailed information of the evolution of Italian regulatory and institutional context; the steps towards planning and implanting the National Registry; a description of regional/interregional registries; the data quality assessment; the methodological models for estimating epidemiological indicators. The National Registry provides a tool for epidemiological surveillance of rare diseases and evaluating health care programs. The Registry has a strong legal support, including the exemptions from the costs associated with the delivery of care; is a web-based registry in compliance with the legal and ethical requirements; is a population-based registry, although the regional coverage is heterogeneous; provides important public health indicators. The National Registry is connected with other interregional, regional and international registries.

A congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome on 22 February 2012, to illustrate the results, to discuss and agree among all actors on actions to improve further the performance of the National Registry. On 25 February 2013, a second congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome, aiming at sharing the state of the art of patient registries in Italy. Over the last few years, data collection for the National Registry of Rare Diseases was improved, reaching a territory coverage of the 97% in 2012 (compared with 62% of 2009), due to the improvement of the surveillance system both at national or regional level. Publication of the second ISTISAN Report on National Registry and Regional/Interregional Registries for rare diseases is in progress.

The CNMR also provides support to spontaneous independent registries promoted by patients and run by clinicians: in the last few years the Italian Registry of Paroxysmal Nocturnal Haemoglobinuria and Cystic Fibrosis have been established, with the assistance of CNMR. Registry initiatives for rare diseases will be a focus of the future National Plan for Rare Diseases.

The CNMR coordinates EPIRARE, a project co-funded by the DG-SANCO, which involves several EU and non-EU countries. The project’s general objective is to build consensus and synergies to address legal, ethical and technical issues associated with the registration of RD patients and to elaborate a proposal for an EU web-based multi-disease platform. This tool, based on sharing of information and resources, aims at increasing the sustainability of registries, promotes the use of standards and registry quality procedures, and provides an effective way of disseminating the results ([www.epirare.eu](http://www.epirare.eu)).

Italy also participates in European registries such as EUROCAT, EIMD, EURO-WABB, EuroWilson, TREAT-NMD, HAE-registry, RBDD, AIR and EUROCARE CF.

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<sup>335</sup> <http://www.iss.it/binary/publ/cont/undici20WEB.pdf>

### Neonatal screening policy

In Italy, neonatal screening is mandatory for cystic fibrosis, congenital hypothyroidism and phenylketonuria (Law 104, 5 February 1992). Some Regions perform screening of additional diseases including adrenal hyperplasia, biotinidase deficiency, maple-syrup urine disease, and galactosaemia. Other Regions, including Tuscany, Sicily and Emilia Romagna, adopted wider neonatal screening programs to include a number of metabolic disorders, based on the guidelines developed by scientific societies. According to SIMMESN (*Società Italiana per lo Studio delle Malattie Metaboliche Ereditarie e lo Screening Neonatale*<sup>336</sup>), about one fifth of the Italian newborn population underwent an expanded screening in 2011. UNIAMO FIMR sent a position paper on this subject as a Memorandum for the XII Social Affairs Commission of the Chamber of Deputies, on Draft Law No. 5,440 Conversion into law of Decree-Law of 13 September 2012 n. 158, laying out urgent measures to promote the development of the country by a higher level of protection of health, calling for a gradual expansion of neonatal screening programs for all rare diseases for which there is evidence of appropriateness, and not only for rare diseases for which treatments are available. However, it will be mandatory to define a common set of standards, procedures and methodologies at the national level to ensure an effective, fair and appropriate disease screening as well as to assure adequate health and social post screening management.

At European level, the “Tender on EU newborn screening practices” had the aims of identifying and evaluating all aspects deemed relevant to the implementation of a public health action in newborn screening (NBS), taking into consideration the views of professionals, patients and health authorities. This project, funded by European Commission DG SANCO, was coordinated by CNMR–ISS, with the intent to support actions at the Community level, to identify the strategies which the European Commission could adopt to promote the implementation and improvement of NBS programmes in EU. All relevant documents elaborated by the Tender and the final reports are available at the [www.iss.it/cnmr](http://www.iss.it/cnmr) website. In line with the results obtained during this Tender, in 2011 the Italian Ministry of Health funded a project on neonatal screening aimed at harmonising access to health services in the Italian Regions. The project, coordinated by the CNMR–ISS, is carried out in collaboration with the Ministry of Health, the Italian Agency for Regional Health Services (Age.Na.S), the Interregional Rare Diseases Board (*Tavolo Interregionale Malattie Rare*), and two Italian Scientific Societies (SISMESN and SIGU).

In November 2013, a hearing at the Senate took place concerning a proposal to reorganise and rationalise the different regional health care systems in the field of newborn screening in order to harmonize the regional activities. Existing regional differences in neonatal screening policies can be explained because the screening of additional diseases, besides the diseases cited in law to be tested (cystic fibrosis, congenital hypothyroidism and phenylketonuria) represents an extra-LEAs (Essential Levels of care) service for citizens. So, the cost of the screening of additional diseases is completely at the charge of the Regions. To appropriately tackle this issue, in 2013 the Interregional Rare Diseases Board has established a working group in order to elaborate a document describing the state of the art, specific health policies developed by the Regions in this area and some proposed future actions. This document will be presented for approval to the Health Commission in early 2014. It clearly advocates the common definition of the diseases, the screening of which should be included into the LEA list, in order to overcome regional differences. Furthermore, it underlines the necessity to consider expanded newborn screening as a part of broader and comprehensive care pathways developed for patients affected by the diseases screened.

The Stability Law of December 2013 (art. 1, paragraph 229) has granted the experimental widening of national neonatal screening of metabolic disorders with €5 million.

### Genetic testing

Italy is monitoring genetic test use since the 1980s, and this monitoring has expanded recently to include clinical and laboratory activities carried out by Medical Genetic Institutes and also private laboratories since 2009<sup>5,6</sup>. This census, promoted by SIGU (Italian Society of Human Genetics), surveys the services provided by Italian Medical Genetic Centres and involves the NHS bodies, the IRCCSs (Excellence Centres for Healthcare and Research), the University Institutes, the CNR (Research National Council) laboratories, and private laboratories. Data collection takes into account the typology of the Institutes, number and functions of the laboratory staff, cytogenetic analyses, genetic-molecular and immunogenetics analyses, and clinical activities, including genetic counselling. Certified quality systems adopted by the Institutes and the adequacy of some genetic tests have been also checked.

The survey concerning the 2011 data was carried out in 2012. The census was made possible thanks to the collaboration of the Bambino Gesù Children Hospital, Orphanet-Italy, and SIGU. On the whole, 517 services

<sup>336</sup> [www.sismme.it/it/documents/rt\\_screening/rt\\_screening\\_2011.pdf](http://www.sismme.it/it/documents/rt_screening/rt_screening_2011.pdf)

hosted by 268 Hospitals or Institutions were surveyed, including 145 clinical genetic services, and 153 cytogenetic, 198 molecular genetics and 21 immunogenetics laboratories. The 53% of services are located in the Northern regions, the 20% in the Central regions, 17% in the Southern regions, and 10% in Sicily and Sardinia. About 74% of these services were accredited and 55% certified.

In 2013, the Working Group on Cytogenetic of the SIGU approved and disseminated a set of guidelines for cytogenetic diagnosis, which came 20 years after the previous set of guidelines in this area.

The CNMR-ISS is in charge of carrying out the National External Quality Control Scheme for genetic tests. This scheme includes molecular and cytogenetic tests and has been addressed to public laboratories which provide genetic tests. This activity is dependent on a Steering Committee, composed of experts who evaluate the results of cytogenetic and molecular genetic tests. All strategies used for the project have been discussed and determined through a consensus by the Steering Committee. In 2009, this scheme was extended also to private genetic laboratories. A Steering Committee, composed of experts, evaluates the results of cytogenetic and molecular genetic tests. All strategies used for the project have been discussed and determined through a consensus by the Steering Committee. In 2009, a fee for participation was introduced by a national decree for all participant public and private laboratories. At the end of each trial of external quality control, each laboratory receives its own results. In addition, the CNMR-ISS organises a national Conference to illustrate the main results. To date eight rounds have been completed and overall 112 laboratories have been monitored in the context of the National External Quality Control Scheme. In particular, as regard molecular genetics, in 2012, national experts have assessed laboratory performance on genotyping, interpretation, and reporting of test results for a total of 404 different DNA samples sent to 68 public and private laboratories. In addition, 75 laboratories participated in one or more schemes of constitutional or cancer cytogenetic quality control.

The CNMR-ISS is a member of the management board of the European Molecular Genetics Quality Network (EMQN<sup>337</sup>), a not-for-profit organisation promoting quality in molecular genetic testing by establishing, harmonising and disseminating best practice. EMQN provides external quality assessment to labs worldwide in collaboration with other organisations, including EuroGenTest, CF Network, ESP, UKNEQAS for Molecular Genetics, RCPA QAP, and the EAA.

Genetic tests for 1101 genes and 1165 diseases are registered in the Orphanet database<sup>338</sup>.

### **National alliances of patient organisations and patient representation**

In Italy, UNIAMO FIMR is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 100 patient organisations representing more than 600 rare diseases. UNIAMO FIMR publishes a newsletter and organises regular meetings and conferences. The goal of this Federation is to serve as a reference and representative voice for rare diseases, bringing opinions of patients and their families in the public health decision-making processes at regional and national level. It is committed in the protection of patients' rights and improvement of the quality of life of rare disease patients and their families. UNIAMO FIMR is currently organising Regional Delegations: a coordination of territorial groups in order to develop or strengthen the relationship of solidarity and cooperation between member organisations and to foster, at local level, initiatives and policies promoted by the Federation. The Federation participates, as patients' representative, in the institutional tables dedicated to rare diseases in Lombardy, Lazio, Puglia and Campania. In addition, UNIAMO FIMR has played an important role in the Lombardy Region, in particular during the discussion of rare disease diagnostic and therapeutic pathways, having been enrolled by patients not officially represented by any territorial association.

In 2012, a framework agreement was signed by UNIAMO FIMR with the Telethon Foundation Onlus-CTFO, to promote access to TNGB genetic biobanks by members of the associations' federation.

In October 2012, the Ministry of Welfare recognised UNIAMO FIMR as an Association of Social Utility.

There is no public funding scheme for activities of the patients' organisations, but national governmental institutions (e.g. the Welfare Ministry) and local institutions support specific actions. Grants for activities of patients' organisations are coming mainly from private sponsorship, charities and income tax donations.

In 2013, within the "*Conoscere per assistere*" project addressed to general practitioners (GPs) and paediatricians (PLS), supported by Farindustria, UNIAMO FIMR, in collaboration with the federation of paediatricians and general practitioners (FIMP, FIMMG), and scientific societies of physicians (SIP, SIMG, SIMGEPED, SIGU) organized 3 training courses in Florence (April), Potenza (May), and Turin (October). The

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<sup>337</sup> <http://www.emqn.org/emqn/Home>

<sup>338</sup> Information extracted from Orphanet in February 2014.

major topics of these courses included: how to suspect a rare disease, how to manage the transition of rare disease patients from paediatric into adult age.

In July-September 2013, on behalf of Eurordis, the President of UNIAMO FIRM worked as a member of the Commission established by the Ministry of Health charged of evaluating the so-called Stamina protocol (a non-scientifically sound treatment for many rare diseases, based on stem cells).

In 2013, UNIAMO FIRM was confirmed as a member of the board of the Biobank Network settled by Telethon Foundation, and of the Interregional Rare Disease Committee.

In 2013, UNIAMO FIRM coordinated the project “*Determinazione Rara*”, an advanced national training programme for the proactive enrolment of patients in research trials, based on workshops with clinicians, researchers and biobankers.

In September 2006, the National Council for Rare Diseases (the “*Consulta*”) was established as a national independent representative body and its activities were hosted by the CNMR-ISS. It was originally composed of 34 members (one for each participating rare disease patient organisation), which was then lowered to 28; these members were elected by 264 rare disease patient organisations’ representatives. The *Consulta* aimed at identifying the priorities in the field of rare diseases, to define the problems, to recognise solutions for the patients and their families, to involve rare disease patients in the legislative bodies’ decisions, and to strengthen the links between RD organisations and the society. By the end of 2010, the *Consulta*<sup>339</sup> constituted itself as a private legal organisation which keeps on executing the tasks entrusted by the Minister of Health and affords some of the daily problems of rare disease patients.

The Council for Neurodegenerative Diseases was established by the Ministry of Labour, Health and Social Affairs, through a Ministerial Decree (27 February 2009). The Council brings together patients organisations for neurodegenerative diseases, such as amyotrophic lateral sclerosis, muscular dystrophy, spinal muscular atrophy, advanced stage muscular dystrophy and locked-in syndrome, experts on these disorders, and representatives from Regions and the Ministry of Health. Based on the final document produced by the Council, a proposal for an agreement among State and Regions on health care pathways has been drawn up and taking into account some modifications proposed by the Interregional Board on Rare Diseases. The final version of the Agreement has been signed in 2011. Following this Agreement some Regions have developed interregional collaboration for the definition of common health-care pathways, supported by the parallel development of specific modules within the existing RD information systems with the aim of supporting the prescription, made by clinicians working in Centres of expertise, and the delivery not only of drugs, but also of medical devices (i.e. eye-gaze systems). An Agreement between the State and the Regions has been signed in 2013 regarding the development of specific and comprehensive care pathways for patients affected by Hereditary Haemorrhagic Disorders, based on the activity of the already labelled regional-interregional Centres for HHD and involving other professionals working in the RD care networks, as well as in other care settings.

In November 2012, the MIR (*Movimento Italiano dei Malati Rari*) was founded by 15 patients’ associations.

## Sources of information on rare diseases and national help lines

### **Orphanet activity in Italy**

Since 2001, a dedicated Orphanet team was established in Italy, which is hosted by the Bambino Gesù Children Hospital in Rome. This team is in charge of collecting data on rare diseases-related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations, networks) for entry into the Orphanet database. This group was designated in 2010 by the Ministry of Health as the official Orphanet team for Italy. The Orphanet portal is available in Italian and the team maintains also the Orphanet Italy national website<sup>340</sup> and a Facebook page<sup>341</sup>.

On the occasion of the tenth anniversary of Orphanet Italy, an updated Italian Directory of Services, *Annuario Orphanet delle Malattie Rare 2011*, was presented at the Ministry of Health. In attendance was Italian Health Minister, as well as the Director of the Paediatric Hospital Bambino Gesù, hosting the Italian Orphanet headquarters; Orphanet country coordinator and Scientific Director at Paediatric Hospital Bambino Gesù; President of Farindustria, which financed this second book, and President of UNIAMO FIRM.

In December 2011, the Italian Minister of Health, Prof. Renato Balduzzi, presented the “*Relazione sullo stato sanitario del paese 2009-2010*” (Report on country sanitary status 2009-2010). For the very first time, the

<sup>339</sup> [www.cndmr.it](http://www.cndmr.it)

<sup>340</sup> <http://www.orphanet-italia.it/national/IT-IT/index/homepage/>

<sup>341</sup> <https://it-it.facebook.com/OrphanetItalia>

Italian Ministry of Health identified Orphanet as a reference source for rare diseases and orphan drugs, stressing the relevance of the joint action established between the Ministry of Health and Orphanet-Italia.

In May 2011, Orphanet Italy signed a collaboration agreement with *Fondazione Cesare Serono* linking the two web sites in order to spread information on rare diseases to a broader public.

From September 2011 onwards the Italian Society of Anesthesia, Analgesia and Intensive Paediatric Care (SIAATIP) collaborates with Orphanet Italy to develop the "Orphanet Emergency" guidelines, designed to improve the hospital emergency management of rare diseases, through recommendations about the care of patients who need medical treatment under emergency.

In November 2011, Orphanet Italy set up a partnership with the company Genzyme who provides financial support for the translation in Italian of the bi-monthly newsletter OrphaNews.

In January 2013, in the perspective of implementing the Orphanet database, Orphanet Italy launched a survey and set up a collaboration with the Italian Inter-regional Technical Board for Rare Disorders to collect data on the Centres of Reference officially recognized and established by Regions. All regional coordinators of the Italian National Network for Rare Diseases were involved in this process and more than 700 Centres of Reference for rare diseases were identified in Italy and registered in the Orphanet database.

### **Official information centre for rare diseases**

The Ministry of Health organised a specific section for Rare Diseases<sup>342</sup>, providing several information, including the list of rare diseases present in the ministerial decree 279/2001.

The CNMR-ISS plays a key role in disseminating information on rare diseases through the official website<sup>343</sup> and the Italian national helpline for rare diseases "*Telefono Verde Malattie Rare*". The website (in Italian and English), updated weekly, is addressed to health operators and institutions, social workers, associations, patients and their families and, in general, the public at large. The site has been structured on two levels: the central site containing general information, and satellite websites containing specific projects and different topics, including Registries (Italian National Registry for Rare Diseases, Italian National Registry for Orphan Drugs, Italian Network of National Registries of Congenital Anomalies), Orphan drugs, Guidelines, Narrative medicine, Folic Acid Italian Network, European projects, Genetic Tests, Patient Organisations. The section "Centres for rare diseases in Italy" lists all Centres accredited by Regions for diagnosis and treatment, which can be searched by disease, code number, Region, etc. Moreover, all contact details of the Regional Coordination Centres are available.

### **Help line**

The Italian national helpline for rare diseases "*Telefono Verde Malattie Rare*" (no. 800.89.69.49) was set up at CNMR-ISS on February 2008, and funded by the Ministry of Health. This helpline collaborates with all stakeholders, including the Ministry of Health for legislative and regulatory issues, and it is advertised on CNMR-ISS web page<sup>344</sup>. The line is free and available five days per week (from 9 am to 1 pm). From abroad it is possible to access the line information by using the e-mail address [tvmr@iss.it](mailto:tvmr@iss.it). A group of psychologists, sociologists and medical doctors trained and experienced on telephone counselling, public health policies and management of rare diseases are involved in this activity. The aim of the service is to inform health operators, social workers, patients and their families, and the public at large, on rare diseases (including exemptions from the costs of medical care in Italy), and to address them to the national/Regional network of specialised centres. *Ad hoc* literature researches are made for specific questions. Information about patient organisations, orphan medicinal products, and clinical trials running in Italy and abroad are also provided. A web based system is used for data collection and to provide information, also using national and international databases (e.g. Orphanet, PubMed, ClinicalTrials.gov, etc.). The Italian national helpline for rare diseases is a member of the European Network of Rare Disease Help Lines.

In 2012, the CNMR-ISS started collaborations and training activities for regional help lines (i.e. Contact Centre of Tuscany Coordination Centre for rare diseases) and with Patients' Associations (i.e. Foundation "W Ale –Alessandra Bisceglia").

Some Regions (Veneto, Lombardy, Tuscany, and others) have established help line services to provide information on rare diseases, dedicated health services and provisions to patients, families, professionals, and the public at large.

<sup>342</sup> <http://www.salute.gov.it/malattieRare/malattieRare.jsp>

<sup>343</sup> [www.iss.it/cnmr](http://www.iss.it/cnmr)

<sup>344</sup> [www.iss.it/cnmr](http://www.iss.it/cnmr)

### **Other sources of information on rare diseases**

Information for patients and health professionals is available from websites run by Centres for rare diseases present in some Regions. A specific e-mail address ([esenzioni@sanita.it](mailto:esenzioni@sanita.it)) at the Ministry of Health provides information on issues concerning LEA services and co-payment exemption for rare disease patients. Online Regional information is also available. Other services offered by patient organisations, although they are heterogeneous in their coverage.

The website [www.malattirari.it](http://www.malattirari.it) set up by UNIAMO FIMR, provides both general information on legislative and administrative issues and orphan medicinal products, and, at regional level, specific information managed in collaboration with patients' organisations and health professionals.

Many regions have developed their own websites dedicated to rare diseases, as well as help lines for health operators and patients.

On December 2011, OrphaNews-Italia<sup>13</sup> was launched by national Orphanet team. This online bulletin offers a complete translation into Italian of the contents of OrphaNews-Europe, and is available from Orphanet-Italy homepage and from the Orphanet Italian country site. OrphaNews-Italia is published online on a regular basis, one week after the publication of the English version. At the end of 2013, 38 issues were published and the total number of registered readers was 4031.

### **Guidelines**

The Ministry of Health and ISS are involved in the National Guidelines System (NGS), which is officially entitled to issue guidelines and to make available any other document drawn up by the Consensus Conferences carried out by NGS. Guidelines published by CNMR-ISS, as part of NGS, include those for Down's syndrome, alternating hemiplegia, hereditary epidermolysis bullosa. Guidelines for tuberous sclerosis and aniridia are under development.

In order to promote the development of high quality best practice guidelines and their use in Italy and across Europe, CNMR-ISS organised national and international training courses (9-11 July 2012) providing participants (health care professionals, policy makers, patients) with the opportunity to learn about the core methodology used to develop best practice guidelines. In addition, CNMR-ISS encourages international debate on the role and quality of best practice guidelines in the field of rare diseases. In particular, a workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February 2012, aimed at sharing experiences and knowledge and discussing critical methodological issues due to the specificity of rare diseases.

In 2012, CNMR, 13 institutional partners and one SME have been awarded with a grant by the European Commission, under the Seventh Framework Programme (FP7/2007-2013) for a four-year research project entitled RARE-BestPractices ([www.rare-bestpractices.eu](http://www.rare-bestpractices.eu)), commencing in January 2013. RARE-BestPractices is a platform for sharing best practices for the management of rare diseases. This project brings together a team of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, rare disease epidemiology and public health. The overall aim of the project is to improve the care of patients by disseminating globally best practices for the management of persons with rare diseases. The CNMR acts as coordinator of 14 partners across Europe, all with strong commitment in research on rare diseases, public health and evidence based medicine. The project's aims to provide reliable informative resources for the rare disease community by creating a collection of methodologically trustworthy and up-to-date guidelines for the management of rare disease; to develop a standard methodology suitable for the development of RD guidelines; to set up training activities and training tools targeted at key stakeholders for the production of high quality rare disease guidelines. Other key elements of the platform are the identification of mechanisms to address the limitations of the evidence, set priorities for rare disease research and propose improvements in pre-approval and post-marketing studies.

RARE-Bestpractices has supported the creation of a new international open access, online, peer-reviewed journal: "Rare Disease and Orphan Drugs" (RARE Journal - <http://rarejournal.org/rarejournal>). RARE is a science journal, published three times per year focusing on relevant aspects of public health, health policy and clinical research on rare diseases.

About 85 *Percorsi Diagnostico-Terapeutico-Assistenziali-PDTA* (Diagnostic Therapeutic Care guidelines), dedicated to diagnosis, treatment and clinical management of rare diseases, have been developed since 2010 by the Lombardy Region<sup>345</sup>.

The working group of the National Committee for Bioethics (CNB) and the National Committee for Biosecurity, Biotechnology and Life Sciences (CNBBSV) published two reports in 2010 dealing respectively with the issues related to the long storage of biological samples obtained by neonatal screenings, and susceptibility

<sup>345</sup> <http://malattierare.marionegri.it/content/view/111>



testing and personalised medicine. In 2011, the CNB drafted a document relating to orphan medicinal products for people with rare diseases<sup>346</sup>.

### Training and education initiatives

In Italy, a second level Master degree in rare diseases is organised by the University of Turin. Rare diseases are present in the undergraduate training and post-graduate courses of the Optional Integrated Degree Course of Medicine and School of Specialisation at the Universities of Padua, Siena and Pisa.

The CNMR-ISS organises residential courses and learning activities dedicated to the empowerment of patients, health professionals and policy makers<sup>347</sup>. This program is included within the project "Rare diseases: from monitoring to training" funded by the Ministry of Health.

The CNMR and ISS External Relations Office have developed in several Regions a project for training the general practitioners (GP) and paediatricians looking for rare diseases, in order to reduce delay in diagnosis, to manage patients' care appropriately in the framework of the Italian rare diseases network, and to improve communication skills. To reach this goal, the courses employ an interactive method, Problem-Based Learning (PBL). PBL is an instructional approach that uses a problem as a didactic initial stimulus. Learning is achieved by working in small groups assisted by a trained PBL facilitator at the explanation or solution of the problem. The GPs' and paediatricians' participation to the courses has been active and all professionals got positive results in learning assessment questionnaires. The training showed that PBL enhances participant activity and provides the opportunity to practice skills, so that they can produce changes in professional practice, and, ultimately, in health care outcomes. In order to improve the training model, patient organisations were involved in new courses, in collaboration with the "W Ale - Alessandra Bisceglia" Foundation, aiming at training GPs and paediatricians on congenital vascular malformations.

In 2013, the CNMR organised a course (using cooperative learning method) for the "W Ale - Alessandra Bisceglia" Foundation volunteers, aiming to set up and carry out a specific helpline to inform health operators, social workers, patients and their families, and the public at large, on congenital vascular malformations and related disabilities. The W Ale helpline will start in 2014, in collaboration with the Italian national helpline for rare diseases "*Telefono Verde Malattie Rare*".

The CNMR coordinates the "Story Telling on Record" (S.T.o.Re. – [www.storeproject.eu](http://www.storeproject.eu)): a 2-year European partnership funded in the Lifelong Learning Programme (Leonardo da Vinci Multilateral Partnerships August 2013 -July 2015). The project involves 7 partners from 6 countries and foresees 4 partners' meetings and a final conference in Italy. The objective is to design an action-research that includes training participants, giving them the knowledge and the skills necessary to design, test and train people in the use of Integrated Medical Records (IMRs), and organise courses on the use of IMRs for health care system personnel, in the rare and chronic diseases. The results of this project will be disseminated through a dedicated website, scientific reports and two booklets (toolkits in English and in the partners' languages, tailored to patient organisations and to health institutions and professionals).

The CNMR carried out the first International Summer School "Rare Diseases and Orphan Drug Registries" (ISS, Rome - 16-20 September 2012). The course took the participants through the main concepts and practical steps to be undertaken in the establishment and management of a rare diseases registry, to ensure its usefulness, soundness and sustainability. The course provided basic notions on the methodology of observational studies with a view to the specificity of rare disease registries, on the selection of data elements with a focus on the interoperability of rare disease registries, on quality assurance, and on the technical and legal tools to be adopted for protecting patients' data confidentiality. The course consisted of frontal presentations followed by small group exercises, using the cooperative learning method.

The second International Summer School "Clinical Practice Guidelines on Rare Diseases" was organised by CNMR (ISS, Rome, 8-12 July 2013). The course took the participants through the development process of clinical practice guidelines, by providing the basics of clinical practice guideline and evidence synthesis approaches. The course format consisted of brief presentations followed by individual or small group exercises for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

A major role in educating medical doctors is carried out by patients' organisations (e.g. UNIAMO FIMR through the projects "Knowing to assist" and "Mercury", see the "National alliances of patient organisations and patient representation" section).

<sup>346</sup> [http://www.governo.it/bioetica/pdf/Maklattie\\_rare\\_25112011](http://www.governo.it/bioetica/pdf/Maklattie_rare_25112011)

<sup>347</sup> <http://www.iss.it/cnmr/appu/index.php?lang=1&tipo=56&anno=2011>

The Italian Telethon Foundation and Orphanet-Italy joined their respective competences and contact networks in October 2012 to meet the patients' needs and support health professionals via a training course entitled "*e-patients, e-parents, e-doctors: le malattie rare via web – opportunità e rischi*". Suited for all stakeholders of the rare disease community, this event provided an opportunity to discuss web services and social networks as tools for professionals, patients and their families. During the course, health professionals, journalists, and IT experts presented their experiences to guide the community in using the web as a tool to break the isolation rare diseases can impose. A round table was animated by communication experts on the responsible use of Internet.

On 15 April 2013, the Orphanet team held a training course in Rome for health professionals from the Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

In 2013, the ISS Press Office and CNMR, in cooperation with the Italian Ministry of Health, developed '*Con gli occhi tuoi*' (through your eyes): a communication project addressed to schools, aiming to implement inclusion practices for fragile children in the classrooms and to raise awareness of rare diseases as a public health issue. The project was developed in collaboration with the Ministry for Education, University and Research, the Italian Federation of Rare Diseases UNIAMO FIMR, the Bambino Gesù Children Hospital and with the support of the centre for Health Pastoral Care, Diocese of Rome. The project will include a web-based video tale and a guidebook for teachers (aimed to enable teachers to repeat the experience in other schools, using cooperative learning techniques). The project results will be disseminated in the Rare Disease Day 2014.

### **National rare disease events in 2013**

Since February 2008, UNIAMO FIMR coordinates the Rare Disease Day events organised by its members throughout the national territory. It provides them with information leaflets, posters, gadgets, T-shirts and banners, created in collaboration with Farindustria, the Serono Foundation and Novartis. Awareness was achieved through over one hundred local events, in squares, sports halls and schools and through many articles and interviews on rare diseases in newspapers and on TV.

In 2013, a gala evening was organised in Rome on 27 February by UNIAMO FIMR, followed by a dedicated conference entitled "Health is solidarity: a common commitment to fight against rare diseases" in collaboration with ISS, the Diocese of Rome, and Rome's medical school. The congress was the opportunity to reflect on advances in the field and priority issues. A Play/Decide session on cross-border healthcare and other relevant issues was organised also by UNIAMO FIRM at Sapienza University in Rome with the participation of students from faculties of medicine and nursing. A flash-mob was also organised to mark the day.

Other events in 2013 included: MaRE UNIAMO FIMR meeting (Rome, 29 January 2013), The National Registry and Regional and Interregional Registries of Rare Diseases meeting (Rome, 25 February 2013), UNIAMO workshop on quality evaluation of centres of expertise (Rome, 1 March 2013), O.Ma.R Prize for Journalism on Rare Diseases and Orphan Drugs (Lake Garda, 11 March 2013), AMMI Convention on Rare Diseases (Rome, 22 March 2013), Rare Diseases and Congenital Disorders seminar (Arezzo, 9 November 2013), International Conference on del22q Rome, 24-25 May 2014, DEBRA International Congress, Rome, 20 September 2013.

### **Hosted rare disease events in 2013**

Amongst the events announced in Orphanews Europe were: EUCERD Joint Action Europlan Workshop on Key Indicators for National Plans/Strategies for Rare Diseases (Rome, 25 March 2013), DEBRA International Congress (Rome, 20 September 2013), International Meeting on Angelman Syndrome (Rome, 11 October 2013), 2nd International Workshop Rare Disease and Orphan Drug Registries (21-22 October 2013, Rome), 5th European Symposium on Rare Anaemias (15-16 November 2013, Ferrara), Second Symposium on ATP1A3 in Disease Genotype/Phenotype Correlations, Modelling and Identification of Potential Targets for Treatment (23-24 September 2013, Rome), International Summer School on Rare Disease and Orphan Drug Registries (16-20 September 2013, Rome), Haemophilia Centres Certification System Across Europe (11 July 2013, Rome), 5th International Meeting on Pulmonary Rare Diseases and Orphan Drugs (8-9 February 2013, Milan), International Summer School on Clinical Practice Guidelines on Rare Diseases (8-12 July 2013, Rome).

### **Research activities and E-Rare partnership**

#### ***National research activities***

In Italy, there are efforts to coordinate research between Regions, Italian Drug Agency (AIFA)<sup>348</sup>, Ministry of Health and ISS. Funds for rare diseases research are granted by Ministry of Health, ISS, AIFA and Ministry of

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<sup>348</sup> <http://www.agenziafarmaco.gov.it/>

Education, University and Research, Telethon, patient organisations and a few charities. The last Health Ministry call for projects for rare diseases<sup>349</sup> had a total budget of €8 million. The call for projects was published in 2008 and 13 projects were granted in 2010.

A bilateral agreement between Italy (ISS) and USA (NIH) was established with the purpose of developing and increasing research in different fields, including rare diseases since 2002. This agreement is still active.

AIFA issued calls to fund independent researches on the development of orphan medicinal products. In particular, AIFA financed a three-year initiative, launched in 2005, to support clinical research on drugs of interest to the NHS where commercial support is inadequate: one of the concerned areas was the field of rare diseases and orphan medicinal products. Three topics were included in the clinical research area concerning rare diseases: the benefit-risk profile of orphan medicinal products designated by EMA; the benefit-risk profile of off-label drug use (and in particular generics); the benefit-risk profile of drugs for non-responders to standard treatments. Projects in these topic areas were granted for a maximum of €300,000, with the therapy costs funded separately. From 2008 onwards rare diseases and orphan medicinal product research are funded by the Ministry of Health, within the general health research call, with a specific budget reserved for rare diseases research. A specific call to fund research projects on rare diseases was issued by the Ministry of Welfare in 2009.

In 2013 Telethon was able to fund 230 research projects on rare genetic diseases, thanks to the fundraising activities in 2012.

Foundations and associations promote campaigns funding genetic research or research on specific diseases. Voluntary funds are collected through general taxation.

#### **Participation in European research projects**

Italian research teams participate/participated in 123 rare disease related FP7 projects and coordinated 27 projects.

#### **E-Rare**

Italy, represented by ISS, is a partner of the E-Rare project and took part in all three Joint Transnational Calls. Italy participated in 12 of the 13 consortia selected for funding by the first call. In the second E-Rare transnational call, Italy participated in 8 of the 16 consortia/projects selected for funding with a budget of about €1 million. Italy participated in the 3<sup>rd</sup> Joint Transnational Call in 2011 and Italian teams have been funded to participate in 7 of the selected consortia. Italy did not take part in the 4<sup>th</sup> Joint Transnational Call in 2012. Italy took part in the 5<sup>th</sup> Joint Transnational Call in 2013 with Italian teams participating in 4 out of the 12 selected consortia.

#### **IRDIRC**

The ISS and Italian Telethon Foundation are committed members of IRDiRC.

#### **Orphan medicinal products<sup>350,351</sup>**

AIFA is the main body in charge of the introduction of orphan medicinal products into the Italian market. The National Registry of Orphan Drugs includes data on diagnosis and follow-up of patients treated with orphan medicinal products. These drugs are authorised at central level by EMA (European Medicines Agency) and reimbursed by NHS. The National Registry of Orphan Drugs, established by AIFA and managed in collaboration with the National Centre for Rare Diseases, surveys forms for each rare disease and its related drugs, and collects, checks and analyses data sent by Regional Centres authorised to distribute these drugs. The goal of the registry is to have a nationwide coverage, to address all Italian Centres qualified to distribute and prescribe orphan medicinal products.

#### **Orphan medicinal product committee**

There is no specific orphan medicinal product committee at national level in Italy.

<sup>349</sup> [http://www.quotidianosanita.it/cronache/articolo.php?&&articolo\\_id=1144&cat\\_1=1&cat\\_2=0](http://www.quotidianosanita.it/cronache/articolo.php?&&articolo_id=1144&cat_1=1&cat_2=0)

<sup>350</sup> This section has been written using information from the KCE reports 112B: *Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* pp.49-53.

<sup>351</sup> This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision pp.15-16.

### **Orphan medicinal product incentives**

AIFA has established an innovative funding scheme (*Fondo AIFA 5%*). Established under Article 48 of Law 326/2003 and operative since 2005, the Italian pharmaceutical companies are required to donate 5% of their promotional expenditure to an independent research fund. The fund collects €45 million each year: half of this allowance is used for the reimbursement of orphan and life-saving drugs awaiting market entry, while the other half is aimed at supporting independent research, drug information programs and pharmaceutical vigilance. This funding program for independent clinical research on drugs is open to researchers working in public and non-profit institutions. One of the research areas of the program is dedicated to orphan medicinal products for rare diseases. At the beginning of 2009, three calls for proposals (2005-2007) had been finalised and 69 studies received funding in the area of rare diseases. Since 2008, however, rare diseases and orphan medicinal product research were not listed among the priority areas.

### **Orphan medicinal product market availability situation**

In Italy, 55 out of the 72 orphan medicinal products approved by EMA are launched on the market. The cost of 49 of them is fully paid by NHS, based on a therapeutic indication, while 6 of them are reimbursed under special circumstances (Law 648/96) and (Law 326/2003 art.48). The other EMA approved drugs have a pending request at AIFA by the companies in charge of pricing and reimbursement<sup>352</sup>. A list of orphan medicinal products with European marketing authorisation and the date of their publication in the Official Gazette concerning their marketing in Italy is available<sup>353</sup>.

### **Orphan medicinal product pricing policy**

Prices of all medicines for reimbursement by the NHS, including hospital-only drugs, are set by AIFA. Two interministerial committees are involved in this process, the Pricing and Reimbursement Committee and the Technical-Scientific Commission<sup>15</sup>.

### **Orphan medicinal product reimbursement policy**

In Italy drugs are catalogued in A and C classes, depending on their reimbursement. Costs of class A drugs are totally paid by NHS and free of charge for citizens, while class C drugs are paid entirely by patients. Many Regions in the last years have supplied class C drugs to their population, while other Regions, bound to strong budgetary limits and measures to contain their health care cost levels and trends, have been forced to not provide extra LEA services to their citizens, including C Class drugs. Reimbursement is granted for all orphan medicinal products which follow the centralised marketing authorisation procedure. Moreover, for all drugs which are not currently classified in class A, reimbursement is regionally based within “extra LEA services”, which means further services decided by the individual Regions and covered by their own economic resources.

Some orphan medicinal products can only be dispensed if the details of the patient are entered into the National Registry of Orphan Drugs, containing information on diagnosis and follow-up of the patient<sup>354</sup>.

The RD Interregional Board has issued a document, approved by the National Health Commission, defining a proposal for the transfer of data regarding orphan drugs prescription from regional registries directly to AIFA, as many information systems set up at regional level collect this information routinely from clinicians working in Centres of expertise.

### **Other initiatives to improve access to orphan medicinal products**

Italy also has an off-label, compassionate use procedure, regulated by Law 648/96<sup>355</sup> (a list of eligible drugs is annexed to this law). The Technical Committee of AIFA can include a given medication in the official list allowing it to be prescribed at the NHS charge, if for a specific disease there is no therapeutic choice. Three types of medical products can be included: innovative drugs for which the sale is authorised abroad, but not in Italy; drugs which have not yet received an authorisation, but have undergone clinical trials; and drugs to be used for a therapeutic indication different from the one which had been authorised<sup>356</sup>. A Ministerial Decree of

<sup>352</sup> According to the Final Report of the European National Conference, 11-13 November 2010.

[http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/final\\_report\\_italy\\_europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf) p16.

<sup>353</sup> [http://www.iss.it/binary/orfa2/cont/elenco\\_farmaci\\_orfani\\_autorizzati\\_in\\_Italia\\_2013.pdf](http://www.iss.it/binary/orfa2/cont/elenco_farmaci_orfani_autorizzati_in_Italia_2013.pdf) (document accessed March 2014 and last updated in July 2013).

<sup>354</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Access Issues, Donald Macarthur (2011) p.83

<sup>355</sup> Law 23-12-1996 n. 648. Conversione in legge del D.L. 21 October 1996, n. 536, recante misure per il contenimento della spesa farmaceutica e la rideterminazione del tetto di spesa per l'anno 1996 (published in GU 23 December 1996, n. 300).

<sup>356</sup> KCE reports 112B: Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 p.50.

8 May 2003<sup>357</sup> allows for the prescription (paid by the producer) of drugs not yet authorised, but subjected to phase II or III clinical trials for the same therapeutic indication, for which a favourable evaluation in terms of efficacy and safety is expected.

The off-label use of a drug at the expense of NHS is allowed and provided to hospitalised patients, as envisaged by article 3, paragraph 2 of Law Decree<sup>358</sup> 23/1998, when decided by a doctor on condition that this decision is made on a named patient basis, documented evidence is provided, and no other treatment is available. Medicines with non-approved indications are supplied through the “fondo AIFA 5%”.

The Ministerial Decree 11/2/1997 allows the import of unauthorised orphan medicinal products on a patient basis: in this instance, the payer is the Region or the NHS, in the case of hospital or reference centre use<sup>359</sup>.

At the end of 2010, an agreement between central Government and the Regions has established that ‘potential/important therapeutic innovations’ are automatically included on the regional formularies, so they should be available simultaneously and quickly across Italy<sup>15</sup>.

In 2013, the RD Interregional Board produced a document, approved by the National Health Commission, defining common modalities and pathways to access home cared infusion therapies for RD patients.

### **Other therapies for rare diseases**

No specific information reported.

### **Orphan devices**

No specific information reported.

### **Specialised social services**

Respite care services, including “respite interventions” for families, either in residential or semi-residential structures, are included among the national LEA services and are mainly provided by governmental or accredited institutions, but are unevenly distributed within Italy and sometimes are provided by the private sector: full or partial reimbursement is offered and some patient organisations provide services free of charge. Lodging, meals and other housing services are to be paid for by patients, or by municipalities, in the case of low-income situations.

Therapeutic recreational programmes are provided, although unevenly, by local authorities’ social services under the administration of the municipalities. The institutional framework is complex: at governmental level, this competence belongs to the Ministry of Social Affairs, but the legislative power in terms of social policies is under the exclusive responsibility of Regions (Constitutional Law no. 3 October 18, 2001). It is the competence of the State to determine the essential level of benefits relating to civil and social rights that must be guaranteed throughout the national territory; the municipalities are the holders of administrative functions relating to social interventions undertaken at local level (Law n.328 November 8, 2000). Some municipalities assure public services, but more often services are run by private bodies (companies or patient organisations) commissioned by social authorities.

Some summer camps are informally or formally organised by patient organisations (e.g. the Dynamo Camp in Tuscany). These services are sometimes fully reimbursed, or there is a partial contribution according to the family income.

Additional social and/or financial support is available for families and patients with disabilities (Law Decree n. 509, 23 November 1988). Services promoting social integration of patients with disabilities in schools and the workplace are provided by the Government. The provision of specialised social services is thus unevenly distributed at national level. The average per-capita social spending of municipalities varies from €30 to €250<sup>21</sup>, and it is not considered satisfactory because the rules of access to services and the sharing costs are different in Regions. Furthermore there is a reduction in available resources: in years 2008-2011 there was a 89% cut of the National Welfare Fund, down from €1 billion 200 million to €69 million, only covered in part by Regions and municipalities.

<sup>357</sup> Ministerial Decree 8 May 2003 *Uso terapeutico di medicinale sottoposto a sperimentazione clinica* (published in GU 28 July 2003, n. 173).

<sup>358</sup> Law Decree 17-2-1998 n. 23 *Disposizioni urgenti in materia di sperimentazioni cliniche in campo oncologico e altre misure in materia sanitaria*. (published in GU 17 February 1998, n. 39).

<sup>359</sup> EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Hahl, F. Bachner (2011) p54.

<sup>21</sup> *Istat 2008: Gli interventi e i servizi sociali dei comuni singoli e associati*.

[http://www3.istat.it/salastampa/comunicati/non\\_calendario/20110419\\_00/testointegrale20110419.pdf](http://www3.istat.it/salastampa/comunicati/non_calendario/20110419_00/testointegrale20110419.pdf)

## DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 IN ITALY

### **National plan/strategy for rare diseases and related actions**

In 2011, a working group was established at the Ministry of Health in Rome to thoroughly analyse the issues related to the National Plan for Rare Diseases and to draft the preliminary document. On 23 February 2012, a conference was organised at the Chamber of Deputies, and a white paper presented, with the aim of encouraging the government to put in place the rare diseases plan. Between March and April 2012 both Orphanet and UNIAMO organised public consultation on rare diseases with the aim of providing input from stakeholders into the process. The working group of the Ministry of Health preparing the draft of the national plan concluded in June 2012, and the document was sent by the Ministry of Health to AIFA for comments, and subsequently again to the Ministry of Health for final assessment. The document was presented in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step was for the document to be implemented by the stakeholders, from January to February 2013. Their comments were evaluated and included in the document in March 2013 by the Ministry of Health and sent for approval by the permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano.

In January 2013, UNIAMO FIMR organized in Rome a meeting with patients' representatives focused on the discussion of the Draft Plan for Rare Diseases. The contributions then forwarded to the Ministry of Health.

In April, UNIAMO FIMR started organizing the second EUROPLAN Conference 2012-2015, by setting the Steering Committee and activating the thematic working groups through face to face meetings and a virtual web platform set up *ad hoc*. The working groups included a broad representation of the key stakeholders.

### **Rare Diseases Interregional Board**

In 2013, the Health Commission officially adopted two other documents elaborated by the RD Interregional Board: one dealing with the identification of common regional modalities and pathways for the delivery of home cared therapies to RD patients; another one, addressed in particular to AIFA, containing the Regions' proposals regarding the main open issues in the field of the drug provision to RD patients. The contents of both these documents have been shared with the Interregional Pharmaceutical Board, in which all Regional Pharmaceutical Services are represented. Furthermore, the collaboration with the Pharmaceutical Interregional Board has led to the production of a list of off-label drugs and drugs marketed abroad for rare diseases, partially refundable by AIFA to Regions, which normally cover with their budget these costs.

In 2013, two working groups have been established in the context of the Interregional Board on RD. They will conclude their mandate in early 2014 with the approval of two documents representing the state of the art and the Regions' position and proposals on the following two issues: expanded newborn screening and telemedicine. Both these documents will be submitted in 2014 for final approval to the Health Commission.

### **Registries**

On 25 February 2013, a second congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome, aiming at sharing the state of the art of patient registries in Italy. Over the last few years, data collection for the National Registry of Rare Diseases was improved, reaching a territory coverage of the 97% in 2012 (compared with 62% of 2009), due to the improvement of the surveillance system both at national or regional level. Publication of the second ISTISAN Report on National Registry and Regional/Interregional Registries for rare diseases is in progress.

### **Neonatal screening policy**

In November 2013, a hearing at the Senate took place concerning a proposal to reorganise and rationalise the different regional health care systems in the field of newborn screening in order to harmonize the regional activities. Existing regional differences in neonatal screening policies can be explained because the screening of additional diseases, besides the diseases cited in law to be tested (cystic fibrosis, congenital hypothyroidism and phenylketonuria) represents an extra-LEAs (Essential Levels of care) service for citizens. So, the cost of the screening of additional diseases is completely at the charge of the Regions. To appropriately tackle this issue, in 2013 the Interregional Rare Diseases Board has established a working group in order to elaborate a document describing the state of the art, specific health policies developed by the Regions in this area and some proposed future actions. This document will be presented for approval to the Health Commission in early 2014. It clearly

advocates the common definition of the diseases, the screening of which should be included into the LEA list, in order to overcome regional differences. Furthermore, it underlines the necessity to consider expanded newborn screening as a part of broader and comprehensive care pathways developed for patients affected by the diseases screened.

The Stability Law of December 2013 (art. 1, paragraph 229) has granted the experimental widening of national neonatal screening of metabolic disorders with €5 million.

### **Genetic testing**

In 2013, the Working Group on Cytogenetic of the Italian Society of Human Genetics (SIGU) approved and disseminated a set of guidelines for cytogenetic diagnosis, which came 20 years after the previous set of guidelines in this area.

The CNMR-ISS is in charge of carrying out the National External Quality Control Scheme for genetic tests. This scheme includes molecular and cytogenetic tests and has been addressed to public laboratories which provide genetic tests. To date eight rounds have been completed and overall 112 laboratories have been monitored in the context of the National External Quality Control Scheme

### **National alliances of patient organisations and patient representation**

In Italy, UNIAMO FIMR is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 100 patient organisations representing more than 600 rare diseases. In 2013, within the “*Conoscere per assistere*” project addressed to general practitioners (GPs) and paediatricians (PLS), supported by Farindustria, UNIAMO FIMR, in collaboration with the federation of paediatricians and general practitioners (FIMP, FIMMG), and scientific societies of physicians (SIP, SIMG, SIMGEPED, SIGU) organized 3 training courses in Florence (April), Potenza (May), and Turin (October). The major topics of these courses included: how to suspect a rare disease, how to manage the transition of rare disease patients from paediatric into adult age.

In July-September 2013, on behalf of Eurordis, the UNIAMO FIRM President worked as a member of the Commission established by the Ministry of Health charged of evaluating the so-called Stamina protocol (a non-scientifically sound treatment for many rare diseases, based on stem cells).

In 2013, UNIAMO FIRM was confirmed as a member of the board of the Biobank Network settled by Telethon Foundation, and of the Interregional Rare Disease Committee.

In 2013, UNIAMO FIMR coordinated the project “*Determinazione Rara*”, an advanced national training programme for the proactive enrolment of patients in research trials, based on workshops with clinicians, researchers and biobankers.

An Agreement between the State and the Regions was signed in 2013 regarding the development of specific and comprehensive care pathways for patients affected by Hereditary Haemorrhagic Disorders, based on the activity of the already labelled regional-interregional Centres for HHD and involving other professionals working in the RD care networks, as well as in other care settings.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activity in Italy***

In January 2013, in the perspective of implementing the Orphanet database, Orphanet Italy launched a survey and set up a collaboration with the Italian Inter-regional Technical Board for Rare Disorders to collect data on the Centres of Reference officially recognized and established by the Regions. All regional coordinators of the Italian National Network for Rare Diseases were involved in this process, and more than 700 Centres of Reference for rare diseases were identified in Italy and registered in the Orphanet database.

### **Guidelines**

In 2012, CNMR, 13 institutional partners and one SME have been awarded with a grant by the European Commission, under the Seventh Framework Programme (FP7/2007-2013) for a four-year research project entitled RARE-BestPractices ([www.rare-bestpractices.eu](http://www.rare-bestpractices.eu)), commencing in January 2013. RARE-BestPractices is a platform for sharing best practices for the management of rare diseases. This project brings together a team of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, rare disease epidemiology and public health. The overall aim of the project is to improve the care of patients by disseminating globally best practices for the management of persons with rare diseases. The CNMR acts as coordinator of 14 partners across Europe, all with strong commitment in research on rare diseases, public health and evidence based medicine. The project’s aims to provide reliable informative resources for the rare disease community by creating a collection of methodologically trustworthy and up-to-date guidelines for

the management of rare disease; to develop a standard methodology suitable for the development of RD guidelines; to set up training activities and training tools targeted at key stakeholders for the production of high quality rare disease guidelines. Other key elements of the platform are the identification of mechanisms to address the limitations of the evidence, set priorities for rare disease research and propose improvements in pre-approval and post-marketing studies.

RARE-Bestpractices has supported the creation of a new international open access, online, peer-reviewed journal: "Rare Disease and Orphan Drugs" (RARE Journal - <http://rarejournal.org/rarejournal>). RARE is a science journal, published three times per year focusing on relevant aspects of public health, health policy and clinical research on rare diseases.

### **Training and education initiatives**

In 2013, the CNMR organised a course (using cooperative learning method) for the "W Ale - Alessandra Bisceglia" Foundation volunteers, aiming to set up and carry out a specific helpline to inform health operators, social workers, patients and their families, and the public at large, on congenital vascular malformations and related disabilities. The W Ale helpline will start in 2014, in collaboration with the Italian national helpline for rare diseases "*Telefono Verde Malattie Rare*".

The CNMR coordinates the "Story Telling on Record" (S.T.o.Re. – [www.storeproject.eu](http://www.storeproject.eu)): a 2-year European partnership funded in the Lifelong Learning Programme (Leonardo da Vinci Multilateral Partnerships August 2013 - July 2015). The project involves 7 partners from 6 countries and foresees 4 partners' meetings and a final conference in Italy. The objective is to design an action-research that includes training participants, giving them the knowledge and the skills necessary to design, test and train people in the use of Integrated Medical Records (IMRs), and organise courses on the use of IMRs for health care system personnel, in the rare and chronic diseases. The results of this project will be disseminated through a dedicated website, scientific reports and two booklets (toolkits in English and in the partners' languages, tailored to patient organisations and to health institutions and professionals).

The second International Summer School "Clinical Practice Guidelines on Rare Diseases" was organised by CNMR (ISS, Rome, 8-12 July 2013). The course took the participants through the development process of clinical practice guidelines, by providing the basics of clinical practice guideline and evidence synthesis approaches. The course format consisted of brief presentations followed by individual or small group exercises for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

On 15 April 2013, the Orphanet team held a training course in Rome for health professionals from Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

In 2013, the ISS Press Office and CNMR, in cooperation with the Italian Ministry of Health, developed '*Con gli occhi tuoi*' (through your eyes): a communication project addressed to schools, aiming to implement inclusion practices for fragile children in the classrooms and to raise awareness of rare diseases as a public health issue. The project was developed in collaboration with the Ministry for Education, University and Research, the Italian Federation of Rare Diseases UNIAMO FIMR, the Bambino Gesù Children Hospital and with the support of the centre for Health Pastoral Care, Diocese of Rome. The project will include a web-based video tale and a guidebook for teachers (aimed to enable teachers to repeat the experience in other schools, using cooperative learning techniques). The project results will be disseminated in the Rare Disease Day 2014.

### **National rare disease events in 2013**

Since February 2008, UNIAMO FIMR coordinates the Rare Disease Day events organised by its members throughout the national territory. It provides them with information leaflets, posters, gadgets, T-shirts and banners, created in collaboration with Farmindustria, the Serono Foundation and Novartis. Awareness was achieved through over one hundred local events, in squares, sports halls and schools and through many articles and interviews on rare diseases in newspapers and on TV.

In 2013, a gala evening was organised in Rome on 27 February by UNIAMO FIMR, followed by a dedicated conference entitled "Health is solidarity: a common commitment to fight against rare diseases" in collaboration with ISS, the Diocese of Rome, and Rome's medical school. The congress was the opportunity to reflect on advances in the field and priority issues. A Play/Decide session on cross-border healthcare and other relevant issues was organised also by UNIAMO FIRM at Sapienza University in Rome with the participation of students from faculties of medicine and nursing. A flash-mob was also organised to mark the day.

Other events in 2013 included: MaRE UNIAMO FIMR meeting (Rome, 29 January 2013), The National Registry and Regional and Interregional Registries of Rare Diseases meeting (Rome, 25 February 2013), UNIAMO workshop on quality evaluation of centres of expertise (Rome, 1 March 2013), O.Ma.R Prize for



Journalism on Rare Diseases and Orphan Drugs (Lake Garda, 11 March 2013), AMMI Convention on Rare Diseases (Rome, 22 March 2013), Rare Diseases and Congenital Disorders seminar (Arezzo, 9 November 2013), International Conference on del22q Rome, 24-25 May 2014, DEBRA International Congress, Rome, 20 September 2013.

#### **Hosted rare disease events in 2013**

Amongst the events announced in Orphanews Europe were: EUCERD Joint Action Europlan Workshop on Key Indicators for National Plans/Strategies for Rare Diseases (Rome, 25 March 2013), DEBRA International Congress (Rome, 20 September 2013), International Meeting on Angelman Syndrome (Rome, 11 October 2013), 2nd International Workshop on Rare Disease and Orphan Drug Registries (21-22 October 2013, Rome), 5th European Symposium on Rare Anaemias (15-16 November 2013, Ferrara), Second Symposium on ATP1A3 in Disease Genotype/Phenotype Correlations, Modelling and Identification of Potential Targets for Treatment (23 - 24 September 2013, Rome), International Summer School Rare Disease and Orphan Drug Registries (16-20 September 2013, Rome), Haemophilia Centres Certification System Across Europe (11 July 2013, Rome), 5th International Meeting on Pulmonary Rare Diseases and Orphan Drugs (8-9 February 2013, Milan), International Summer School on Clinical Practice Guidelines on Rare Diseases (8-12 July 2013, Rome).

#### **Research activities and E-Rare partnership**

##### ***National research activities***

In 2013 Telethon was able to fund 230 research projects on rare genetic diseases, thanks to the fundraising activities in 2012.

##### ***E-Rare***

Italy took part in the 5<sup>th</sup> Joint Transnational Call in 2013 with Italian teams participating in 4 out of the 12 selected consortia.

#### **Orphan medicinal products**

##### ***Orphan medicinal product reimbursement policy***

The RD Interregional Board has issued a document, approved by the National Health Commission, defining a proposal for the transfer of data regarding orphan drugs prescription from regional registries directly to AIFA, as many information systems set up at regional level collect this information routinely from clinicians working in Centres of expertise.

##### ***Other initiatives to improve access to orphan medicinal products***

In 2013, the RD Interregional Board produced a document, approved by the National Health Commission, defining common modalities and pathways to access home cared infusion therapies for RD patients.

## **1.16. LATVIA**

#### **Definition of a rare disease**

Stakeholders in Latvia accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals and that rare diseases are life-threatening or chronically debilitating diseases.

#### **National plan/strategy for rare diseases and related actions**

Work has recently been finished on a national plan by the working group, which included health care specialists and representatives from the Ministry of Health. In December 2011, the plan was written and submitted to the Ministry of Health for evaluation. The costs related to rare diseases are currently included in the national health care budget. A public consultation of the plan was launched in 2012 and the results were analysed by the Ministry of Health. A number of meetings with different stakeholders were held, and as a result, the plan was further elaborated. The plan was adopted in 2013, no additional funding has been secured, therefore major activities are related to update of regulations concerning rare diseases. The activities are now being implemented including the approval of an act concerning registries and plans to include Orphacodes and ICD codes in the congenital anomalies and cancer registries.

A National Cancer Control Programme (2009-2015) was stipulated by regulations No.48 of the Cabinet of Ministers of the Republic of Latvia (adopted on the 29 January, 2009), and included rare cancers. In August 2009, a regulation was introduced which allowed for the compensation of medicines for children with rare diseases.

The Cardiovascular Health Improvement Action Plan (2013-2015) was adopted in 2013 and includes activities in field of health promotion, improving cardiovascular diseases treatment and early diagnostic on congenital malformation of the heart.

### **Centres of expertise**

There are currently no official designated centres of expertise for rare diseases in Latvia but a meeting was held in 2013 to discuss possible criteria for national centres of expertise. A legal framework for centres of expertise, including those for rare diseases, is expected in the future. Currently the Latvian State University Children's Hospital provides genetics services, hospital specialists deal with children with haematological, oncological and endocrinological diseases. The Riga East University Hospital has a specialised clinic (Chemotherapy and haematology clinic) in which haemophilia A, haemophilia B, Factor XII deficiency and von Willebrand disease receive diagnostics and treatment (in this hospital, rare oncological diseases also can be treated, e.g. Burkitt's lymphoma, Langerhans cell histiocytosis, Mantle-cell NHL, multiple endocrinology neoplasia, Erwing's sarcoma, Wilm's tumour, Waldenström macroglobulinemia and others). Pauls Stradins University hospital has services in different rare diseases area: cardiology, nephrology, vascular diseases (Arteriovenous vascular malformations, lymphatic disorders, aortic pathology, endarteritis, carotid tumors, etc.), oftalmology, oncology, gastroenterology, endocrinology, pulmonology. A rare cardiovascular diseases network (Poland, Lithuania and Latvia through the P. Stradins Clinical University Hospital, Centre of Cardiology), started in May 2011 and finished in January 2013.

The Ministry of Health, Orphanet team and experts from 3 University hospitals have been started work on developing national criteria for centres of expertise to be registered in Orphanet database and met in February 2013 to discuss this issue.

### **Registries**

There is no separate registry for rare diseases but the National Plan for rare diseases foresees activities for evaluation and improvement of existing patient registries to start centralised data collection about rare disease patients. The Centre for Disease Prevention and Control is the supervising authority and keeper of Register of patients with particular diseases, including cancers, congenital anomalies (some of these are rare diseases). There is a plan to pilot use the Orpha code as well as OMIM codes for rare diseases in the register of patients with congenital anomalies and cancers. Latvia contributes to the EUROcare (Eurocare-5 study) European registry, RARECAREnet, and the Joint Action EUROCAT.

Specialists from university hospital centres collect rare disease patient data, for example, at the Latvian Cardiology Centre is Pulmonary Arterial Hypertension patient's data base. The Centre of Endocrinology of Pauls Stradins University hospital has created several data bases of patients with rare endocrine diseases: acromegaly, Cushings disease, MEN syndrome. These data bases are created for follow-up purposes, as well as serve to as a source of scientific information. Congenital malformation data base is held by the Genetics clinic at the Latvian State University Children's Hospital.

### **Neonatal screening policy**

In Latvia, newborns are screened for phenylketonuria and congenital hypothyroidism Data about screened newborns in maternity units are collected in the Newborns Registry supervised by The Center for Disease Prevention and Control.

### **Genetic testing**

The Regulations of the Cabinet of Ministers prescribe genetic analysis paid via the state budget. Any laboratory, that has a contract for the provision of services and appropriate technical resources, can perform these tests. In Latvia are not genetic analysis reference laboratories.

A number of cytogenetic laboratory technologies have been approved for number of chromosomes and structure determination as well as molecular biological laboratory technologies for the determination of gene mutation.

Regulations of the Cabinet of Ministers describe the procedures for the organisation and financing of health care and the types and amounts of medical treatment services that are be paid from the State budget, including genetic analysis.

If genetic analysis for some reason cannot be performed in Latvia and that this analysis is necessary to prevent irreversible deterioration of health status or loss of vital functions, these tests can be performed abroad and they can be funded using the State budget.

Genetic testing is available in Medical Genetics Clinic of Latvian State University Children's Hospital, Molecular Laboratory, Riga Stradins University, Scientific Laboratory and in Latvian BioMedical Research and Study Center. No national guidelines and specific conditions for reimbursement of expenses related to the tests have yet been determined. Genetic testing in other EU and EFTA states is possible with a E112/S2 form if genetic testing is a health care service usually financed from the state budget and this service cannot be provided in the Republic of Latvia or cannot be provided within a reasonable period of time. Mostly it is provided for children with life-threatening or treatable conditions.

In some cases university clinics collaborate and send samples to Latvian Biomedical Centre of Research and Studies for genetic testing. For example, genetic testing of all family members of patients with MEN syndrome is being financed in term of scientific project.

Diagnostic tests are registered as available in Latvia for 10 genes and an estimated 11 diseases in the Orphanet database<sup>360</sup>.

### **National alliances of patient organisations and patient representation**

There is no alliance in Latvia, but there is a patient organisation dedicated to rare diseases, the Latvian Rare Disease Organisation Caladrius<sup>361</sup> launched in 2009. The mission of the organisation is to provide patients with the relevant information and support and to represent patients. In 2010 Caladrius established a fund to help rare disease patients who could not otherwise fund their treatments: the organisation had obtained public benefit organisation status to legally collect funds for this action. There are plans to create an alliance of rare diseases patient organisations and chronic patient organisations at national level. Until now there were 8-9 organisations who share information and collaborate together in this area. Rare diseases patient organisations lack the capacity to establish an alliance.

In Latvia are a number of other rare diseases and rare diseases-related patient organisations, including Latvia Haemophilia Society, the Society for People with Disabilities Motus Vitae, the Phenylketonuria Society, Pulmonary Hypertension Society and Society of Cystic fibrosis. These organisations often collaborate with each other and in 2013 had many activities, for example, Motus Vitae joined the International ALS/MND Alliance and arranged the international conference VII Nordic ALS Alliance meeting in Latvia "Baltic Bridge": Services for people living with ALS/MND (there participated patients with their assistants, medical professionals, social workers and Health Care Institutions from Denmark, Finland, Estonia, Russia, Iceland and Latvia). On 21 June 2013 I AM BREATHING was screened in Latvia by Motus Vita.

Latvian patient associations participated actively in 2013 in a Cystic Fibrosis Europe Association organised campaign which included the presentation of the film about cystic fibrosis patients of Latvia in European Parliament in Brussels on 14 November 2013. The aim of the campaign was to work out a strategy to obtain equal health care rights and to promote the accessibility of Cystic Fibrosis diagnostics and therapy for Cystic Fibrosis patients in all Europe.

The Latvia Hemophilia Society has strong cooperation with European Hemophilia Consortium and World Federation of Hemophilia, as well as other people with bleeding disorders communities around the world.

Ziedosim.lv is a non-governmental organisation which financially supports children and families to confirm a diagnosis of rare diseases by sending patients or medical samples abroad<sup>362</sup>.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Latvia***

The Ministry of Health of the Republic of Latvia has designated The Centre for Disease Prevention and Control as the representative of the Republic of Latvia to participate in the Joint Action Orphanet Europe since April 2012. The Orphanet team is currently hosted by the Centre for Disease Prevention and Control and is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Latvia for entry into the Orphanet database. The Orphanet Latvia country site was launched in April 2012 and regularly updated by the Orphanet team.

<sup>360</sup> Information extracted from the Orphanet database (January 2014).

<sup>361</sup> [www.caladrius.lv](http://www.caladrius.lv)

### **Official information centre on rare diseases**

There is no information centre for rare diseases in Latvia other than Orphanet. Web based information is available for a limited number of diseases (rare and non-rare) and certain information is maintained by using the state budget. Information was added about some common conditions in Latvian for the patients and general practitioners. According to Directive (2011/24) of patients' rights in cross-border healthcare, Latvia has a focal point for providing information concerning the Latvian health care services and the services offered in different countries, including rare diseases. The Latvian National Health Service functions as this contact point.

### **Help line**

There are non-rare disease specific help lines run by the state, some by the state budget, to help patients to access health care and psychological support, but no help line dedicated to rare diseases.

A helpline for Cystic fibrosis patients is offered during office hours at the Children's University hospital.

### **Other sources of information on rare diseases**

Information on rare diseases is available regarding paediatric rheumatic diseases<sup>363</sup>, lysosomal diseases (Gaucher disease, Fabry disease and Hunter syndrome)<sup>364</sup>, pulmonary hypertension<sup>365</sup>, bleeding disorders<sup>366</sup>, and via PHL Latvia<sup>367</sup>.

### **Guidelines**

In Latvia clinical guidelines for RD at national level have not been approved. The Centre of Endocrinology of Pauls Stradins University hospital in collaboration with Riga East University hospital endocrinologists and Latvian State University Children's Hospital endocrinologists issued in 2013 "Diagnostic algorithms of rare endocrine diseases". These recommendations contain information of patients with a suspected rare endocrine disease in an organised and short form. The recommendations are aimed to help general practitioners and endocrinologists to think about rare diseases when presented with certain types of patients.

### **Training and education initiatives**

Every year the "Baltic metabolic specialist meeting" is held; the 2013 was held in Riga. The meetings bring together most geneticists and laboratory specialists from Baltic countries. Pauls Stradins University hospital organises post-diploma educational courses for different specialists in most areas of medicine, endocrinology among them. The programme usually covers not only the most common clinical conditions but rare diseases also.

In 2013, the Latvian Haemophilia Society intensified cooperation with Lithuanian Haemophilia Society in order to provide disease specific training for physiotherapists who work with people with bleeding disorders in Latvian State University Children's Hospital and the Riga East University Hospital. The adult haemophilia treatment centre in The Riga East University Hospital also runs various training sessions for nurses and other medical staff to raise awareness and knowledge of bleeding disorders and related health issues.

### **National rare disease events in 2013**

The Rare Disease Association Caladrius and the Centre for Disease Prevention and Control of Latvia marked the day by an event entitled "Rare and Friendly". In support of rare disease patients in Latvia. Children, musicians Jenny May and Intars Busulis and hockey club Dinamo Riga participated in a photo shoot with patients. These sessions were not only to provide a pleasant surprise for patients with rare diseases, but also to show that people with rare illnesses are as important as the other members of the community, but they need public support to obtain the necessary health care. The event was followed by a press conference for public and media representatives about genetic and rare diseases

In July 2013, Latvia Hemophilia Society, one of the oldest patient organisations in Latvia, celebrated its 20th anniversary.

### **Hosted rare disease events in 2013**

No hosted events were reported.

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<sup>363</sup> <http://www.printo.it/pediatric-rheumatology/information/Lettonia/index.htm>

<sup>364</sup> <http://lus.dev.zvirbulis.lv/lv/sakums>

<sup>365</sup> <http://lus.dev.zvirbulis.lv/lv/sakums>

<sup>366</sup> [www.hemofilija.lv](http://www.hemofilija.lv)

<sup>367</sup> [www.phlatvia.lv](http://www.phlatvia.lv)

## **Research activities and E-Rare partnership**

### ***National research activities***

Funding is available for rare disease projects (through state budget, charities and pharmaceutical companies) although funds are not specifically earmarked for rare disease research. However rare diseases have not been included in the priority directions of science and research.

Local activities are organised by the University hospitals, for example, Pauls Stradins University Hospital collaborated with Latvian Biomedical Centre of Research and Studies in term of research in the area of rare endocrine diseases. This collaboration includes genotyping of family members for specific mutations, genetic counselling, search for genetic markers etc.

### ***Participation in European research projects***

A research team in Latvia participates in one of the FP7 projects related to rare diseases.

### ***E-Rare***

Latvia is an observer of the E-Rare project.

### ***IRDiRC***

Latvian funding agencies do not currently contribute funds to the IRDiRC.

## **Orphan medicinal products**

The State Agency of Medicines of Latvia is responsible for regular collecting and distributing of the information on medicines, including orphan medicinal products, as well as for collecting and compiling the information on the safety, evaluating drug risks and coordinate measures of medicine use risk mitigation, according to Regulations No. 1006 of the Cabinet of Ministers (adopted on December 7, 2004) "State Agency of Medicines Statutes".

### ***Orphan medicinal product committee***

A representative of Latvia is a member of the Committee for Orphan Medicinal Products (COMP) of European Medicines Agency.

### ***Orphan medicinal product incentives***

*The Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* reported that in Latvia "the State Agency of Medicines is entitled, due to considerations of health protection, to make a decision (after discussion with the Minister for Health) regarding the fee exemption or reduction for activities associated with the evaluation, registration or re-registration of a medicinal product if the medicinal product (with or without orphan designation pursuant to Regulation 141/2000) is intended to the treatment of a rare disease."<sup>368</sup>

Under the centralised procedure, companies submit a single marketing-authorisation application to the European Medicines Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation for Orphan medicinal products is valid in all European Union (including Latvia) and EEA-EFTA states.

### ***Orphan medicinal product market availability situation***

The State Agency of Medicines of Latvia's includes the medicinal products registered in the Republic of Latvia and the centrally registered medicinal products (including orphan medicinal products) in a register<sup>369</sup> of medical products of the Republic of Latvia (according to Regulations No. 376 of the Cabinet of Ministers (adopted on May 9, 2006) "Procedures for the Registration of Medicinal Products").

The following orphan medicines were marketed in Latvia in 2013: *Cystadane, Diacomit, Evoltra, Exjade, Gliolan, INCRELEX, Jakavi, Kuvan, Myozyme, Myrin 100, Nexavar, Pedeia, Revatio, Sprycel, Tassigna, Volibris, Wilzin*. In 2013, compared to 2012, 3 new orphan drugs were launched on the market: *Evoltra, Exjade, Myozyme* and 3 orphan drugs were no longer placed on the market: *Litak, Mozobil, Yondelis*. Medicinal products: *Aldurazyme* and *Ventavis* which previously were designated as an orphan medicines and were placed on the market in 2012 are no longer designated as orphan medicines in Europe.

<sup>368</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)* (pp16-17)

<sup>369</sup> <http://www.zva.gov.lv/index.php?id=112&top=112&large=>

### **Orphan medicinal product pricing policy**

There are no specific provisions for the pricing of orphan drugs. There have not been any developments in this area

### **Orphan medicinal product reimbursement policy**

Since 2009, some orphan medicinal products for children are available as a part of the special programme "Medical treatment of rare diseases for children" for Children's University Hospital, Riga. Within this programme, there are provided some orphan medicinal products like Elaprase, Cystadane, Increlex, Kuvan.

Orphan medicinal products are partially available via the reimbursement system. Dasatinibum, Nilotinibum are included in the positive reimbursement list.

2% of reimbursement budget is intended to individual reimbursement with limitation up to 10 000 LVL/year for a single patient. Within this individual reimbursement, the following orphan medicinal products are provided: Revatio, Volibris, Nexavar, Cystadane, Diacomit, Thalidomide.

### **Other initiatives to improve the availability of orphan medicinal products**

The *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* reported that in Latvia "The State Agency of Medicines may issue [...] distribution authorisation for medicinal products not registered in Latvia if the medicinal product is intended for treatment of a rare disease (for an individual patient on the basis of prescription or for use in a health care institution on the basis of a written request)."<sup>370</sup>

### **Orphan devices**

There were no orphan devices placed on the market in 2012

### **Other therapies for rare diseases**

No specific information reported.

### **Specialised social services**

Respite care services are available and the categories of patients eligible for reimbursement are described in the "Procedures for the Organisation and Financing of Health Care" (Regulations of the Cabinet of Ministers No. 1046, adopted on 19 December 2006). Therapeutic recreational programmes are also available and costs are included in the national health care budget. There are existing government-run services promoting social integration of those with handicaps, including the school environment and work place.

As of 1 January 2013 a new service for persons with disabilities (including persons with disabilities of rare diseases) has been launched, a municipality based service of an assistant for performing activities outside home (to get to a place where person work, learn, get to the rehabilitation institution etc.). An assistant service is eligible to: persons with Group I or Group II disability<sup>371</sup>, on the basis of conclusion by the State Medical Commission for the Assessment of Health Condition and Working Ability on the necessity for a service of an assistant; persons with disability aged 5 to 18 years<sup>372</sup>, on the basis of conclusion by the State Medical Commission for the Assessment of Health Condition and Working Ability on the necessity for special care due to severe functional impairments. The service of an assistant amounts to 40 hours a week within the territory of Latvia (except for persons with Group I visual disability who receive a benefit for using a service of an assistant 10 hours a week and who receive a service up to 30 hours a week if a service of assistant exceeds 10 hours a week that is specified by the municipality social service office).

<sup>370</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (pp16-17)

<sup>371</sup> For the persons from 18 years of age depending upon the level of limitation of physical or mental abilities shall be determined to have the following:

- a) Group I disability – very severe disability,
- b) Group II disability – severe disability,
- c) Group III disability – moderately expressed disability.

<sup>372</sup> For a person up to the age of 18 disability is determined without being divided into groups.

## RARE DISEASE ACTIVITIES IN 2013 IN LATVIA

### National plan/strategy for rare diseases and related actions

Work has recently been finished on a national plan by the working group, which included health care specialists and representatives from the Ministry of Health. In December 2011, the plan was written and submitted to the Ministry of Health for evaluation. The costs related to rare diseases are currently included in the national health care budget. A public consultation of the plan was launched in 2012 and the results were analysed by the Ministry of Health. A number of meetings with different stakeholders were held, and as a result, the plan was further elaborated. The plan was adopted in 2013, no additional funding has been secured, therefore major activities are related to update of regulations concerning rare diseases. The activities are now being implemented including the approval of an act concerning registries and plans to include Orphacodes and ICD codes in the congenital anomalies and cancer registries.

The Cardiovascular Health Improvement Action Plan (2013-2015) was adopted in 2013 and includes activities in field of health promotion, improving cardiovascular diseases treatment and early diagnostic on congenital malformation of the heart.

### Centres of expertise

There are currently no official designated centres of expertise for rare diseases in Latvia but a meeting was held in 2013 to discuss possible criteria for national centres of expertise. A legal framework for centres of expertise, including those for rare diseases, is expected in the future.

The Ministry of Health, Orphanet team and experts from 3 University hospitals have been started work on developing national criteria for centres of expertise to be registered in Orphanet database and met in February 2013 to discuss this issue.

### Guidelines

In Latvia clinical guidelines for RD at national level have not been approved. The Centre of Endocrinology of Pauls Stradins University hospital in collaboration with Riga East University hospital endocrinologists and Latvian State University Children's Hospital endocrinologists issued in 2013 "Diagnostic algorithms of rare endocrine diseases". These recommendations contain information of patients with a suspected rare endocrine disease in an organised and short form. The recommendations are aimed to help general practitioners and endocrinologists to think about rare diseases when presented with certain types of patients.

### Training and education initiatives

Every year the "Baltic metabolic specialist meeting" is held; the 2013 was held in Riga. The meetings bring together most geneticists and laboratory specialists from Baltic countries. Pauls Stradins University hospital organises post-diploma educational courses for different specialists in most areas of medicine, endocrinology among them. The programme usually covers not only the most common clinical conditions but rare diseases also.

In 2013, the Latvian Haemophilia Society intensified cooperation with Lithuanian Haemophilia Society in order to provide disease specific training for physiotherapists who work with people with bleeding disorders in Latvian State University Children's Hospital and the Riga East University Hospital. The adult haemophilia treatment centre in The Riga East University Hospital also runs various training sessions for nurses and other medical staff to raise awareness and knowledge of bleeding disorders and related health issues.

### National rare disease events in 2013

The Rare Disease Association Caladrius and the Centre for Disease Prevention and Control of Latvia marked the day by an event entitled "Rare and Friendly". In support of rare disease patients in Latvia. Children, musicians Jenny May and Intars Busulis and hockey club Dinamo Riga participated in a photo shoot with patients. These sessions were not only to provide a pleasant surprise for patients with rare diseases, but also to show that people with rare illnesses are as important as the other members of the community, but they need public support to obtain the necessary health care. The event was followed by a press conference for public and media representatives about genetic and rare diseases

In July 2013, Latvia Hemophilia Society, one of the oldest patient organisations in Latvia, celebrated its 20th anniversary.

### Specialised social services

As of 1 January 2013 a new service for persons with disabilities (including persons with disabilities of rare diseases) has been launched, a municipality based service of an assistant for performing activities outside home (to get to a place where person work, learn, get to the rehabilitation institution etc.). An assistant service is eligible to: persons with Group I or Group II disability<sup>373</sup>, on the basis of conclusion by the State Medical Commission for the Assessment of Health Condition and Working Ability on the necessity for a service of an assistant; persons with disability aged 5 to 18 years<sup>374</sup>, on the basis of conclusion by the State Medical Commission for the Assessment of Health Condition and Working Ability on the necessity for special care due to severe functional impairments. The service of an assistant amounts to 40 hours a week within the territory of Latvia (except for persons with Group I visual disability who receive a benefit for using a service of an assistant 10 hours a week and who receive a service up to 30 hours a week if a service of assistant exceeds 10 hours a week that is specified by the municipality social service office).

In 2013 PHA Latvia financially supported the first pulmonary endarterectomy for CTEPH patient, organised the Summer Health camp for 40 rare disease patients and their relatives (caregivers), including children with rare diseases and their parents, managed the Charity Sport games to seek fundraising for PAH patients, and proceeded the oxygen home care therapy supporting for PAH patients.

## 1.17. LITHUANIA

### Definition of a rare disease

Stakeholders in Lithuania accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

On 18 October 2012, the national plan for rare diseases was approved by Order No V-938 of the Minister of Health, and a national rare diseases coordination committee was formed, including delegated experts from university hospitals, universities, non-governmental organisations, state institutions representatives to oversee the plan. The plan aims to establish a common approach on rare diseases, to raise public awareness, and to ensure prevention, early diagnosis, efficient treatment, improvement of quality of life and social support for patients suffering from rare diseases. It also includes the optimisation of health care services and rational allocation of available resources, as well as measures for improving the assessment of medicinal products and medical devices. There will be no specific budget for the plan so actions will have to be financed through the existing health budget. There was a Europlan conference<sup>375</sup> on 14 November 2013 under the auspices of the Lithuanian presidency to discuss the implementation of the plan.

Expenses for health care services and drugs for rare diseases patients are reimbursed from the Compulsory Health Insurance Fund budget as for other groups of patients, e. g. are not separated from total Compulsory Health Insurance Fund except specific allocations for reimbursement of rare medicinal products and devices. Additionally, expenses for the treatment of rare cases abroad are reimbursed from Compulsory Health Insurance Fund budget; compensation for orphan medicinal products and medicinal devices for rare diseases and conditions are paid from a selected part of the budget of the Compulsory Health Insurance Fund (Order No. 151 of 20 March 1998 of the Ministry of Health). In 2013 10,4 million litas (about 3 million euros) were allocated to reimbursing rare medicinal products and devices.

### Centres of expertise

There are no official centres of expertise in Lithuania, but two centres (Centre for Medical Genetics in Vilnius University Hospital Santariškių Clinics and Centre for Rare diseases at the Hospital of Lithuanian University of Health Sciences Kaunas Clinics) provide genetics services and diagnostic services for rare diseases to the

<sup>373</sup> For the persons from 18 years of age depending upon the level of limitation of physical or mental abilities shall be determined to have the following:

- a) Group I disability – very severe disability,
- b) Group II disability – severe disability,
- c) Group III disability – moderately expressed disability.

<sup>374</sup> For a person up to the age of 18 disability is determined without being divided into groups.

<sup>375</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-lithuania.pdf>



Lithuanian population. Currently centres of competence are established in university hospitals by the order of the head of the university hospitals (Vilnius University Hospital Santariškių Clinics and Lithuanian University of Health Sciences Kaunas Clinics). These university hospitals provide diagnostics, treatment, research, training and health care services by teams of health professionals based on multidisciplinary approach. Procedures of national designation are under preparation.

A coordinating centre for diagnosis, treatment and management of rare diseases was established at the Vilnius University Hospital Santariškių Clinics in November 2012. An outpatient clinic for cystic fibrosis patients was established in 2011.

Both Vilnius University Hospital Santariškių Clinics and Lithuanian University of Health Sciences Kaunas Clinics has Coordinating Centres for rare diseases and centres of competence for different diseases are working under their supervision.

A coordination centre for children with rare diseases has been established at Vilnius Children's Hospital<sup>376</sup>.

### **Registries**

Under the Law of National Information resources the establishment of a National Registry can only be founded with the appropriate legal background.

Currently no National Rare Disease Registry exists in Lithuania. Each Academic Hospital uses its own local rare disease database. The main rare disease database is maintained by the Centre for Medical Genetics at Vilnius University Hospital Santariškių Clinics.

At the Hospital of Lithuanian University of Health Sciences, all centres for rare diseases register their own rare diseases patients. Many of these Centres are seeking to become partners of appropriate European registries.

Establishment of various diseases registries is quite a long and costly process, this is why Lithuania is looking to innovate by establishing electronic, platform-based registries during the period of implementation of E-Health project 2013-2015. Registries of separate diseases (rare included) will function as subsystem of National E-Health information system and will be integrated into common data network.

Lithuania contributes to the EURO CARE CF registry.

### **Neonatal screening policy**

Newborn screening programmes are in place for phenylketonuria and hypothyroidism (Order No. V-865 of the Minister of Health of the Republic of Lithuania of 6 December 2004 "Regarding the Approval of Universal Screening of Newborns for Inborn Metabolism Disorders Procedures").

The basic prices paid from Compulsory Health Insurance Fund budget for the newborn screening programmes for phenylketonuria and hypothyroidism were reassessed and approved by the Order No. V-962 of the Minister of Health of the Republic of Lithuania in 10 November 2011.

An Order of the Minister of Health (2012-05-28 No V-470) in 2012 approved obligatory screening of newborns' vision.

The mandatory screening of newborns' hearing was approved by the Order of the Minister of Health (No V-612, 2013-06-11) in 2013.

### **Genetic testing**

Genetic testing is provided for patients of high risk group according to Ministry of Health Decree Nr.V-522 of 23 June 2005; the expenses related to this testing are reimbursed from Compulsory Health Insurance Fund budget.

Diagnostic tests are registered as available in Lithuania for 51 genes and an estimated 29 diseases in the Orphanet database<sup>377</sup>. Different laboratories can perform several diagnostic tests which are registered in the local institutional database.

Genetic testing is available in two main University Hospitals and several private laboratories. Only the clinical geneticist can order the genetic testing at academic hospitals, as established in Order of Minister of Health on 2012-08-02, No. V-745.

Reference genetic testing laboratories do not exist in Lithuania. Different genetic testing laboratories apply adapted guidelines/protocols for Lithuania.

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<sup>376</sup> <http://www.vaikuligone.lt>

<sup>377</sup> Information extracted from the Orphanet database <http://rarejournal.org/rarejournal>

Basic prices for reimbursement of genetic testing are approved by the Order of Minister of Health on 2011-11-10, No. V-962. Genetic testing abroad is reimbursed on referral by the University Hospital's consilium and decision made by Commission at the Ministry of Health (Order of Minister of Health 2010-08-16 No. V-729).

### **National alliances of patient organisations and patient representation**

Although there is no alliance of rare disease patient organisations in Lithuania, a Council of Representatives of Lithuanian Patient Organisations is in place which brings together about 20 different non-governmental patient organisations (including rare disease) and seeks to achieve common goals and rights. There are several separate patient organisations for patients with rare diseases, including phenylketonuria, rare oncological diseases, Alpha-1-antitrypsin deficiency, haemophilia, patients with impaired hearing, cystic fibrosis, rare pituitary disorders "Ausvis", genetic neuromuscular disorders "Sraunija", kidney diseases "Gyvastis". There is a general Alliance of Patient Organisations in Lithuania, covering rare diseases patient organisations as well<sup>378</sup>.

Patient organisations receive funding mainly from private sponsorship, donations and income tax donations. Patient organisations are represented at the Compulsory Health Insurance Council, and at the Council of Representatives of Patient Organisations under the Ministry of Healthcare. Members of patient organisations are involved into working groups organised by orders of the Ministry of Health, Parliament, and the representatives of patient organisations also participate in the Patient's Rights and Damage for Health Compensation Commission at the Ministry of Health. Members of patient organisations were involved in elaborating the national plan for rare diseases as well.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Lithuania***

Since 2004 there is a dedicated Orphanet team in Lithuania, currently hosted by the Centre for Medical Genetics at Vilnius University Hospital Santariškių Clinics. The Ministry of Health designated this team as the official Orphanet team for Lithuania in 2010 in the context of the Orphanet Europe Joint Action. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also manages the Orphanet Lithuania<sup>379</sup> national website in Lithuanian.

#### ***Official information centre on rare diseases***

The only official common information source on rare diseases in Lithuania is Orphanet.

#### ***Helpline***

General help lines (e.g. providing psychological support) exist, although there is no help line dedicated to provide information on rare diseases.

Two National contact points (State Health Care Accreditation Agency and The National Health Insurance Fund) dedicated to providing information for patients seeking treatment and diagnostics abroad were designated by the Order of the Minister of Health on 10 December 2012 (No V-1123).

#### ***Other sources of information on rare diseases***

The website of Coordinating Centre on Rare Diseases at the University Children's Hospital at the Vilnius University Hospital Santariškių Clinics provides web-based information<sup>380</sup>.

Web-based information of the Adult Cystic Fibrosis Centre of the Hospital of Lithuanian University of Health Sciences Kaunas Clinics can be found on <http://www.kmuk.lt/cfcentras/index.php>. Information about Primary Immunodeficiency, dedicated to patients and physicians can be found on [www.imunodeficitas.lt](http://www.imunodeficitas.lt).

Lithuania is a partner in the ECORN-CF project which maintains a website and forum for patients with cystic fibrosis, their relatives and any other interested parties where they can ask questions and obtain answers from experts. Although the EC-funding of this project has ended, the service continues to be sustained through other sources of financing.

### **Guidelines**

A "National agreement for cystic fibrosis diagnostic and treatment: evidence based methodical recommendations"<sup>381</sup> was published in the journal *Paediatric pulmonology and allergology* (Vol. XIII, Nr. 2): this

<sup>378</sup> <http://www.pacienturyba.lt>

<sup>379</sup> <http://www.orpha.net/national/LT-LT>

<sup>380</sup> [http://www.vaikuligone.lt/centras.php?cen\\_id=16](http://www.vaikuligone.lt/centras.php?cen_id=16)

agreement was reached in October 2010 between paediatricians and pulmonologists and concerns best practice for cystic fibrosis treatment.

A national agreement for cystic fibrosis diagnostic, treatment and management for adults was reached and published in journal *Pulmonology, immunology and allergology* (1(8), 2011)

Management of Wilson's disease, HFE hemochromatosis and Budd-Chiari syndrome is based on EASL, AASLD clinical practice guidelines. Centre-based protocol for the diagnosis and multidisciplinary management of tuberous sclerosis complex is prepared at the Phacomatosis Centre, Kaunas Clinics. Management of other rare diseases is based on European or International recommendations.

### **Training and education initiatives**

A training program for the improvement in rare diseases diagnostics for doctors has been initiated and a training cycle called "Rare diseases" has been introduced for medical students.

### **National rare disease events in 2013**

The "National Activities Related to Rare Diseases" conference was held in Vilnius on 14 November 2013, under the auspices of the EU Lithuanian presidency. The conference brought together representatives of patient organisations, academics, healthcare professionals, public authorities and others. The participants gathered to exchange experience on management of rare diseases, implementation of national plans and strategies with regard to rare diseases, progress of the establishment of rare diseases centres, readiness to participate in the activities of European reference networks, research in the area of rare diseases, and examination of difficult clinical cases of rare diseases.

Many of articles dedicated to the Rare Disease Day 2013 were publicised using the mass media. Also, an official opening of the Centre of Rare Gastrointestinal and Liver Diseases at the Hospital of Lithuanian University of Health Sciences Kaunas Clinics was announced on the same day.

Various topics on rare diseases were delivered during the following meetings: Annual conference Pulmonology, Allergology and Clinical Immunology 3 May 2013 in Kaunas, the Conference on Diagnosis and treatment of gastrointestinal neuroendocrine tumours 17 May 2013, Kaunas, the 12th conference of Baltic child neurology association 30 May – 1 June 2013, Kaunas, and the Seminar on cystic fibrosis 8 November, Seimas of the Republic of Lithuania, Vilnius.

Also the conference dedicated for the Rare Disease Day was held in Vilnius University Children's Hospital. Social media has also been highly involved in Rare Disease Day campaign. This year periodicals and online portals have shared stories about rare disease patients, the importance of diagnostics and problems that they face every day.

### **Hosted rare disease events in 2013**

On 14 November 2013 the conference "National Activities Related to Rare Diseases" was held in Vilnius, under the auspices of Lithuanian presidency. The Conference was organised in collaboration with Vilnius University, Lithuanian University of Health Sciences, European Commission, EURORDIS and the expert speakers from Italy, Bulgaria, Germany, Spain and Baltic countries were welcomed.

### **Research activities and E-Rare partnership**

#### ***National research activities***

In recent years funding is available for fundamental research and research concerning medicinal products: this second area of research is in particular targeted by the European Union Structural Assistance Operational Programme 2007-2013 for Economical Growth and research projects for rare diseases may receive financial support by taking part in tendering processes. Additionally, in 2007 the Government of the Republic of Lithuania adopted the Lithuanian Research and Development Priorities for 2007-2010 (Governmental Decree No. 166, 7 February 2007) which also includes as a priority the development of medicinal products, including those targeting rare diseases.

An academic research project in Lithuania entitled "National hereditary childhood cancer research platform" which focuses on six genetic diseases (von Hippel-Lindau syndrome, Li-Fraumeni syndrome, Multiple endocrine neoplasia syndromes - MEN1 and MEN2, Familial adenomatous polyposis and Type 2 Neurofibromatosis), molecular epidemiology and establishing of molecular diagnostic facility as well as information dissemination concerning rare diseases is on-going. In collaboration with the Institute for Digestive Research of Lithuania University of Health Sciences, the Centre of Rare Gastrointestinal and Liver Diseases

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<sup>381</sup> <http://www.pediatrija.org>

carries out research on C282Y, H63D, and S65C mutations in hereditary HFE-hemochromatosis gene, frequency of the c.3207C>A (p.H1069Q) mutation in ATP7B gene of Lithuanian patients with hepatic presentation of Wilson's disease. A national research project in cystic fibrosis is "Genetic, microbiological, functional and clinical data of adult cystic fibrosis patients from 2009" is ongoing.

#### **Participation in European research projects**

Lithuanian teams participate, or have participated, in 4 FP7 rare disease related projects.

#### **E-Rare**

Lithuania is not currently part of the E-Rare consortium.

#### **IRDiRC**

Lithuanian funding agencies do not currently contribute funding to the IRDiRC.

#### **Orphan medicinal products**

##### **Orphan medicinal product committee**

A committee, set up by the National Health Insurance Fund under the Ministry of Health, responsible for taking decisions on medicines and medical treatment for very rare diseases and conditions. Lithuania as an EU MS has a national representative at the COMP.

##### **Orphan medicinal product incentives**

No specific activity reported.

##### **Orphan medicinal product market availability situation**

Orphan medicinal products are available in the same way as the medicines authorised in all EU states. The website of the Lithuanian State Medicines Control Agency<sup>382</sup> provides information including the list of authorised medicines but does not give any other information concerning orphan medicinal products apart from that provided by the EMA concerning orphan medicinal products with EU market authorisations.

29 centrally authorised products were marketed in Lithuania in 2011. These include Arzerra (ofatumumab), Atriance (nelarabine), Busilvex (busulfan), Evoltra (clofirabine), Fabrazyme (agalsidase beta), Gliolan (5-aminolevulinic acid hydrochloride), Glivec (imatinib), Increlex (mecasermin), Inovelon (rufinamide), Litak (cladribine), Lydodren (mitotane), Mozobil (plerixafor), Nexavar (sorafenib), Orfadin (nitisinone), Pedea (ibuprofen), Revatio (sildenafil), Rvlimid (lenalidomide), Revolade (eltrombopag), Sprecel (dasatinib), Tassigna (nilotinib), Tepadina (thiotepa), Thalidomide Celgene (thalidomide), Torisel (temsirolimus), Tracleer (bosentan monohydrate), Trisenox (arsenic trioxide), Ventavis (iloprost), Volibris (ambrisentan), Wilzin (zinc), Yondelis (trabectedin). The majority of these medicines were marketed, other were available on patient basis. In addition, nationally authorised anagrelide (Thromboreductin) and inhaled tobramycin (Tobramycin Norameda) were available in 2011.

##### **Orphan medicinal product pricing policy**

No specific activity reported.

##### **Orphan medicinal product reimbursement policy**

According to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*<sup>383</sup> concerning Lithuania, "compensation for orphan medicinal products and medicinal products for rare diseases and conditions is paid for out of the funds earmarked for that purpose in the budget of the compulsory health insurance fund (Ministry of Health Decree No 151 of 20 March 1998; Official Gazette, 1998, No 33-894; 1999, No 7-159). A list of reimbursed medical products is available (the last update is dated 2 February 2009, Ministry of Health Decree No V-52, regarding the amendment of Order No.49 of 28 January 2000 "Regarding the Approval of the List of Reimbursed Medicinal Products"). Individuals are compensated for the purchase of medicinal products for rare diseases and conditions on presentation of specialist doctors' reports, following a decision by the committee, set up by the the National Health Insurance Fund under the Ministry of Health, responsible for taking decisions on medicines

<sup>382</sup> <http://www.vvkt.lt/>

<sup>383</sup> Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p17)

and medical treatment for very rare diseases and conditions and on cases for which no provision has been made (Decree of the Director of the National Health Insurance Fund under the Ministry of Health No 1K-149 of 22 November 2005; Official Gazette, 2005, No 139-5037).”

#### **Other initiatives to improve access to orphan medicinal products**

No specific activity reported.

#### **Other therapies for rare diseases**

No specific activity reported.

#### **Orphan devices**

The Committee at the National Health Insurance Fund under the Ministry of Health responsible for taking decisions on medicines and medical treatment for very rare diseases and conditions also makes decisions on compensation of orthopaedic hardware in rare diseases and conditions.

#### **Specialised social services**

Respite care services are available and are organised by municipalities and hospital clinics: the Centre of Children’s Development at Vilnius University Children’s Hospital, the Kaunas Children’s Development Clinic and day care centres for mentally disabled patients at municipal level. Therapeutic recreational programmes are available and are provided by local authorities under the administration of municipalities and directed at government level by the Ministry of Social Security and Labour. Some municipalities provide public services but these services are mostly run by private bodies (either companies or patient groups) commissioned by the social authorities. Educational camps are available for children, organised by the Ministry of Education. Rehabilitation issues are regulated by Healthcare Ministerial Order No. V-50 (17 January 2008) “Regarding the Organisation of Medical Rehabilitation and Sanatorium”. Governmental services are available to promote social integration including integration in schools and the work place of patients with disabilities: this includes personalised secondary training syllabi and a special integration programme for sick and disabled persons for the labour market.

## **RARE DISEASE ACTIVITIES IN 2013 IN LITHUANIA**

#### **National plan/strategy for rare diseases and related actions**

On 18 October 2012, the national plan for rare diseases was approved by Order No V-938 of the Minister of Health, and a national rare diseases coordination committee was formed, including delegated experts from university hospitals, universities, non-governmental organisations, state institutions representatives to oversee the plan. There was a Europlan conference<sup>384</sup> on 14 November 2013 under the auspices of the Lithuanian presidency to discuss the implementation of the plan.

In 2013 10,4 million litas (about 3 million euros) were allocated to reimbursing rare medicinal products and devices.

#### **Registries**

Establishment of various diseases registries is quite a long and costly process, this is why Lithuania is looking to innovate by establishing electronic, platform-based registries during the period of implementation of E-Health project 2013-2015. Registries of separate diseases (rare included) will function as subsystem of National E-Health information system and will be integrated into common data network.

#### **Neonatal screening policy**

The mandatory screening of newborns’ hearing was approved by the Order of the Minister of Health (No V-612, 2013-06-11) in 2013.

<sup>384</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-lithuania.pdf>

### **Training and education initiatives**

A training program for the improvement in rare diseases diagnostics for doctors has been initiated and a training cycle called "Rare diseases" has been introduced for medical students.

### **National rare disease events in 2013**

The "National Activities Related to Rare Diseases" conference was held in Vilnius on 14 November 2013, under the auspices of the EU Lithuanian presidency. The conference brought together representatives of patient organisations, academics, healthcare professionals, public authorities and others. The participants gathered to exchange experience on management of rare diseases, implementation of national plans and strategies with regard to rare diseases, progress of the establishment of rare diseases centres, readiness to participate in the activities of European reference networks, research in the area of rare diseases, and examination of difficult clinical cases of rare diseases.

Many of articles dedicated to the Rare Disease Day 2013 were publicised using the mass media. Also, an official opening of the Centre of Rare Gastrointestinal and Liver Diseases at the Hospital of Lithuanian University of Health Sciences Kaunas Clinics was announced on the same day.

Various topics on rare diseases were delivered during the following meetings: Annual conference Pulmonology, Allergology and Clinical Immunology 3 May 2013 in Kaunas, the Conference on Diagnosis and treatment of gastrointestinal euroendocrine tumours 17 May 2013, Kaunas, the 12th conference of Baltic child neurology association 30 May – 1 June 2013, Kaunas, and the Seminar on cystic fibrosis 8 November, Seimas of the Republic of Lithuania, Vilnius.

Also the conference dedicated for the Rare Disease Day was held in Vilnius University Children's Hospital. Social media has also been highly involved in Rare Disease Day campaign. This year periodicals and online portals have shared stories about rare disease patients, the importance of diagnostics and problems that they face every day.

### **Hosted rare disease events in 2013**

On 14 November 2013 the conference "National Activities Related to Rare Diseases" was held in Vilnius, under the auspices of Lithuanian presidency. The Conference was organised in collaboration with Vilnius University, Lithuanian University of Health Sciences, European Commission, EURORDIS and the expert speakers from Italy, Bulgaria, Germany, Spain and Baltic countries were welcomed.

## **1.18. LUXEMBOURG**

### **Definition of a rare disease**

Stakeholders in Luxembourg accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10'000 individuals.

### **National plan/strategy for rare diseases and related actions**

The Task Force on Rare Diseases Luxembourg ("*Groupe de travail maladies rares*") was created in 2005 to analyse the needs of rare disease patients in the country and to develop a national strategy for improvement. This Task Force carried out a survey ("*Rare diseases: a national survey on the situation of persons with rare diseases in Luxembourg*"<sup>385</sup>) carried out between May 2006 and February 2007 aimed at analysing the strengths and weaknesses of the healthcare system and the experiences of rare disease patients. The results of this survey were published on 28 February 2011<sup>386</sup>. The results of the survey show that, as in many other European countries, obtaining a diagnosis is often difficult for rare diseases patients in Luxembourg; that medical and scientific knowledge is often insufficient, as Luxembourg does not have university hospitals or specialised investigation centres; that often there is a lack of information on diseases or specialised treatment centres nearby. Due to the small size of the country, the proximity to a huge number of university hospitals in the

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<sup>386</sup> *Les maladies rares: Enquête sur la situation des personnes atteintes de maladies rares au Grand-Duché de Luxembourg*  
<http://www.sante.public.lu/fr/catalogue-publications/maladies-traitements/maladies-rares/index.html>

neighbouring countries Belgium, Germany and France, and the fact that most medical doctors are trained in these universities, good professional collaboration with specialised centres abroad has been in action for many years. Also the orientation of patients (patients with rare diseases, but also patients needing highly specialised care such as complicated surgical interventions, very specialised diagnostic interventions for more frequent diseases) to a specialist or a specialised centre abroad is a procedure foreseen via the national sickness fund. According to the results of the survey, 44 % of patients with rare diseases residing in Luxembourg have been oriented by their treating doctor for diagnostic purposes to specialised centres abroad. The medical care of 54 % of the patients is delivered in Luxembourg, 22% are followed for medical purposes in specialised centres in the neighbouring countries (Germany, Belgium and France), and for 24% a shared medical care program has been established between local doctors or hospital departments and abroad specialists. 50% of patients travel 1 to 5 times a year abroad for medical care, knowing however that the distances to these centres in general do not exceed 500km. Patients often lament the lack of coordination between the health professionals; there is a lack of quality care for a large number of rare pathologies; parts of the care and treatment might not be covered by the sickness fund and so there are inequalities in the access to a diagnosis, treatments and care; and rare diseases might have serious social consequences. A list of recommendations have been made on the basis of these results including: the elaboration of a national plan for rare diseases; the improvement of information and awareness of rare diseases; a guarantee of equal access to diagnosis, care and treatment; the provision of specific help services for patients with rare diseases and their families; support of rare disease patient organisations and their involvement in national rare disease actions; intensification of international collaboration; promotion of advanced research; and support for the sustainability of rare disease initiatives at national level.

Concertation for the elaboration of a national strategy was reinforced at national level in 2013 based on a broad interdisciplinary Europlan conference. A number of meetings were held before the November 2013 Europlan conference<sup>387</sup> to raise awareness amongst key stakeholders from different domains (political, medical, patient associations, education, social services, reimbursement etc.) regarding specific problems linked to rare diseases. A great majority of the addressed stakeholders participated very actively in the Europlan conference which aimed to contribute to the identification of concrete proposals for the elaboration of a national strategy. This endeavour will be carried on in 2014/2015.

#### **Centres of expertise**

There are currently no official centres of expertise for rare diseases in Luxembourg.

#### **Registries**

Luxembourg contributes to the EURO CARE CF European registry. A cancer registry is under construction, which will include also the registration of rare cancers. A special effort has been made since 2013 to include Orphacodes when possible to the cause of death registration.

#### **Neonatal screening policy**

A national neonatal screening programme is in place for phenylketonuria (since 1968), congenital hyperthyroidism (since 1978), congenital adrenal hyperplasia (since 2001) and Medium-Chain Acyl-CoA Deficiency (since 2008).

#### **Genetic testing**

Modifications of the regulations concerning the sickness fund are undertaken to improve the reimbursement of genetic tests.

#### **National alliances of patient organisations and patient representation**

The Luxembourg Association for Neuromuscular and Rare Disorders (ALAN absl.) was established in 1998 to represent patients with neuromuscular diseases: since 2006 they have provided support for other rare disease patients for whom there is no other patient organisation. The association organises informative events, counselling, guidance and self-help groups and is involved in the work of the Task Force on Rare Diseases Luxembourg. There are other patient organisations for single or groups of rare diseases. There is the intention to create an alliance of rare disease patient organisations.

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<sup>387</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-luxembourg.pdf>

## **Sources of information on rare diseases and national help lines**

### ***Orphanet activities in Luxembourg***

Since 2006, Luxembourg cooperates with Orphanet, through one contact member situated at the Ministry of Health.

### ***Official information centre for rare diseases***

The Task Force has plans to put into place a national rare diseases platform which offers medical and social services, a rare disease hotline, counselling, self-help groups, specialised information on rare diseases and guidelines of best practices. A guide to all medical, paramedical and social services available to rare disease patients and their family should also be made available online.

### ***Help line***

A rare disease help line is one of the activities to be hosted by the national rare diseases platform.

### ***Other sources of information on rare diseases***

Increasing knowledge and use of the Orphanet database by medical professionals and the general public has been observed.

### ***Good practice guidelines***

In general health professionals will adopt good practice guidelines existing abroad, guidelines identified by the Orphanet database or elaborated by recognised centres of expertise abroad.

### ***Training and education initiatives***

No specific information reported.

### ***National rare disease events in 2013***

During 2013 several awareness-raising activities were organised by ALAN absl partly together with other partners. To mark Rare Disease Day 2013, a day of festivities was organised to raise public awareness and funding. An art exhibition dealing with different aspects of rare diseases ran from December 2013 to February 2014

A major event was the organisation of a Europlan national conference<sup>388</sup> on 19-20 November 2013 with the participation of members from the European Commission, Eurordis and EUCERD, gathering a huge number of national key stakeholders from the medical, the political and the social security fields. Many patient associations participated, as well as research centres and social services. The aim of the conference was to contribute to: increasing the awareness of the specific problems linked to rare diseases, identifying key persons for the contribution in the existing taskforce, identifying the main problems existing in the area of rare diseases, defining priorities for action, and beginning the formulation of the national rare disease strategy.

### ***Hosted rare disease events in 2013***

The meetings of the EUCERD were hosted by the European Commission in Luxembourg in 2013.

## **Research activities and E-Rare partnership**

### ***National research activities***

An annual rare disease telethon, organised by the Lions Club, raises money and pools this with that of the AFM (*Association française contre les myopathies*) which then redistributes these funds to research projects, a small amount comes back to Luxembourg for work with patients.

### ***Participation in European research projects***

Teams from Luxembourg participate in 3 FP7 rare disease related projects, involving a number of research institutes such as the Luxembourg Centre for Systems Biomedecine and the Centre for Public Health Research (in particular for cancers and rare cancers).

### ***E-Rare***

No information

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<sup>388</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-luxembourg.pdf>



### **IRDIRC**

A member from the National Taskforce participates as an observer in IRDiRC. However, there are no funding has been committed by agencies from Luxembourg.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

The Pharmacy and Medicines division of the Directorate of Health/Ministry of Health is dealing with the accessibility of orphan drugs in Luxembourg. The Task Force aims to create a national medical commission to consult on issues regarding exceptional access to and reimbursement of orphan medicinal products.

#### ***Orphan medicinal product incentives***

No specific information reported.

#### ***Orphan medicinal product market availability situation***

The orphan medicinal product/medicines for rare diseases available in Luxembourg in 2013<sup>389</sup> were: Replagal, Fabrazyme, Aldurazyme, Myozyme, Elapraxe, Zavesca, Kuvan, Nplate, Revolade, Firazyf, Tracleer, Volibris, Revatio, Increlex, Somavert, Cayston, Tobi Podhaler, Litak, Atriance, Vidaza, Dacogen, Yondelis, Adcetris, Nexavar, Sprycel, Tasigna, Torisel, Jakavi, Trisenox, Xagrid, Mepact, Mozobil, Soliris, Ilaris, Esbriet, Thalidomide Pharmion, Revlimid, Inovelon, Duodopa, Vyndaqel, Exjade and Savene.

#### ***Orphan medicinal product pricing policy***

No specific information reported.

#### ***Orphan medicinal product reimbursement policy***

No specific information reported.

#### ***Other initiatives to improve access to orphan medicinal products***

No specific information reported.

### **Orphan devices**

No specific information reported.

### **Other therapies for rare diseases**

No specific information reported.

### **Specialised social services**

No specific information reported.

## **RARE DISEASE ACTIVITIES IN 2013 IN LUXEMBOURG**

### **National plan/strategy for rare diseases and related actions**

Concertation for the elaboration of a national strategy was reinforced at national level in 2013 based on a broad interdisciplinary Europlan conference. A number of meetings were held before the November 2013 Europlan conference<sup>390</sup> to raise awareness amongst key stakeholders from different domains (political, medical, patient associations, education, social services, reimbursement etc.) regarding specific problems linked to rare diseases. A great majority of the addressed stakeholders participated very actively in the Europlan conference which aimed to contribute to the identification of concrete proposals for the elaboration of a national strategy. This endeavour will be carried on in 2014/2015.

<sup>389</sup> As of April 2013.

<sup>390</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-luxembourg.pdf>

## Registries

A special effort has been made since 2013 to include Orphacodes when possible to the causes of death registration.

## National rare disease events in 2013

During 2013 several awareness-raising activities were organised by ALAN absl partly together with other partners. To mark Rare Disease Day 2013, a day of festivities was organised to raise public awareness and funding. An art exhibition dealing with different aspects of rare diseases ran from December 2013 to February 2014

A major event was the organisation of a Europlan national conference<sup>391</sup> on 19-20 November 2013 with the participation of members from the European Commission, Eurordis and EUCERD, gathering a huge number of national key stakeholders from the medical, the political and the social security fields. Many patient associations participated, as well as research centres and social services. The aim of the conference was to contribute to: increasing the awareness of the specific problems linked to rare diseases, identifying key persons for the contribution in the existing taskforce, identifying the main problems existing in the area of rare diseases, defining priorities for action, and beginning the formulation of the national rare disease strategy.

## Hosted rare disease events in 2013

The meetings of the EUCERD were hosted by the European Commission in Luxembourg in 2013.

## 1.19. MALTA

### Definition of a rare disease

Stakeholders in Malta accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategy for rare diseases and related actions

There is currently no national plan/strategy for rare diseases in place in Malta. A Task Force for the implementation of the key requirements for Member States for the Council Recommendations on a European action in the field of rare diseases was set up in October 2010. An advanced first draft of the National Plan on Rare Diseases was completed in 2012. An internal consultation exercise was also completed. A public consultation will be held in 2014. There will probably be a policy commitment to rare diseases in the near future but there may not be a budget specifically for these actions.

### Centres of expertise

There are currently no official reference centres of expertise for rare diseases in Malta (see "Pilot European Reference Networks"). Assistance by local government for treatment abroad (namely in the UK) is possible through a bilateral health agreement between the two countries. Further agreements with other EU Member States are being sought, developed and completed. For example, since 2012 Malta is sending patients to centres in Italy for specialised investigation and treatment such as lung transplants. There is only one potential centre of expertise (and indeed also one referral centre) which comprises the major acute general hospital; Mater Dei Hospital. This hospital caters for the majority of the secondary and tertiary healthcare provision in Malta. It is a teaching hospital (in conjunction with the University of Malta) and it is a public hospital. In addition, from 2014 onwards it is also planned to house the new Oncology Hospital which is currently under construction on the Mater Dei Hospital site.

### Registries

There is currently no system for the designation of registries for rare diseases in Malta. However work has been done on the possible sources of data on rare disease patients in order to assess feasibility for future steps.

<sup>391</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-luxembourg.pdf>

During 2013 Malta started looking actively at the feasibility of introducing a suitable coding system, specifically Orphacodes. This will be further followed up in 2014. Malta contributes to the EUROCAT European registry as well as the RARECARE and EUROCCARE projects through the Malta National Cancer Registry. It is also participating in EPIRARE and PARENT projects.

#### **Neonatal screening policy**

Neonatal screening is available for haemoglobinopathies and hypothyroidism.

#### **Genetic testing**

Genetic studies (karyotyping and molecular genetic studies) in fetuses and neonates born with congenital malformations or rare syndromes are available. There are 3 consultant geneticists and 2 genetics laboratories in Malta, the Molecular Genetics Laboratory and Cytogenetics Laboratory. The indicated genetic tests that are not performed in house are referred to a reference laboratory/centre abroad. The funding for these tests is covered by the local health authorities.

#### **National alliances of patient organisations and patient representation**

Until Rare Disease Day 2013, Malta did not have an official national alliance of rare diseases patient organisations. However, this role is increasingly being assumed by the Malta Blood Donors Association, in founding and registering a National Alliance for Rare Diseases, which will be better known as The Malta Alliance for Rare Disorders (MARD).

MARD aims to intensify the awareness amongst the general public and decision-makers about rare diseases and their impact on patients' lives. Its objectives are designed primarily for patients, patients' organisations and their representatives, bringing together other stakeholders such as politicians, public authorities, policy-makers, industry representatives, researchers, health professionals and individuals who have a genuine interest in rare diseases. MARD will be representing EURORDIS in Malta.

#### **Sources of information on rare diseases and national help lines**

##### ***Orphanet activities in Malta***

The government of Malta has not designated a national Orphanet team for Malta to date.

##### ***Official information centre for rare diseases***

There is no official information centre on rare diseases in Malta to date.

##### ***Help line***

Although there is no official help line for rare diseases, the agency Sapport provides support by telephone to all disabled people that request it. This service is funded by the government.

##### ***Other sources of information on rare diseases***

No reported information.

#### **Guidelines**

No reported information.

#### **Training and education initiatives**

There are currently no initiatives specifically dedicated to rare disease-specific training and education in Malta.

#### **National rare disease events in 2013**

To mark Rare Disease Day 2013, the Malta Blood Donors Association organised a number of events, including media events and meetings with political decision-makers.

#### **Hosted rare disease events in 2013**

No specific activity reported.

#### **Research activities and E-Rare partnership**

##### ***National research activities***

Funding for research into haemoglobinopathies and other rare genetic disorders is available through various sources (including the European Structural Funds, Ithantet and the University of Malta). Despite the lack of

specific research programmes for rare diseases, there are a significant number of research projects in the field underway at the University of Malta with funding provided by the University, through the European Union or via private charities.

#### **Participation in European research projects**

A team in Malta is currently participating in one of the rare disease related FP7 projects.

##### ***E-Rare***

Malta is not currently a partner for the E-Rare project.

##### ***IRDiRC***

Malta is not currently a partner in IRDiRC.

#### **Orphan medicinal products**

Since the start of 2010 Malta participated in the project “Assessing Drug Effectiveness” (an initiative of the Swedish Presidency) and is currently participating in the project “Mechanism of Coordinated Access to Orphan Medicinal Products” (an initiative of the Belgian Presidency). Malta is also participating in the BBMRI initiative of the EU.

##### ***Orphan medicinal product committee***

Orphan medicinal products are registered through the centralised procedure and Malta has a member on the Committee for Orphan Medicinal Products and on the Committee for Human Medicinal Products of the European Medicines Agency.

##### ***Orphan medicinal product incentives***

No specific reported activity.

##### ***Orphan medicinal product market availability situation***

There is no information about the number of orphan medicinal products which are available on the private market. Information gathered by the Directorate of Pharmaceutical Affairs shows that only two orphan medicinal products are purchased and placed on the market and are not provided through the government system for free medicinals: Ecteinascidin 743 (Yondelis) and Sorafenib tosylate (Nexavar). In addition, 39 orphan medicinal products were available within the National Health Scheme in 2013(see below).

##### ***Orphan medicinal product pricing policy***

With regards to reimbursement processes within the National Health Scheme, if an orphan medicinal product is approved through the Exceptional Medicines Treatment Policy, there will be no specific provisions for pricing. However, when a request for introduction into the Government Formulary List is submitted and approved, the pricing policy as for all other new medicines applies. The Pricing Policy for the National Health Scheme was launched in 2010 and updated in January 2014.

##### ***Orphan medicinal product reimbursement policy***

The Government Formulary List contains a number of orphan medicinal products which are reimbursed according to government entitlement policies. The Exceptional Medicines Treatment Policy allows for specific provisions for the reimbursement of orphan medicinal products, which are either not listed on the Government Formulary List or are not according to government policies.

The following orphan medicinal products with EU market authorisation were reimbursed in 2013<sup>392</sup>: Amifampridine, Anagrelide, Azacitidine, Bosentan, Caffeine citrate, Celecoxib, Cladribine, Clofarabine, Dasatinib, Deferasirox, Eptacog Alfa (Recombinant Factor VIIa), Human Cytomegalovirus Immunoglobulin, Irinotecan\*, Lenalidomide, Levamisol hydrochloride, Mercaptopurine liquid, , Nilotinib, Octreotide LAR\*, Para-amino Salicylic Acid\*, Peg-Asparigase\*, Pegvisomant, Plerixafor, Rofinamide, Sildenafil, Sulindac\*, Thalidomide, Thiotepe, Tobramycin (inhalation solution), Topotecan. The drugs available within the National Health Scheme are either on the national Government Formulary List or approved through the Exceptional Medicines Treatment Policy and are fully reimbursed and available for dispensing, free of expense to the patients entitled to them.

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<sup>392</sup> Source: Directorate of Pharmaceutical Affairs, Ministry for Health (10 April 2013)

### **Other initiatives to improve access to orphan medicinal products**

All medicinal products must be authorised before they can be marketed in the European Union. However, a treatment option for patients in the European Union suffering from a disease for which no satisfactory authorised alternative therapy exists or who cannot enter a clinical trial, may be the use of an unauthorised medicinal product in a compassionate use programme. Compassionate use programmes are intended to facilitate the availability to patients of new treatment options under development.

To obtain an authorisation in line with compassionate use, as per Article 83 of Regulation (EC) No 726/2004 on compassionate use, applicants submit a request to the Licensing Authority. The product being applied for under compassionate use needs to be specifically under evaluation in the centralised authorisation procedure at the European Medicines Agency.

Off-label use is the use of a product outside its licensed indications. Off-label use is possible at the responsibility of the prescribing physician.

### **Other therapies for rare diseases**

No specific activity reported.

### **Orphan devices**

There are no specific initiatives in place concerning orphan devices in Malta. To date, Malta has retained the view that an EU regulation on orphan medical devices is neither necessary nor beneficial and that the current legal framework already caters for rare diseases.

### **Specialised social services**

There are limited respite care services and there is an element of co-payment, as with all other residential long-term care services. Therapeutic recreational programmes are also available, and subsidies are available: these services are provided by not-for-profit organisations. There is close liaison between health and education authorities to support children in the mainstream schools for the implementation of inclusive education. This includes support to teachers to provide inclusive education at national level. A wide range of services by health care professionals are offered in the community by the health care division through Primary Health Care services such as speech Language services and physiotherapy. In addition, there are also social security benefits for those with disabilities.

## **RARE DISEASE ACTIVITIES IN 2013 IN MALTA**

### **National plan/strategy for rare diseases and related actions**

An advanced first draft of the National Plan on Rare Diseases was completed in 2012. An internal consultation exercise was also completed. A public consultation will be held in 2014. There will probably be a policy commitment to rare diseases in the near future but there may not be a budget specifically for these actions.

### **Registries**

During 2013 Malta started looking actively at the feasibility of introducing a suitable coding system, specifically Orphacodes. This will be further followed up in 2014.

### **National alliances of patient organisations and patient representation**

Until Rare Disease Day 2013, Malta did not have an official national alliance of rare diseases patient organisations. However, this role is increasingly being assumed by the Malta Blood Donors Association, in founding and registering a National Alliance for Rare Diseases, which will be better known as The Malta Alliance for Rare Disorders (MARD).

MARD aims to intensify the awareness amongst the general public and decision-makers about rare diseases and their impact on patients' lives. Its objectives are designed primarily for patients, patients' organisations and their representatives, bringing together other stakeholders such as politicians, public authorities, policy-makers, industry representatives, researchers, health professionals and individuals who have a genuine interest in rare diseases. MARD will be representing EURORDIS in Malta.

### National rare disease events in 2013

To mark Rare Disease Day 2013, the Malta Blood Donors Association organised a number of events, including media events and meetings with political decision-makers.

## 1.20. THE NETHERLANDS

### Definition of a rare disease

Regulation (EC) 141/2000 on orphan medicinal products defines a rare disease: the prevalence of a rare disease is not higher than five per 10,000 individuals. The Netherlands will take no initiatives to amend the definition.

### National plan/strategy for rare diseases and related actions

The Health insurance Act is at the basis of the Netherlands' health care system. All patients, including patients with a rare disease, are entitled to diagnosis, care and rehabilitation in line with this Act.

The Minister of Health, Welfare and Sport, Mrs. E. Schippers, sent a letter (with annex) to Parliament on 29 February 2012, in which she expounded the strategy of the Dutch government regarding rare diseases for the years 2012-2015. Some important points in this report are the following:

- Strengthening the role of university hospitals with regard to patient care and research in rare diseases (and centres of expertise);
- Funding (only university hospitals) is designated for care and research;
- Improving reimbursement of orphan medicinal products applied in university hospitals starting 1 January 2012 and in the out-patient setting (starting in 2013). This new policy will not hinder the accessibility of orphan medicinal products;
- The Steering Committee on Orphan Drugs was dissolved (as of 31 December 2011), but stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise;
- ZonMw (The Netherlands Organisation for Health Research and Development) assume tasks not taken up by the stakeholders that remain from the tasks of the former Steering Committee. The ministry of Health, Welfare and Sport provides funding for the years 2012-2015;
- The Forum Biotechnology and Genetics (also fully subsidised by the ministry of Health, Welfare and Sport) will assume more responsibility on rare diseases and orphan medicinal products;
- A statement on screening.

In addition to this strategy, preparations for a national plan on rare diseases for all stakeholders have started. The Netherlands Organisation for Health Research and Development (ZonMw), has been commissioned by the Ministry of Health, Welfare and Sport to coordinate the input for a National Plan following up on the initial work of the Dutch Steering Committee on Orphan Drugs.

The input of all stakeholders was collected via information from different meetings organised in the last year and via working groups and the website, coordinated by ZonMw/NPZZ and under the auspices of a sounding board especially formed for this task (<http://www.npzz.nl/>). The website will make public the preparatory documents for the National Plan. In January-March 2012, stakeholders started collecting possible solutions for the issues raised and discussing these on the website and in a public hearing in April 2012. A meeting was organised on 28 August 2012 in Amsterdam to present the first draft of the national plan for rare diseases.

A second draft was presented on the website in January 2013. The National Plan for Rare Diseases received input from all stakeholders and was adopted in October 2013<sup>393</sup> and presented on 10 October 2013 by a delegation of The Netherlands Organization for Health Research and Development (ZonMw) to Minister Schippers of Health, Welfare and Sport (VWS). On 14 November the Minister sent the plan along with her reaction to Parliament. The Dutch National Plan identifies bottlenecks and recommendations, and it encourages field parties to feel responsible. The key bottlenecks for the plan include lack of knowledge about rare diseases, insufficient medical research on causes and course of rare diseases as well as inability of patient organisations to work well together. The plan recommends emphasising knowledge about rare disease

<sup>393</sup> [http://www.euoplanproject.eu/newsite\\_986989/Resources/docs/NATIONALPLANS\\_NETHERLANDS\\_nl.pdf](http://www.euoplanproject.eu/newsite_986989/Resources/docs/NATIONALPLANS_NETHERLANDS_nl.pdf)

through training and establishment of expert centers, make the information widely accessible to diverse audiences; make financial resources available for research and development of treatment as well as maintaining consistent policy for claims and reimbursement of orphan drugs. Finally the plan aims to appoint a director or coordinator to promote all recommendations, and avoid fragmentation and unnecessary duplication within the rare disease field.

### **Centres of expertise**

All stakeholders – and also the government - support the idea that the (follow-up) care and research for patients with rare diseases should be concentrated in, and/or coordinated from, a limited number of centres, in order to guarantee expert care and to stimulate research. In order to stimulate the development of centres of expertise in the Netherlands the Steering Committee on Orphan Drugs developed criteria for expertise centres together with different stakeholders (hospitals, doctors, patients, researchers). These criteria are in line with the criteria established by the EUCERD. The Dutch Government asked the University Medical Centres to work on a plan for concentration of rare disease expertise.

The Dutch Federation of University Medical Centres (NFU) presented their plan at the Conference on the National Plan in August 2012. Here it was stated that the NFU would present their 'list' with centres of expertise early 2013. This list with identified centres will be checked with the information in the Orphanet database and the information collected by the National Patient Alliance for Rare and Genetic Disease (VSOP);

### **Registries**

There is no comprehensive national patient registry in the Netherlands, or designation process, but several patient registries exist for specific rare diseases, including registries maintained by patient organisations and at the main clinical reference centres.

The expertise of several partners involved in the research of rare inborn errors of metabolism (IEM) has been assembled in the Orphan Disease Registry Consortium. Pooling of expertise will greatly support registry of these metabolic diseases in The Netherlands and will lead to improved guidelines for treatment and monitoring as well as a better understanding in the future. This project delivered one thesis in 2012: Fabry disease; studies on diagnosis, screening and patient's perspective. Another result of this project is that the national web-based facilitating registry for inborn errors of metabolism has been further developed<sup>394</sup>.

To assist patient organisations in the setting up of patient registries and biobanks, VSOP launched the website [www.biobanken.net](http://www.biobanken.net).

A registry of all patients referred with an abnormal neonatal screening result (NEORAH) has been put into place at the RIVM (National Institute for Public Health and the Environment) for two rare diseases (AGS and sickle cell disease). Furthermore the Netherlands contributes to European registries including ECARUCA, EIMD, TREAT-NMD, AIR, EUROCARE CF, EPCOT, X-ALD and EUROCAT.

### **Neonatal screening policy**

In the current neonatal screening program in the Netherlands 18 rare disorders are diagnosed: phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, cystic fibrosis (2010), biotinidase deficiency, galactosaemia, glutaric aciduria type I, HMG-CoA lyase deficiency, holocarboxylase synthase deficiency, homocystinuria, isovaleric acidemia, maple syrup urine disease, MCAD deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, sickle cell disease, tyrosinemia type I, longchain hydroxyacyl-CoA dehydrogenase deficiency and very-long-chain acyl-CoA dehydrogenase deficiency.

The Dutch Health Council has been asked by the Ministry of Health to present their advice about expanding neonatal screening for other (rare) diseases. Screening is not primarily oriented towards rare diseases, but aimed at those diseases for which some form of treatment is available. In other words establishing a diagnosis in a patient via screening should in theory lead to a gain in health. This can also be the case for rare diseases.

### **Genetic testing**

All eight University Medical Centres are licensed for clinical genetics; to provide counselling and pre- and postnatal testing. Services include genetic counselling, chromosome analysis, biochemical (enzyme) diagnostics and DNA-diagnostics. Genetic counselling is offered locally or in out-clinics affiliated to the centre. All services are offered regionally except for the DNA-diagnostics which, since their start in 1988, operate at a national level. Preimplantation Genetic Diagnosis (PGD) is offered in one University Medical Centre, being connected

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<sup>394</sup> <https://ddrmd.nl/index.php/>

with several other genetic centres by 'transport PGD'. Patient request for PGD for new genetic indications are seen by both a local and national PGD ethics committee.

All genetic laboratories are accredited according to ISO 15189 (international standard for medical laboratories). Each DNA laboratory provides a specific package of gene tests; tests for the more frequent genetic disorders, like breast cancer are offered by more centres. Tests for rare diseases are usually performed in one laboratory only, but the rare disease diagnostics is in flux due to the application of multigene packages for heterogeneous disorders and the emergent application of the whole genome sequencing. Expertise and research is leading in the portfolio of tests offered. Diagnostic tests for 1113 genes and an estimated 1059 diseases are registered in the Orphanet database<sup>395</sup>.

Genetics services in the Netherlands are funded by the private health insurance companies through a special budget. Diagnostic tests are reimbursed on the condition that there is a medical reason to do this test. For tests that are not available in the Netherlands, samples can be sent abroad. Molecular genetic laboratories have distributed the tests according to specific expertise that is available.

### **National alliances of patient organisations and patient representation**

VSOP is the Dutch national alliance of patient organisations for rare and genetic disease, representing 67 of such organisations in The Netherlands ([www.vsop.nl](http://www.vsop.nl)). VSOP deals with specific, mutually shared issues related to rare and genetic disease in health care policy; perinatal care, including preconception care; biomedical research; prevention; standards of care; orphan medicines, paediatric medicine, ethical and societal issues. VSOP works in partnership with other Dutch patient umbrella organisations (NPCF, CG-Raad, PlatformVG) that are dealing with issues that may also effect people with rare disorders.

VSOP has an equal voice in several national governmental bodies dealing with health care and research policy relevant to rare diseases: the Dutch Health Council (Gezondheidsraad), the national PGD committee, the RIVM prenatal and neonatal screening committees, the Forum Biotechnology and Genetics, ZonMw, CBG advanced therapy committee, etc. VSOP works in partnership with both member and non-member patient organisations to improve quality of care, quality of life and to stimulate research. With regards to the designation of centres of expertise, VSOP works together with Orphanet and the umbrella of academic medical centres (NFU) to bring in the patient perspective and stimulate quality and cooperation. VSOP actively participates in the development and future implementation of the Dutch National Plan for Rare Diseases.

Most disease specific organisations in The Netherlands, including organisations for rare diseases, receive between €25,000 and €35,000 governmental funding per year. The VSOP was successful in the acquisition of project grants from other sources, like governmental funds, charities and EU-funded programs, making it possible to have about 15 employees working for the quality of life of people with rare and genetic diseases and their families. However, the structural governmental funding of VSOP will end in 2014.

In addition the VSOP and all other patient organisations receive vouchers, worth €18,000, to be combined with 6 other vouchers (patient organisations) to realise patient-driven projects. In total 18 projects started with 201 vouchers from patient organisations. Three vouchers projects were specifically dedicated to rare diseases, with a total budget of €1.5 million

VSOP has a strong European and international orientation. It represents the European patient umbrella EURORDIS in The Netherlands and participates on behalf of EGAN ([www.egan.eu](http://www.egan.eu)) in several European projects (e.g. Gencodys, GRIP, ECRIN-IA, EUPATI, Europlan, and currently in negotiation: Asterix and Closed) and committees, like the COMP at EMA, London and the ESHG Quality Committee. VSOP also initiated 'Preparing for life' an international strategy for preconception care. In 2012, cooperation in this field started with WHO.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in the Netherlands***

Since 2004, there is a dedicated Orphanet team in the Netherlands, currently hosted by the Leiden University Medical Centre. The Leiden University Medical Centre was designated by the Ministry of Health, Welfare and Sport in 2010 as the official Orphanet team for the Netherlands. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, bio banks, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also manages the Orphanet Netherlands<sup>396</sup> national website in Dutch which was launched in 2011.

<sup>395</sup> Data extracted from orphanet in January 2014.

<sup>396</sup> <http://www.orpha.net/national/NL-NL/index/homepage/?lng=FR>



A collaboration has been established between Orphanet and the Erfocentrum, the Dutch National Genetic Resource and Information Centre. Erfocentrum provides information about genetic diseases to the Dutch general public and for that purpose it has written Dutch abstracts for approximately 500 rare genetic diseases. All of these abstracts are validated by clinical geneticists and patient organisations. This collaboration allows Orphanet to use the Erfocentrum abstracts to provide information about rare diseases to the Dutch-speaking public. Hyperlinks, leading to the Erfocentrum website containing the Dutch abstracts, will be added to the disease-pages on Orphanet.

Starting February 2012, the entry of new specialised Dutch clinics in the Orphanet database is validated by the Scientific Advisory Board of Orphanet the Netherlands. Being represented in this board, VSOP contacts patient organisations to give their perspective on applications of (candidate) centre, using the EUCERD criteria.

#### **Official information centre for rare diseases**

As of 31 December 2011, the Steering Committee was disbanded by the government: however ZonMw (the Netherlands Organisation for Health Research and Development) was stimulated to install a general information desk at the secretariat for rare diseases with as main objective to coordinate the plan on RD (NPZZ). With a small financial incentive (€30 000) ZonMw has stimulated the development of new information portals for researchers and small pharmaceutical companies about orphan drugs. After this project this portal should be embedded within the Dutch Pharmaceutical Umbrella Organisations: Biofarmind and Nefarma.

#### **Help line**

The most used help line for rare disorders is the Erfocentrum ERFO line, providing information on genetic and rare diseases and pregnancy/reproduction related questions. This line can be reached by phone and e-mail.

The Royal Dutch Association of Pharmacists (KNMP) has developed in collaboration with the Steering Committee on Orphan Drugs the website [www.farmanco.knmp.nl/weesgeneesmiddelen](http://www.farmanco.knmp.nl/weesgeneesmiddelen) which publishes practical information on European registered orphan medicinal products, in particular for pharmacists but patients can also make use of it.

Information on neonatal screening is available from the National Institute for Public Health and the Environment (RIVM)<sup>397</sup>, both for the general public, parents and physicians. Information is also provided by the many Dutch patient organisations, pharmaceutical companies and the Federation of University Hospitals, etc.

#### **Other sources of information on rare diseases**

The website [www.erfelijkheid.nl](http://www.erfelijkheid.nl) contains a database of approximately 500 rare diseases with information for both lay-persons and professionals. In 2013, 50 new rare diseases (all chromosome disorders) were added to the database. In addition, public information is available on genetic, biomedical and pregnancy related issues<sup>398</sup>. Since 2010 videos were added to the website. In 2012 ten new videos were produced and added. Using videos, disease characteristics can be visualised in order to improve the dissemination of information for both patients and medical professionals.

While [www.erfelijkheid.nl](http://www.erfelijkheid.nl) is successfully reaching an audience of patient, their family and the general public, Erfocentrum also participates in the website [www.huisartsengenetica.nl](http://www.huisartsengenetica.nl), which focuses on general practitioners. Erfocentrum also provides news on genomics and rare diseases via email to more than 100 patient organizations and via Twitter to over 400 medical professionals and organisations.

#### **Guidelines**

VSOP hosts a website dedicated to good practice guidelines for rare diseases. On this website, [www.zorgstandaarden.net](http://www.zorgstandaarden.net), standards of care for rare diseases developed by VSOP are published, to be used by healthcare providers. Both generic themes and disease-specific standards are worked out. In addition, in 2012 VSOP finished 33 treatment guidelines for general practitioners carried out in close collaboration with the related patient organisations and the Dutch College of General Practitioners (NHG). Ten additional guidelines are in preparation.

Clinical guidelines on mitochondrial diseases and on Guillain-Barré syndrome (GBS) were launched in 2012. The alliance for Neuromuscular Diseases developed in cooperation with medical specialists specific information for GBS which patient can take with them (to the GP and others), in line with the project 'Patient

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<sup>397</sup> [www.rivm.nl/pns/hieiprik](http://www.rivm.nl/pns/hieiprik)

<sup>398</sup> These sites provide further web based information: [www.biomedisch.nl](http://www.biomedisch.nl); [www.zwangernu.nl](http://www.zwangernu.nl); [www.zwangerwijzer.nl](http://www.zwangerwijzer.nl); [www.slikeerstfoliumzuur.nl](http://www.slikeerstfoliumzuur.nl); [www.prenatalescreening.nl](http://www.prenatalescreening.nl)

as information carrier'. The patient organisation VKS (Adults, Children and Metabolic disorders) developed 20 new healthcare pathways for metabolic diseases.

### **Training and education initiatives**

At governmental level, training and education initiatives in the field of rare diseases are not foreseen, because these are the remit of universities and professional organisations. The Boerhaave Committee (at Leiden University Medical Centre) organises the annual Princess Beatrix Fund Symposium on Neuromuscular Diseases for medical specialists and their assistants. There is still a growing interest at college and university students to write a paper on rare diseases or orphan medicinal products.

Training for health care providers on prenatal and neonatal screening is organised at a regular basis by the National Institute for Public Health and the Environment. Documents used in training are available at the website<sup>399</sup>.

### **National rare disease events in 2013**

On 2 March<sup>400</sup>, events for Rare Disease Day were organised by ZonMw, Genzyme and VSOP. A gathering of over 300 adults and children was organised in Utrecht to serve as inspiration to promote research and better care for rare diseases. The children enjoyed creative and cultural programs, while adults participated in an informative meeting. In addition, the annual Angel Awards were also handed out.

A Europlan National Conference was held on 14 & 15 November 2013 in The Hague, co-organised by VSOP and Eurordis with the aim of exploring the provisions and implementation of the newly published Plan for Rare Diseases.

### **Hosted rare disease events in 2013**

Amongst the rare disease events announced in OrphaNews Europe were: 3rd European Rett Syndrome Conference Maastricht, "Research Update & Preventive Management" (17-19 October 2013, Maastricht), 6th International Conference on Children's Bone Health (22-25 June 2013, Rotterdam).

### **Research activities and E-Rare partnership**

#### ***National research activities***

A multi-annual research programme started in 2011 at The Netherlands Organisation for Health Research and Development (ZonMw) with a funding of €13.4 million. The main objective of this is to stimulate translational research in rare diseases with the aim of developing therapies. Three projects were each awarded a €3 million grant under this ZonMw Priority Medicines for Rare Diseases and Orphan Drugs (PM Rare) research programme<sup>401</sup>. The projects involve research that could potentially lead to new therapies for rare diseases and are to be carried out by public-private partnerships. Those selected are: antisense therapy for several major rare diseases; gene-corrected stem cells for curative treatment of severe combined immunodeficiency; and towards treatment of MELAS syndrome: drug development based on newly identified compounds.

ZonMw, the Netherlands Organisation for Health Research and Development, funds health research and stimulates use of the knowledge developed to help improve health and healthcare in the Netherlands. ZonMw's main commissioning organisations are the Ministry of Health, Welfare and Sport and the Netherlands Organisation for Scientific Research. Within several ZonMw programmes, RD research is financed (e.g. Efficacy research OD, Stem cell and Gene therapy, HTA, screening)<sup>402</sup>.

There are tax reductions for R&D in high-tech start-ups from which orphan medicinal product companies can benefit. There are also several programmes from the Ministry of Economic Affairs to facilitate start-ups and SME's (Innovation Fund) that orphan medicinal product companies can benefit from.

In 2011, the Netherlands Organisation for Scientific Research made €22.5 million available to a consortium including 8 Dutch University Medical Centres and other research institutes and universities in order to establish a national biobanking infrastructure, the Biobanking and Biomolecular Resources Research Infrastructure Netherlands (BBMRI-NL), which will integrate clinical materials and data gathered over many years with the goal of improving access to human samples. Such samples are important to rare disease and orphan medicinal product research. In 2011, 26 new projects started. In the databank are (October 2012) 191 Dutch Biobanks and over 500 000 participants. In 2013 new projects will be able to be granted.

<sup>399</sup> For instance information for screeners and information on the diseases screened: [www.rivm.nl/pns/hielprik/films](http://www.rivm.nl/pns/hielprik/films).

<sup>400</sup> [www.zeldzameziektendag.nl](http://www.zeldzameziektendag.nl)

<sup>401</sup> <http://www.zonmw.nl/nl/programmas/programma-detail/priority-medicines-zeldzame-ziekten-en-weesgeneesmiddelen-rare/algemeen/>

<sup>402</sup> <http://www.zonmw.nl/nl/themas/thema-detail/zeldzame-ziekten-en-weesgeneesmiddelen/thema-detail/>

The VU University Medical Centre in Amsterdam is working together with the Dutch Neuromuscular Diseases Association in the development of an n-of-1 trial service. The project investigated whether such trial treatments, to be facilitated by the n-of-1 trial service, could be reimbursed by the Dutch basic health insurance. It is also examining whether the results of this type of research may be sufficient for authorities to decide on the effectiveness of an off-label medicine and its reimbursement for future patients with the rare disease in question.

#### **Participation in European research projects**

Dutch teams participate (or participated) in 102 FP7 rare disease related projects and are also coordinators of 21 projects.

#### **E-Rare**

The Dutch Organisation for Health Research and Development (ZonMw) participates in E-Rare 1 (2006-2010) and E-Rare 2 (2010-2014), and participated in the 4<sup>th</sup> Joint Transnational Call in 2012: teams from the Netherlands participate in 8 out of the 11 consortia selected for funding. In 2013, ZonMw did not participate in the 5<sup>th</sup> Joint Transnational Call.

#### **IRDiRC**

The Netherlands Organisation for Health Research and Development (ZonMw) and the pharmaceutical enterprise Prosensa are committed members of the IRDiRC.

#### **Orphan medicinal products**

##### **Orphan medicinal product committee<sup>403</sup>**

In 2011 the Steering Committee focused on the draft for a national plan in close cooperation with different stakeholders. However, it was decided that the Steering Committee would not be funded by the Dutch government after December 2011 and no longer existed as a governmental committee from 2012 onwards. Stakeholders in the former Steering Committee on Orphan Drugs will assume more tasks and responsibility in their own area of expertise in the future with the Netherlands Organisation for Health Research and Development ZonMw taking more responsibility and assuming a number of tasks from the former Steering Committee. Notably, the coordination of the development and implementation of a national strategy will be from 2012 onwards assumed by a secretariat at ZonMw and the sounding board on the National Plan. This plan will not only cover Orphan Drugs but also Rare Diseases.

##### **Orphan medicinal product incentives**

A waiver can be granted for the registration fee of a medicinal product if the medicinal product is already registered in one or several other EU member states and if the prevalence of the indicated disease is less than 1 in 200.000 inhabitants in the Netherlands. In the case of orphan medicinal products for a rare disease for which no alternative treatments exist, there is no obligation for companies to provide pharmacoeconomic data. In individual cases this may also be the case for orphan medicinal products for a disease with a prevalence no more than 5 persons per 10,000 for which an alternative treatment does exist.

The programme for Expensive and Orphan Medicines (2007-2014) aims to investigate the effectiveness of expensive drugs and of expensive orphan medicinal products and the development of HTA methodology to help the Dutch Health Care Insurance Board in its advice on reimbursement. In the scope of this programme, several projects on registered orphan medicinal products have already been selected. As of 1 January 2009, the subsidy scheme Orphan Designation Dossier (ODD) is in action. This is an initiative of the Dutch Steering Committee on Orphan Drugs and is executed by the Netherlands Organisation for Health Research and Development (ZonMw). This initiative will help stimulate the development of orphan medicinal products in the Netherlands by providing Dutch pharmaceutical Small and Medium-sized Enterprises (SMEs) a small subsidy for the costs of writing and submitting the ODD to the EMA.

##### **Orphan medicinal product market availability situation**

In the Netherlands, all orphan medicinal products with EU market authorisation are available on the market. The government decides which of the products will be reimbursed. Therefore it is necessary to file a reimbursement dossier at the Dutch Health Care Insurers Board (CVZ), the advisory body concerning reimbursement. If there is no registered drug for a rare disease, the treatment can be paid for if the disease is

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<sup>403</sup> Also the former Dutch Steering Committee OD had a broader assignment than only OD

very rare (less than 1 in 150 000 inhabitants) and there no other alternative and there is scientific evidence about using the drug for the specific disease. Costs are covered by the health insurer, the health care insurance company can obtain scientific advice at CVZ about evidence.

#### **Orphan medicinal product pricing policy**

The minister will start the negotiation with pharmaceutical companies about pricing (*see evaluation of conditional reimbursement in the section below*).

#### **Orphan medicinal product reimbursement policy**

In the Netherlands the following orphan medicinal products are reimbursed: Aldurazyme, Arzerra, Carbaglu, Cayston, Cystadane, Diacomit, Elaprased, Evoltra, Exjade, Fabrazyme, Firdapse, Glivec, Increlex, Kuvan, Lysodren, Mepact, Myozyme, Naglazyme, Nexavar, Nplate, Orfadin, Prialta, Replagal, Revatio, Revlimid, Revolade, Signifor, Siklos, Soliris, Somavert, Sprycel, Tassigna, TOBI podhaler, Torisel, Tracleer, Ventavis, Vidaza, Volibris, Votubia, Wilzin, Xagrid, Yondelis, Zavesca.

The following orphan medicinal products are available when ordered by a physician or a pharmacist either through a hospital budget or on a named-patient basis: Atriance, Busilvex, Ceplene, Esbriet, Firazyf, Gliolan, Inovon, Litak, , Mozobil, Peda, Photobarr, Peyona, Plenadren, Riloncept Regeneron, Savene, Tepadina, Thalidomide, Trisenox, , VPRIV and Vyndaquel.

In 2012, the Dutch Health Care Insurance Board (CVZ) addressed the country's Minister of Health concerning the conditional reimbursement of three rare disease products deemed "too expensive". These products target lysosomal storage disorders: a treatment for Pompe disease and Fabry disease treatment. Health Minister Edith Schippers has been advised to cut public funding for the treatments, although babies diagnosed with Pompe disease would continue to have their treatment supported by State funding under the proposal. The minister will start the negotiation with pharmaceutical companies about pricing. During this negotiation the drugs were reimbursed from 2013.

#### **Other initiatives to improve access to orphan medicinal products**

A physician may prescribe non-authorised drugs (e.g. drugs, including orphan medicinal products, authorized elsewhere or even not authorised anywhere), but only with an approval of the Health Inspectorate. The prescribed drug is not reimbursed, unless the health insurer chooses to do so. Apart from these provisions, there are no other initiatives regarding access.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Orphan devices**

There are no (new) initiatives regarding orphan devices.

#### **Specialised social services**

Respite care services are available, imbedded in the general health care system.

## **RARE DISEASE ACTIVITIES IN 2013 IN THE NETHERLANDS**

### **National plan/strategy for rare diseases and related actions**

The National Plan for Rare Diseases was adopted in October 2013<sup>404</sup> and presented on 10 October 2013 by a delegation of The Netherlands Organization for Health Research and Development (ZonMw) to Minister Schippers of Health, Welfare and Sport (VWS). On 14 November the Minister sent the plan along with her reaction to Parliament. The Dutch National Plan identifies bottlenecks and recommendations, and it encourages field parties to feel responsible. The key bottlenecks for the plan include lack of knowledge about rare diseases, insufficient medical research on causes and course of rare diseases as well as inability of patient organisations to work well together. The plan recommends emphasising knowledge about rare disease through training and establishment of expert centers, make the information widely accessible to diverse

<sup>404</sup> [http://www.euoplanproject.eu/newsite\\_986989/Resources/docs/NATIONALPLANS\\_NETHERLANDS\\_nl.pdf](http://www.euoplanproject.eu/newsite_986989/Resources/docs/NATIONALPLANS_NETHERLANDS_nl.pdf)

audiences; make financial resources available for research and development of treatment as well as maintaining consistent policy for claims and reimbursement of orphan drugs. Finally the plan aims to appoint a director or coordinator to promote all recommendations, and avoid fragmentation and unnecessary duplication within the rare disease field.

### Sources of information on rare diseases and national help lines

#### **Other sources of information on rare diseases**

website [www.erfelijkheid.nl](http://www.erfelijkheid.nl) contains a database of approximately 500 rare diseases with information for both lay-persons and professionals. In 2013, 50 new rare diseases (all chromosome disorders) were added to the database. In addition, public information is available on genetic, biomedical and pregnancy related issues<sup>405</sup>. Since 2010 videos were added to the website. In 2012 ten new videos were produced and added. Using videos, disease characteristics can be visualised in order to improve the dissemination of information for both patients and medical professionals.

While [www.erfelijkheid.nl](http://www.erfelijkheid.nl) is successfully reaching an audience of patient, their family and the general public, Erfocentrum also participates in the website [www.huisartsengenetica.nl](http://www.huisartsengenetica.nl), which focuses on general practitioners. Erfocentrum also provides news on genomics and rare diseases via email to more than 100 patient organizations and via Twitter to over 400 medical professionals and organisations.

#### **National rare disease events in 2013**

On 2 March<sup>406</sup>, events for Rare Disease Day were organised by ZonMw, Genzyme and VSOP. A gathering of over 300 adults and children was organised in Utrecht to serve as inspiration to promote research and better care for rare diseases. The children enjoyed creative and cultural programs, while adults participated in an informative meeting. In addition, the annual Angel Awards were also handed out.

A Europlan National Conference was held on 14 & 15 November 2013 in The Hague, co-organised by VSOP and Eurordis with the aim of exploring the provisions and implementation of the newly published Plan for Rare Diseases.

#### **Hosted rare disease events in 2013**

Amongst the rare disease events announced in OrphaNews Europe were: 3rd European Rett Syndrome Conference Maastricht, "Research Update & Preventive Management" (17-19 October 2013, Maastricht), 6th International Conference on Children's Bone Health (22-25 June 2013, Rotterdam).

### Research activities and E-Rare partnership

#### **E-Rare**

In 2013, ZonMw did not participate in the 5<sup>th</sup> Joint Transnational Call.

## 1.21. POLAND

### Definition of a rare disease

In Poland, there is no official definition for rare diseases; however the definition from the regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products of a prevalence of no more than 5 in 10 000 individuals is widely used amongst stakeholders. In Poland this equates to less than 1 900 000 patients (around 5% of the population).

During the several public debates on rare diseases, consideration of the adoption of an additional sub-definition of ultra-rare disease has been suggested as the necessary to be incorporated within the Polish health care system. The preliminary assumption is that the ultra-rare disease definition would be based on a prevalence of no more than 1 in 50 000 individuals.

<sup>405</sup> These sites provide further web based information: [www.biomedisch.nl](http://www.biomedisch.nl); [www.zwangernu.nl](http://www.zwangernu.nl); [www.zwangerwijzer.nl](http://www.zwangerwijzer.nl); [www.slikeerstfoliumzuur.nl](http://www.slikeerstfoliumzuur.nl); [www.prenatalescreening.nl](http://www.prenatalescreening.nl)

<sup>406</sup> [www.zeldzameziektendag.nl](http://www.zeldzameziektendag.nl)

### **National plan/strategy for rare diseases and related actions**

By the end of 2012 a strategic document “National Plan for Rare Disease – the roadmap” was prepared and handed to the Minister of Health. A broad consultation process started, and it was scheduled for completion by June 2013 in order to meet the recommendations of the EU Council by the end of 2013.

The existing National Health Program 2007-2015<sup>407</sup> (health policy paper elaborated by the office of the Prime Minister) covers some issues of the rare diseases in broad understanding of public health. Among the 8 strategic goals addressing main causes of mortality in Poland there is the mention of rare diseases, but they are not exclusively designated. There is currently no specific budget dedicated for rare diseases within the framework of the entire health care system, however specific health interventions are reimbursed in project mode (e.g. therapeutic programs). This does not mean that the treatment of rare diseases is ignored. All diagnosed rare disease cases are treated in the framework of health care system. When reimbursement of orphan medicinal products is possible (within the basket of reimbursed services), therapeutic programs are in place, with an annual budget (2012) equivalent to €33,5 million (same as 2011).

The Rare Disease Task Force, the advisory body to the Minister of Health, initially appointed in 2008, was reorganised in late 2011 to meet new expectations of preparing strategic paper “National Plan for Rare Diseases – the roadmap”. Chaired by representative of the Ministry of Health it consists of: four experts in the field of rare diseases including representative of umbrella patient organisation, representatives of Poland in the EU institutions in the field of rare diseases, Directors of the Departments at the Ministry of Health and representatives of National Health Fund (the payer).

The Rare Disease Task Force cooperates closely with the Parliamentary Group on Rare Diseases with joint meetings dedicated either to general issues of rare diseases or solutions of individual patients’ cases.

In summary, in 2013, a total of 42 meetings, consultations, workshops and conferences were held, with active participation of group of ca 400 experts (clinicians, scientists, patients groups, providers, payers, industry, Members of Parliament, Government Officials, health politicians) to work on the document entitled “The National Plan for Rare Diseases – the roadmap”. The final version (no 12.2) was submitted to the Ministry of Health in December 2012, as scheduled. However, the Plan was not adopted in 2013 as it was decided to further develop the defined areas into concrete actions. The revised plan will be submitted for approval in 2014. Work on an organisational, budgetary and legal framework is scheduled, based on the strategic paper “The National Plan for Rare Diseases – the roadmap” which has been accepted by the Ministry of Health and the Government.

### **Centres of expertise**

In Poland, the healthcare provision for patients with rare diseases is not organised in a specific framework and there are no official centres of expertise for rare diseases. Around 10-15 centres have a reputation for expertise in a given field and conducts diagnostics and treatment to different extents. For instance there was a national coordinating centre for metabolic rare diseases at the Children’s Memorial Health Institute in Warsaw with links to regional centres. A designation policy for centres of expertise is intended to be established.

### **Registries**

There is no national committee dealing with registries, however the Centre of Information Systems has the responsibility to facilitate the Parliament Act of April 2011 on information systems in healthcare, which is in force since January 2012. It states that all registries have to comply with strict requirements, including data safety and protection. Registries had to comply with its requirements by June 2012 including measures for data safety and protection. The Minister of Health in the field of monitoring of healthcare needs, patients health status, prophylaxis and monitoring of health programs, may establish a dedicated registry, issuing a particular Regulation, which may also state a public source of funding. Although this legal regulation is in force, there is no designation process for a unified rare disease registry at the moment.

So far a number of registries by Academia and clinicians are in place, such as the National Registry of Paediatric Cancers and the Polish Registry of Congenital malformations.

Poland took part in the European registries such as EIMD, EHDN, ESID, ERCUSYN, TREAT-NMD, EURO CARE CF, EUROWILSON, EUROGLYCAN, EURO-WABB, SCNIR, RARECARE, and EUROCAT.

### **Neonatal screening policy**

There is a national newborn screening program which in its first phase included: phenylketonuria, congenital hypothyroidism, cystic fibrosis and congenital deafness and as of 2013 includes an additional 20 metabolic

<sup>407</sup> [http://www.mz.gov.pl/data/assets/pdf\\_file/0003/15843/1943\\_001pop.pdf](http://www.mz.gov.pl/data/assets/pdf_file/0003/15843/1943_001pop.pdf) (accessed June 2014)

disorders which can be diagnosed using tandem mass spectrometry. This program is country-wide, regulated and financed by Ministry of Health and coordinated by the Institute of Mother and Child in Warsaw. A screening program for congenital deafness is conducted in collaboration with NGO (The Great Orchestra for Christmas Charity) by Poznań Medical University.

### **Genetic testing**

There are about 35 laboratories (public and private) offering testing for rare diseases. There are no officially designated reference laboratories. Most of them follow external quality control assessments. Diagnostic procedures which are performed in these labs mainly focus on: specific genetic diseases (chromosomal and monogenic disorders), metabolic diseases (selective screening testing for inborn errors of metabolism, lysosomal storage disorders, neuromuscular and haematological diseases, defects in metabolism of carbohydrates, fats, amino acids, purines and pyrimidines, neurotransmitters, as well as disturbances of calcium-phosphate metabolism and energetic processes).

If it is not possible to diagnose a specific disease in Poland the National Health Fund (the payer) may reimburse diagnostic procedures on demand, after a referral (second opinion scheme) from the National or Regional Consultant from the appropriate discipline..

Diagnostic tests are registered as available in Poland for 217 genes and an estimated 323 diseases in the Orphanet database<sup>408</sup>.

### **National alliances of patient organisations and patient representation**

The National Forum for the Therapy of Rare Diseases – ORPHAN, founded in 2005, serves as national alliance for rare disease patients' organisations in Poland. As the umbrella for rare disease associations, the Forum groups together 33 rare diseases patient organisations and it strengthens the cooperation at the national level. The representative of the National Forum was appointed by the Minister of Health as the member of the Rare Disease Task Force, representing the single unanimous voice and position of Polish rare diseases patient organisations during the process of drafting the "National Plan for Rare Diseases – the roadmap". More information about the goals, membership and activities of the organisation are published online<sup>409</sup>.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Poland***

Since 2006 there is a dedicated Orphanet team in Poland, currently hosted by the Children's Memorial Health Institute, in 2010 designated by the Ministry of Health as a partner for the Orphanet Europe Joint Action. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in Poland for entry into the Orphanet database.

Since April 2011 the Orphanet Poland team maintains a national Orphanet Poland national website<sup>410</sup>. In order to improve access to information on rare diseases, orphan medicinal products and Orphanet in Poland, the Polish Orphanet team has translated the documents concerning Orphanet's activities (leaflets), created lists of Polish associations/expert clinics/diagnostics centres and is developing Polish versions of rare disease abstracts and Orphanet Activity Report 2012. Information is available on the Orphanet website.

Orphanet Poland took part in elaborating "The National Plan for Rare Diseases – the roadmap" by participating in Ministry of Health Rare Disease Task Force, and a series of meetings with patient organisations and workshops dedicated to rare diseases which took place in September 2012 in the Children's Memorial Health Institute. Polish Orphanet Coordinators were group leaders of two workshops "Support activities for the preparation of applications for research projects related to rare diseases" and "Exchange of information to gather knowledge about centers of expertise in Poland; Creation of centers of expertise for group of rare diseases based on currently operating centers treating patients with rare diseases; Support for the creation of reliable registries for rare diseases".

#### ***Official information centre for rare diseases***

There is no official information centre on rare diseases in Poland other than Orphanet.

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<sup>3</sup> Information extracted from the Orphanet database (January 2014).

<sup>409</sup> [www.rzadkiechoroby.pl/np](http://www.rzadkiechoroby.pl/np)

<sup>410</sup> [www.orpha.net/national/PL-PL](http://www.orpha.net/national/PL-PL)

### **Helpline**

There is currently no national help line for rare diseases. Some patient organisations run help lines for specific rare diseases.

### **Other sources of information**

No specific activity currently reported.

### **Guidelines**

No specific activity currently reported.

### **Training and education initiatives**

There are some rare disease specific training sessions for professionals. The best known are dysmorphology meetings organised by the Children's Memorial Health Institute (CMHI) in Warsaw, which have been organised on a regular basis for 5 years now, initially as a part of the Dyscerne project. The Department of Medical Genetics of CMHI have organised the course for paediatricians concerning on advances of molecular biology in paediatrics. In addition, some metabolic rare diseases are also presented and discussed during sessions organised every year by the Medical Centre for Postgraduate Education in Warsaw dedicated to the training of physicians or professionals being trained specific medical speciality (paediatricians, neurologists and child neurologists, clinical geneticists etc.). Moreover since 2013 a new medical specialty, paediatric metabolic medicine, has been established, what should improve access for the patients with inborn errors of metabolism to well-educated physicians and facilitate setting of reference centres.

### **National rare disease events in 2013**

The International Rare Disease Day (28 February 2013) was organised by National Forum for the Therapy of Rare Diseases – ORPHAN in the Palace of Culture and Science, which is the most recognisable building in Warsaw. Upon this occasion, topics of the draft paper "National Plan for Rare Disease – the roadmap" have been discussed among patients' families, professionals and parliament representatives and also in several radio, TV and web interviews. The audio-video installation was provided as a platform for patients to share their thoughts and experiences of living with rare diseases. It was a start of a long-term project of "Rare Diseases are Common" campaign. After opening this exhibition appeared in many other places, travelling across Poland. The volunteers "GENE-ius Agents" educated people about rare diseases on Warsaw streets and in public buses.

An awareness raising campaign entitled "Rare diseases are frequent" kicked off at the Polish Europlan Conference on 27-28 September 2013<sup>411</sup>. The European Commission and EURORDIS entrusted to the National Forum for the Therapy of Rare Diseases – ORPHAN to assess the Polish policy towards the issue of rare diseases. On 28 September 2013, during the second day of the Conference a debate and workshop concerning the next steps in relation to the plan was held. The debate tackled philosophical, scientific, and medical issues. Recognised experts in medicine, bioethics and pharmacotherapy along with representatives of the Polish Parliament (Sejm) and national patient organisations attended. Issues regarding evaluation of effectiveness of technology and orphan drugs (HTA) and regulatory restrictions on access to the therapy and issues regarding the prospects for the implementation of the National Plan for Rare Diseases were discussed in details. The purpose of the debate was to reach an unanimous approach and develop recommendations (included in the report) for healthcare policy makers, to let them include the recommendations developed by prominent participants of the health care system focused on rare diseases in their efforts to improve the scope and therapy standards. The recommendations aim to support the Minister of Health in the correct implementation of the state policy regarding rare diseases.

Also a number of meetings for medical students entitled 'Conversations on rare diseases' were also organised across Poland in 2013.

### **Hosted rare disease events in 2013**

Amongst the hosted events organised in 2013 was the 9th European inborn errors of metabolism course in Warsaw, Poland (in collaboration with the Children's Memorial Health Institute) (Warsaw, 25-29 September 2012), Rare diseases and risk of social exclusion (7 October 2013, Warsaw), and the Fourth International Meeting on Primary Central Hypoventilation Syndromes (Warsaw, 13-14 April 2012).

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<sup>411</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-poland.pdf>



## **Research activities and E-Rare partnership**

### ***National research activities***

There is no research programme specifically aimed at rare diseases in Poland. Research on rare diseases are financed within different programmes for state-funded research but there are no specifically allocated funds. Around 10% of projects approved for funding being related to the field of rare diseases. The Polish Ministry of Science and Higher Education usually allocated funding for around ten research projects dedicated to rare diseases in calls for proposals.

### ***Participation in European research projects***

Research teams in Poland participate/have participated in 18 FP7 rare disease related projects.

### ***E-Rare***

Poland is an observer of the E-Rare 2 project. The Polish partner for E-Rare ERA-NET is the National Centre for Research and Development. Poland joined the 2012 Joint Transnational Call but did not receive funding. Poland participated in the 2013 5<sup>th</sup> Joint Transnational Call but Polish teams did not participate in the selected projects.

### ***IRDiRC***

Polish funding agencies have not committed funding to the IRDiRC.

## **Orphan medicinal products**

### ***Orphan medicinal product committee***

There is no specifically dedicated orphan medicinal product committee in Poland.

Accordingly to the new Reimbursement Act (in force since July 2011), the Economics Committee within the Ministry of Health takes responsibility to negotiate market conditions for products applying for reimbursement, including orphan medicinal products.

### ***Orphan medicinal product incentives***

No specific activity reported.

### ***Orphan medicinal product market availability situation***

In 2013 following orphan medicinal products for inborn errors of metabolism have been reimbursed within therapeutic programmes: Cerezyme, Naglazyme, Elaprase, Laronidase, Myozyme, and Cystadane. Other orphan medicinal products (drugs and FSMP) registered outside Poland are available through the individual import.

### ***Orphan medicinal product pricing policy***

Since July 2011 Economics Committee (appointed by the Minister of Health) takes responsibility in pricing on negotiation basis with the market authorisation holder. Following their recommendation the Minister of Health issues public price and reimbursement conditions for the drug. Each medicinal product has to follow HTA requirements of the by Polish Medicinal Health Technology Assessment Agency. In addition to this, the role of HTA has been strengthened.

### ***Orphan medicinal product reimbursement policy***

The system of drug reimbursement changed on 1 January 2012 accordingly to the Reimbursement of drugs, food for special dietary use and medical devices Act, issued 12 May 2011. The new system is unified and application based. The Minister of Health is not able to introduce reimbursement of a new drug without prior official request from the Marketing Authorisation Holder. The application process is costly and has to be supported with comprehensive data (including reimbursement status, price data in other EU Member States, and health technology analysis).

Currently, drugs for some rare diseases are reimbursed through therapeutic programmes. The Minister of Health every second month (I, III, V, VII, IX, XI) announces the official order containing the list of reimbursed medicinal products. Diseases currently covered include: Crohn disease, Prader-Willi syndrome, cystic fibrosis. Additionally, six drugs for rare diseases are reimbursed for patients with Gaucher disease, MPS I, II and VI, Pompe disease, and hyperhomocysteinemia.

### **Other initiatives to improve access to orphan medicinal products**

There is no official compassionate use policy. Life-saving treatment with drugs registered outside of Poland is subject to individual decisions of the Minister of Health and might be reimbursed by the President of the National Health Fund under his consent on a named-patient basis. If a company donates a drug, it is subject to taxation, which further limits potential compassionate use. Furthermore, according to the Reimbursement Act, after the recommendation of the national authority in the field of medicine and opinion of the HTA Agency, the Minister of Health can make a reimbursement decision.

### **Other therapies for rare diseases**

No specific activity reported.

### **Orphan devices**

Since 1 January 2012, according to the Reimbursement Act, the national healthcare package has been continuously supplemented by new medical devices dedicated also to patients with rare diseases. Orphan devices are regularly presented during dysmorphology meetings, national conferences and trainings.

### **Specialised social services**

There are no social services specifically designed for patients for rare diseases, though respite care exists in general and educational centres can provide day care for children and education for patients: these are both privately and publically funded initiatives, provided on an application basis. Some official programmes require for patients to be qualified as disabled in order to participate. Therapeutic recreational services such as camps are eligible for co-funding by the state social care (usually 30% patient co-payment). Patient organisations sometimes provide services which are financed from private funds specifically for rare diseases patients. The state funds the integration of children with special needs, via "integration classes" in schools.

## **RARE DISEASE ACTIVITIES IN 2013 IN POLAND**

### **Definition of a rare disease**

During the several public debates on rare diseases, consideration of the adoption of an additional sub-definition of ultra-rare disease has been suggested as the necessary to be incorporated within the Polish health care system. The preliminary assumption is that the ultra-rare disease definition would be based on a prevalence of no more than 1 in 50 000 individuals

### **National plan/strategy for rare diseases and related actions**

By the end of 2012 a strategic document "National Plan for Rare Disease – the roadmap" was prepared and handed to the Minister of Health. A broad consultation process started, and it was scheduled for completion by June 2013 in order to meet the recommendations of the EU Council by the end of 2013.

In summary, in 2013, a total of 42 meetings, consultations, workshops and conferences were held, with active participation of group of ca 400 experts (clinicians, scientists, patients groups, providers, payers, industry, Members of Parliament, Government Officials, health politicians) to work on the document entitled "The National Plan for Rare Diseases – the roadmap". The final version (no 12.2) was submitted to the Ministry of Health in December 2012, as scheduled. However, the Plan was not adopted in 2013 as it was decided to further develop the defined areas into concrete actions. The revised plan will be submitted for approval in 2014. Work on an organisational, budgetary and legal framework is scheduled, based on the strategic paper "The National Plan for Rare Diseases – the roadmap" which has been accepted by the Ministry of Health and the Government.

### **Neonatal screening policy**

As of 2013 the newborn screening programme includes an additional 20 metabolic disorders which can be diagnosed using tandem mass spectrometry. This program is country-wide, regulated and financed by Ministry of Health and coordinated by the Institute of Mother and Child in Warsaw.

### **Training and education initiatives**

Since 2013 a new medical specialty, paediatric metabolic medicine, has been established, what should improve access for the patients with inborn errors of metabolism to well-educated physicians and facilitate setting of reference centres.

### **National rare disease events in 2013**

The International Rare Disease Day (28 February 2013) was organised by National Forum for the Therapy of Rare Diseases – ORPHAN in the Palace of Culture and Science, which is the most recognisable building in Warsaw. Upon this occasion, topics of the draft paper “National Plan for Rare Disease – the roadmap” have been discussed among patients’ families, professionals and parliament representatives and also in several radio, TV and web interviews. The audio-video installation was provided as a platform for patients to share their thoughts and experiences of living with rare diseases. It was a start of a long-term project of “Rare Diseases are Common” campaign. After opening this exhibition appeared in many other places, travelling across Poland. The volunteers “GENE-ius Agents” educated people about rare diseases on Warsaw streets and in public buses.

An awareness raising campaign entitled “Rare diseases are frequent” kicked off at the Polish Europlan Conference on 27-28 September 2013<sup>412</sup>. The European Commission and EURORDIS entrusted to the National Forum for the Therapy of Rare Diseases – ORPHAN to assess the Polish policy towards the issue of rare diseases. On 28 September 2013, during the second day of the Conference a debate and workshop concerning the next steps in relation to the plan was held. The debate tackled philosophical, scientific, and medical issues. Recognised experts in medicine, bioethics and pharmacotherapy along with representatives of the Polish Parliament (Sejm) and national patient organisations attended. Issues regarding evaluation of effectiveness of technology and orphan drugs (HTA) and regulatory restrictions on access to the therapy and issues regarding the prospects for the implementation of the National Plan for Rare Diseases were discussed in details. The purpose of the debate was to reach an unanimous approach and develop recommendations (included in the report) for healthcare policy makers, to let them include the recommendations developed by prominent participants of the health care system focused on rare diseases in their efforts to improve the scope and therapy standards. The recommendations aim to support the Minister of Health in the correct implementation of the state policy regarding rare diseases.

Also a number of meetings for medical students entitled ‘Conversations on rare diseases’ were also organised across Poland in 2013.

### **Hosted rare disease events in 2013**

Amongst the hosted events organised in 2013 was the 9th European inborn errors of metabolism course in Warsaw, Poland (in collaboration with the Children’s Memorial Health Institute) (Warsaw, 25-29 September 2012), Rare diseases and risk of social exclusion (7 October 2013, Warsaw), and the Fourth International Meeting on Primary Central Hypoventilation Syndromes (Warsaw, 13-14 April 2012).

### **Research activities and E-Rare partnership**

#### ***E-Rare***

Poland participated in the 2013 5<sup>th</sup> Joint Transnational Call but Polish teams did not participate in the selected projects.

## **1.22. PORTUGAL**

### **Definition of a rare disease**

Portugal accepts the definition of rare disease, as stated in the European Regulation on Orphan Medicinal Products, as a disease with a prevalence of no more than 5 in 10 000 inhabitants. This definition has been adopted by the National Plan for Rare Diseases.

<sup>412</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-poland.pdf>

### **National plan/strategy for rare diseases and related actions**

In November 2008 the Portuguese Minister of Health approved the National Plan for Rare Diseases (*"Programa Nacional para as Doenças Raras"*)<sup>413</sup> coordinated, since November 2011, by the Department for Quality in Health at the Directorate-General of Health (DGS).

Its main objectives are the establishment and improvement of national measures, in order to satisfy the needs of people with rare diseases and their families *vis-à-vis* medical services and care, as well as the improvement of the quality and equity of healthcare provided to those people.

Such objectives will be achieved by establishing reference centres for rare diseases, by improving the access of patients to adequate care, by strengthening knowledge and awareness on rare diseases, by promoting innovation in the treatment of rare diseases and in the accessibility to orphan medicinal products, and finally, by ensuring cooperation at national and international levels, including EU countries and those countries having Portuguese as their official language.

This Plan was foreseen to cover all rare diseases, though it was hoped that it would be articulated with other priority national plans, namely with the National Plan for Oncologic Diseases (*"Programa Nacional para as Doenças Oncológicas"*).

An important step in terms of implementing the National Plan for Rare Diseases took place in 2012: a specific card for the identification of people with rare diseases (*"Cartão para a Pessoa com Doença Rara"*) was developed, aiming at disclosing clinical information to medical doctors and also in emergency situations. This card issued by DGS, is currently being distributed. From December 2013 to March 2014 199 cards have been issued.

DGS, together with the former Office of the High Commissioner for Health, co-funded from 2008 to 2011, for a total amount of €1.9 million, projects on rare diseases, which are still being developed by several patient organisations.

The National Programme for Rare Diseases, published by the Directorate-General of Health in 2008, has developed its activity focusing only on the services depending on the Ministry of Health, thus meaning, today, it must be replaced by a broader national strategy with integrated actions, both at inter-sectoral and inter-institutional level. A new Integrated Strategy for Rare Diseases 2014-2020 is currently being finalised, which replaces the previous Programme and aims to ensure that people with rare diseases have better quality of care, based on the evidence that science has been producing, as well as greater celerity and variety of social responses adapted to each case. This new strategy further aims to guarantee that, in an inter-ministerial, inter-sectoral, inter-institutional and integrated way, priorities in the global approach to rare diseases be refocused, bringing together the contributions of competences and resources of all relevant sectors, in order to cause, in a progressive way, a real change in the complex conditions of the people who suffer from these diseases.

### **Centres of expertise**

Legislation is presently being finalised, in order to identify and officially recognise reference centres that might integrate future European Reference Networks.

### **Registries**

The following commissions and/or registries operate under supervision of INSA: National Commission for the Portuguese Registry of Paramyloidosis, National Commission for Lysosomal Storage Diseases, National Registry of Congenital Anomalies (RENAC) and National Newborn Screening Commission.

RENAC data are available since 1996. The most recent report covers the 2008-2010 period. Another report, updating existing information, is being prepared. Two informative newsletters were sent to the hospital services that collaborate with RENAC; to the remaining services, letters were sent renewing the invitation for their participation in RENAC. The information collected on RENAC was also integrated in the report of EUROPERISTAT system. Moreover, RENAC participated in the European Surveillance of Congenital Anomalies (EUROCAT) by sending data related to the Southern region of Portugal; it further participated in the annual meeting of that European Register.

The use of Orpha codes, to code rare diseases in health information systems in Portugal, has been proposed to DGS to be used in the NHS, though it is not yet fully explored.

Upon their own initiative, many patients are also included in international registries. A few Portuguese institutions also participate, or have participated, in European registries, such as E-IMD, TREAT-NMD, EURO CARE CF, EUROCAT, EBAR, SCNIR, CHS, SPATAX, EUROWILSON and EHDN (the European Huntington Disease Network).

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<sup>413</sup> <http://www.portaldasaude.pt/NR/rdonlyres/555DD3B3-45F0-4F74-B633-28889E721BF1/0/i010420.pdf>.

### Neonatal screening policy

The National Programme for Early Diagnosis (“*Programa Nacional de Diagnóstico Precoce*”) started in 1979 at the *former* Institute of Medical Genetics and, initially, it only included the screening of phenylketonuria. *INSA* is nowadays responsible, at both organizational and laboratorial levels, for the national newborn screening programme, which covers *ca.* 100 % of all children born in Portugal.

Currently, the following 26 diseases are screened: Congenital Hypothyroidism, Phenylketonuria (PKU)/ Hiperphenylalaninemia, Tyrosinemia Type I, Tyrosinemia Type II/ III, Maple Syrup Urine Disease (MSUD), Citrullinemia Type I, Argininosuccinic Aciduria, Argininemia, Classic Homocystinuria, Methionine Adenosyltransferase Deficiency (MAT deficiency), Propionic Aciduria (PA), Methylmalonic Aciduria type mut- (MMA, Mut-), Isovaleric Aciduria (IVA), 3-methylcrotonyl-CoA Carboxylase Deficiency (3-MCCD), Glutaric Aciduria Type I (GA I), Methylmalonic Aciduria type Cbl C/D (MMA, Cbl C/D), 3-hydroxy-3-methylglutaric Aciduria (3-HMG), Malonic Aciduria, Medium Chain AcylCoA Dehydrogenase Deficiency (MCAD), Very Long Chain AcylCoA Dehydrogenase Deficiency (VLCAD), Long Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD)/ Trifunctional Protein Deficiency (TFP), Short Chain AcylCoA Dehydrogenase Deficiency (SCHAD), Primary Carnitine Deficiency (CUD), Carnitine Palmitoyl Transferase I Deficiency (CPT I), Carnitine Palmitoyl Transferase II Deficiency (CPT II/ CACT), Glutaric Aciduria Type II (MADD).

### Genetic testing

Genetic testing is available for many rare disorders, though, as in other countries, there is a significant flow of genetic testing over the borders. Diagnostic tests are registered as available in Portugal for 685 genes and an estimated 793 diseases, in the Orphanet database<sup>414</sup>.

Genetic tests are carried out in genetic laboratories within the National Health System (NHS), as is the case of *INSA*<sup>415</sup> (considered the national reference laboratory), as well as in laboratories located or associated with genetic services in public hospitals, and also in private laboratories; besides these, a certain number of labs offer genetic testing at universities and research institutions.

Whenever a specific test is not available in Portugal, there is a formal procedure to perform it abroad. Orpha codes are being implemented on the request form, to ascertain what is done and where, and laboratories’ quality.

In 2013, the number of clinical cases sent abroad for referral amounted to 159, especially for molecular study and laboratorial genetic testing.

Genetic testing in Portugal is regulated mainly by Law no 12/2005, of 26 January 2005. This law defines, among others, the concept of health information and genetic information, the circulation of information and the intervention on human genome within the health system, as well as it establishes the procedure to collect and preserve biological products, for purposes of genetic testing or of research.

A proposal of a Decree that will regulate the aspects of this Law is under preparation. The same process is underway for the licencing of medical genetics laboratories.

As a member of OECD, Portugal is subject to the OECD Best Practice Guidelines for Molecular Genetic Testing, which are to be transposed into national law, through the Decree that will regulate Law 12/2005; Portugal also signed and ratified the Oviedo Convention, but not yet its Additional Protocol concerning Genetic Testing for Health Purposes (2008), currently at its final stage.

### National alliances of patient organisations and patient representation

Portugal has two alliances on rare diseases: *FEDRA* – Portuguese Federation of Rare Diseases (“*Federação Portuguesa de Doenças Raras*”)<sup>416</sup> and *APADR* – Portuguese Alliance of Rare Diseases Associations (“*Aliança Portuguesa de Associações de Doenças Raras*”).

*APADR* was officially established in 2009, and since then, has developed several actions and activities with the aim of improving Portuguese health policy in the field of rare diseases, and also raising awareness to this problem, namely TV and radio spots and a conference on the rare disease day.

*Fedra* published a series of booklets called “Genetic Diseases A to Z”, with articles prepared by expert professionals. It has organized photo exhibitions in the National and in the European Parliament, in order to raise awareness for Rare Diseases problems and for people living with rare diseases, as well as a conference with the participation of Eurordis, FEDER, “European Phd Programme on rare diseases”, Brains for Brain Foundation, European Commission, and the European Commissioner of Health.

<sup>414</sup> Information extracted from the Orphanet database (January 2014).

<sup>415</sup> <http://www.insa.pt/sites/INSA/Portugues/AreasCientificas/Genetica/Paginas/LaboratorioDeReferencia.aspx>

<sup>416</sup> <http://www.fedra.pt>

## Sources of information on rare diseases and national help lines

### **Orphanet activity in Portugal**

The national team of Orphanet has kept available and updated in Portuguese all menus from the international site<sup>417</sup>, all the diseases names, the emergency guides and summaries of diseases (validated by experts in each area). This is an important resource also for all countries of official Portuguese language and the Portuguese communities spread throughout the world (about 240 million Portuguese speaking persons). The team also maintained and kept updated the Orphanet-Portugal website page<sup>418</sup>, and a Facebook page<sup>419</sup>, which have included updated news about initiatives on rare diseases in the country and in Brazil.

By the end of 2013, 1065 abstracts of rare disease and 18 emergency guidelines have been translated and validated into Portuguese and entered in the international database; about 200 new abstracts were also translated, and are now waiting to be validated.

During 2013, Orphanet-Portugal continued to collect and validate and significantly increased the information available in the country on national resources and activities related to rare disease and orphan drugs. These included 145 specialised centres, 111 laboratories (33 diagnostic laboratories and 78 research laboratories), 1041 diagnostic tests, 153 research projects, 23 clinical trials, 70 patient organisations and 19 registries and biobanks, by December 2013; the list of the orphan drugs available in the country (currently 49, in a total of 88 different presentation and/or dosages) is regularly uptake from each one.

The Orphanet-Portugal team also contributed to the development (in English) and subsequent translation and validation into Portuguese of a leaflet on "Genetic Testing Related Health", produced by the Council of Europe and prepared by EuroGentest (a network of excellence funded by the European Commission) and the PPPC (Public and Professional Policy Committee) of the ESHG (European Society of Human Genetics).

This brochure (in Portuguese) was released during the Rare Disease Day 2013 and is available from the Orphanet national webpage<sup>5</sup>.

The national scientific advisory board of Orphanet-Portugal proved to be a valuable resource, providing important information as well as the validation of some data whenever requested.

In addition, as in previous years, the national team has been committed to the diffusion of the Orphanet portal and services to professionals involved in rare diseases, as well as to patients, families and the general public. This is achieved both through the organisation of specific events, and the participation in several scientific meetings and courses with oral or poster communications and lectures.

In 2013, 6 presentations about Orphanet were made at such meetings, one organised (together with Aliança) by Orphanet Portugal (the Rare Disease Day 2013), and one interview about "Orphanet in Portugal" and published in the magazine "Pontos de Vista", distributed by a daily Journal

All this information is intended to help improving and shortening the time before a diagnosis is obtained, and specialised care and treatment of patients with rare diseases is reached, as well as planning and improving the care for persons with rare diseases in the country.

### **Official information centre for rare diseases**

Orphanet is specifically mentioned several times in the National Plan for Rare Diseases, one of the declared aims of which is to "propose measures to support the development of Orphanet Portugal, making it the reference portal for information on rare diseases in Portuguese"<sup>420</sup>.

### **Help line**

The patient organisation *RARÍSSIMAS*, with funding from *DGS*, implemented in 2009 a dedicated call centre, called 'Rare Line' ("*Linha Rara*")<sup>421</sup>. It has been distinguished by Eurordis, for the second year, in the Caller Profile Analysis.

Several other patient associations, as the Portuguese Haemophilia Association, also give advice and support to patients and their families, either online, by email or by phone.

### **Other sources of information on rare diseases**

The Orphanet-Portugal team also deals with many requests for information coming from the country and other Portuguese speaking countries, as well as many Portuguese patients and families living abroad.

<sup>417</sup> <http://www.orpha.net/consor/cgi-bin/index.php?lng=PT>

<sup>418</sup> <http://www.orpha.net/national/PT-PT>

<sup>419</sup> <https://www.facebook.com/Orphanet.PT>

<sup>420</sup> <http://www.portaldasaude.pt/NR/rdonlyres/555DD3B3-45F0-4F74-B633-28889E721BF1/0/i010420.pdf>

<sup>421</sup> [www.linharara.pt](http://www.linharara.pt)

## **Guidelines**

DGS, in collaboration with the Portuguese Medical Association (“*Ordem dos Médicos*”) has been developing a number of clinical guidelines; among these, and in the specific area of rare diseases, three guidelines were issued in 2012, which refer, specifically, to the diagnosis and follow-up of Cystic Fibrosis and Pulmonary Hypertension.

## **Training and education**

There is no formal programme in this area, but some medical schools have lectures on rare diseases and information resources (such as Orphanet), and much work is done in high schools and by patient organisations and health services. All national medical schools have curricular units on basic and/or medical genetics and, some, also on clinical genetics.

The medical specialty of Clinical Genetics was recognised in 1999, at the Portuguese Medical Association, (“*Ordem dos Médicos*”) and implies a 5-year full-time residency program.

A Professional Master’s Course in Genetic Counselling was initiated at the University of Porto, which is one of the five in the EU already accredited by the EBMG (European Board of Medical Genetics). This two-year post-graduation course is an innovative initiative in Portugal for professionals with diverse clinical backgrounds, including clinical psychologists, nurses and others. This full-time programme encompasses bioethics, clinical and genetic epidemiology, genetic counselling principles and techniques, clinical psychology, research methodologies and clinical rotations, as well as one-year training in a recognised medical genetics service and a research project, with special emphasis on rare diseases.

A professional association of genetic counsellors has already been created. Efforts are being made to recognise this new profession both at the national and the EU level.

The Portuguese Society of Human Genetics also approved in 2013 a commission for clinical genetics laboratory, to harmonise education criteria and program for laboratory geneticists; this program has already been accepted by the EBHG.

Two Genetics in Family Medicine courses were organised in 2013, at the Institute of Molecular and Cell Biology (IMCB), in Porto, part of a series of spring and autumn courses, directed mainly to general practitioners, but also other physicians and health professionals. IBMC also has a long-standing programme to receive high school students and teachers for presentations and guided visits to genetic services and research laboratories, all throughout the year.

Some patient associations also organise one-day receptions for medical students, so that they are made aware of rare diseases and rare disease patients.

Raríssimas submitted a project to EEA Grants funding for NGO’s (Programa Cidadania Ativa/Fundação Calouste Gulbenkian) in 2013 and has had the approval for its Marcos’s Centre – Information and training, to run from 2014 until 2015. Several programmes are being defined to address different training needs, including patients, families, health and education professionals, students and volunteers.

## **National rare disease events in 2013**

A conference was held to mark Rare Diseases Day on the theme of “Rare disorders without borders: National and European Realities” on 23 February 2013 in Porto, organised by Aliança Portuguesa de Associações das Doenças Raras (APADR) and Orphanet Portugal. A large number of stakeholders participated and the day ended with discussions on the status of the National Plan and centres of expertise. The Day was well covered in the national press and media.

## **Hosted rare disease events in 2013**

Amongst the rare disease events hosted in Portugal and announced by OrphaNews Europe was the First International Primary Immunodeficiencies Congress (IPIC) (7-8 November 2013, Estoril).

## **Research activities and E-Rare partnership**

### ***National research activities***

The Foundation for Science and Technology (“*Fundação para a Ciência e Tecnologia*” - FCT), a partner of Orphanet Portugal, runs several programmes to fund research on rare diseases. In 2012, FCT funded scientific projects in a total amount of € 583,000. FCT is recommending, after proposal of Orphanet Portugal, that “rare disease” and the respective Orpha code(s) are included as keywords in the application forms for projects, if applicable.

### **Participation in European research projects**

Teams in Portugal have participated/participate in 16 rare disease related FP7 projects.

#### **E-Rare**

Portugal, represented by *FCT* and *DGS*, joined the E-Rare-2 Consortium in 2009. In December 2012, *DGS* was replaced by *INSA* in this Consortium. *FCT* participated in the 4<sup>th</sup> Joint Transnational Call launched in 2012, funding 2 Portuguese teams participating in 2 out of the 11 selected research projects, with a total budget of €341,581. In 2013 Portugal joined the 5<sup>th</sup> Joint Transnational Call but no Portuguese teams participated in the selected projects.

#### **IRDIRC**

Portuguese funding agencies have not yet committed funding to the *IRDIRC*, however through the E-Rare Group of Funder, Portugal was represented at the *IRDIRC* as of the end of 2012.

### **Orphan medicinal products**

In Portugal, regulation of orphan medicinal products is the responsibility of *INFARMED*. A partnership was established in 2010 between *INFARMED* and ORPHANET-Portugal for a monthly update on all orphan medicinal products already approved and available in the country, and the volume of these actually used.

Following legislation establishing the access of patients to therapies involving diseases with enzymatic deficit, *INSA* coordinates and further authorizes these pharmacological treatments. In 2012, the delivery of enzyme replacement therapy amounted to €47.5 million. A list of enzymatic diseases, which benefit from free of charge treatment in public hospitals, is also available.

#### **Orphan medicinal product committee**

There is no such Committee in Portugal.

#### **Orphan medicinal product incentives**

Presently *INFARMED* is not aware of the existence of any specific incentives.

#### **Orphan medicinal product market availability situation**

A list of all orphan medicinal products available and quantities consumed in Portugal is published at the ORPHANET-Portugal entry site. This data is provided and regularly updated by *INFARMED*.<sup>422</sup>

#### **Orphan medicinal product pricing policy**

Orphan medicinal product pricing policy falls under the responsibility of the Ministry of Health. There are no specific provisions in place to define the price of this kind of medicines.

#### **Orphan medicinal product reimbursement policy**

There are no specific provisions in place for the reimbursement of orphan medicinal products. All Portuguese citizens are covered by the National Health Service. The investment of the NHS in orphan medicinal products between January and December 2013 was around €75 million, which represents 7.7 % of the total consumption of medicines in hospitals. It should be noted that there was an increase of 19.4 % in this group of medicinal products, as compared to the same period of 2012.<sup>423</sup>

However, there are special programmes in place to facilitate access to growth hormone therapy, enzymatic therapy and familial amyloid polyneuropathy.

#### **Other initiatives to improve access to orphan medicinal products**

A Special Use Authorisation (*SUA*) procedure is in place to provide access to certain orphan medicinal products. If an orphan medicinal product is not marketed in Portugal, the treating hospital can request a special authorisation from *INFARMED*; if the use is approved, the hospital is directly supplied by the manufacturer and there is no co-payment from the patient<sup>424</sup>.

<sup>422</sup> <http://www.orpha.net/national/PT-PT/index/lista-de-medicamentos-órfãos-disponíveis-em-portugal/>

<sup>423</sup> [http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO\\_DO\\_MERCADO/OBSERVATORIO/ANALISE\\_MENSAL\\_MERCADO/ANALISE\\_MERCADO\\_MEDICAMENTOS\\_CHNM/2013/Rel\\_Medicamentos%20MeioHospitalar\\_dez13.pdf](http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ANALISE_MENSAL_MERCADO/ANALISE_MERCADO_MEDICAMENTOS_CHNM/2013/Rel_Medicamentos%20MeioHospitalar_dez13.pdf)

<sup>424</sup> EMINET – Initial investigation to access the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner (2011), p 57



### **Other therapies for rare diseases**

There are no other initiatives for improving access to other therapies for rare diseases, though several national and multicentric international clinical trials are already under way or being prepared.

### **Orphan devices**

Under the Directive for Medical Devices, there is no specific regulation for this kind of devices. Instead, there is the possibility of issuing an exceptional authorisation, for the specific utilisation of certain devices, for which the conformity assessment procedure, so as to obtain CE marking, has not yet been completed.

In addition, regarding diagnostic tests for rare diseases, these are usually considered as 'in-house tests' because they are manufactured and used only within the same health institution and on the premises of their manufacture, or used on premises in the immediate vicinity, without having been transferred to another legal entity.

### **Specialised social services**

Respite care services exist in the public, private and social sectors, and patients must pay for some services. Other respite facilities are run by patient organisations and some projects have been established with public support.

Generally, all patients with rare disease, and depending on their level of functional ability, have access to the same benefits, as any other citizen in the same situation of dependency.

*RARISSIMAS* has two multidisciplinary centres, which provide clinical care and therapies to patients and families with rare diseases, one in Oporto and the second in the Azores islands.

Besides these centres, *Raríssimas* has now opened Casa dos Marcos, the first Resource Centre for Rare Diseases in Portugal, gathering social and healthcare services and planning to respond in the educational area as well. Casa dos Marcos has both residential services and ambulatory care and is establishing several partnerships, nationally and internationally, developing innovative projects in various domains. In fact, it has a unique model of assistance with a mix offer that includes services under contract with the State (a long-term care unit, a residential unit, an occupational activity centre and an autonomous residential unit) and private services (respite centre; rehabilitation centre; medical and non-medical consultations). It also includes an information and training centre and a research centre on rare diseases. Holiday camps for patients are also run. Casa dos Marcos costs about €10 million (global investment) and *Raríssimas* raised about €8 million from private companies.

There are some therapeutic recreational initiatives organised by hospitals with the support of public or private organisations, which are paid through public and private funding; many programmes are organised by several patient organisations, such as the Portuguese Association for Paramyloidosis. There are some projects to help the integration of patients in daily life, and this offer will hopefully improve under the National Plan for Rare Diseases. Some other patient associations organise respite camps.

## **RARE DISEASE ACTIVITIES IN 2013 IN PORTUGAL**

### **National plan/strategy for rare diseases and related actions**

The National Programme for Rare Diseases, published by the Directorate-General of Health in 2008, has developed its activity focusing only on the services depending on the Ministry of Health, thus meaning, today, it must be replaced by a broader national strategy with integrated actions, both at inter-sectoral and inter-institutional level. A new Integrated Strategy for Rare Diseases 2014-2020 is currently being finalised, which replaces the previous Programme and aims to ensure that people with rare diseases have better quality of care, based on the evidence that science has been producing, as well as greater celerity and variety of social responses adapted to each case. This new strategy further aims to guarantee that, in an inter-ministerial, inter-sectoral, inter-institutional and integrated way, priorities in the global approach to rare diseases be refocused, bringing together the contributions of competences and resources of all relevant sectors, in order to cause, in a progressive way, a real change in the complex conditions of the people who suffer from these diseases.

### **Centres of expertise**

Legislation is presently being finalised, in order to identify and officially recognise reference centres that might integrate future European Reference Networks.

### **Genetic testing**

In 2013, the number of clinical cases sent abroad for referral amounted to 159, especially for molecular study and laboratorial genetic testing.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activity in Portugal***

The national team of Orphanet has kept available and updated in Portuguese all menus from the international site<sup>425</sup>, all the diseases names, the emergency guides and summaries of diseases (validated by experts in each area).

By the end of 2013, 1065 abstracts of rare disease and 18 emergency guidelines have been translated and validated into Portuguese and entered in the international database; about 200 new abstracts were also translated, and are now waiting to be validated.

During 2013, Orphanet-Portugal continued to collect and validate and significantly increased the information available in the country on national resources and activities related to rare disease and orphan drugs. These included 145 specialised centres, 111 laboratories (33 diagnostic laboratories and 78 research laboratories), 1041 diagnostic tests, 153 research projects, 23 clinical trials, 70 patient organisations and 19 registries and biobanks, by December 2013; the list of the orphan drugs available in the country (currently 49, in a total of 88 different presentation and/or dosages) is regularly uptake from each one.

The Orphanet-Portugal team also contributed to the development (in English) and subsequent translation and validation into Portuguese of a leaflet on "Genetic Testing Related Health", produced by the Council of Europe and prepared by EuroGentest (a network of excellence funded by the European Commission) and the PPPC (Public and Professional Policy Committee) of the ESHG (European Society of Human Genetics).

This brochure (in Portuguese) was released during the Rare Disease Day 2013 and is available from the Orphanet national webpage<sup>5</sup>.

In addition, as in previous years, the national team has been committed to the diffusion of the Orphanet portal and services to professionals involved in rare diseases, as well as to patients, families and the general public. This is achieved both through the organisation of specific events, and the participation in several scientific meetings and courses with oral or poster communications and lectures.

In 2013, 6 presentations about Orphanet were made at such meetings, one organised (together with Aliança) by Orphanet Portugal (the Rare Disease Day 2013), and one interview about "Orphanet in Portugal" and published in the magazine "Pontos de Vista", distributed by a daily Journal

### **Training and education**

The Portuguese Society of Human Genetics also approved in 2013 a commission for clinical genetics laboratory, to harmonise education criteria and program for laboratory geneticists; this program has already been accepted by the EBHG.

Two Genetics in Family Medicine courses were organised in 2013, at the Institute of Molecular and Cell Biology (IMCB), in Porto, part of a series of spring and autumn courses, directed mainly to general practitioners, but also other physicians and health professionals. IBMC also has a long-standing programme to receive high school students and teachers for presentations and guided visits to genetic services and research laboratories, all throughout the year.

Raríssimas submitted a project to EEA Grants funding for NGO's (Programa Cidadania Ativa/Fundação Calouste Gulbenkian) in 2013 and has had the approval for its Marcos's Centre – Information and training, to run from 2014 until 2015. Several programmes are being defined to address different training needs, including patients, families, health and education professionals, students and volunteers.

### **National rare disease events in 2013**

A conference was held to mark Rare Diseases Day on the theme of "Rare disorders without borders: National and European Realities" on 23 February 2013 in Porto, organised by Aliança Portuguesa de Associações das Doenças Raras (APADR) and Orphanet Portugal. A large number of stakeholders participated and the day ended with discussions on the status of the National Plan and centres of expertise. The Day was well covered in the national press and media.

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<sup>425</sup> <http://www.orpha.net/consor/cgi-bin/index.php?lng=PT>

### **Hosted rare disease events in 2013**

Amongst the rare disease events hosted in Portugal and announced by OrphaNews Europe was the First International Primary Immunodeficiencies Congress (IPIC) (7-8 November 2013, Estoril).

### **Research activities and E-Rare partnership**

#### ***National research activities***

FCT is recommending, after proposal of Orphanet Portugal, that “rare disease” and the respective Orpha code(s) are included as keywords in the application forms for projects, if applicable.

#### ***E-Rare***

In 2013 Portugal joined the 5<sup>th</sup> Joint Transnational Call but no Portuguese teams participated in the selected projects.

### **Orphan medicinal products**

#### ***Orphan medicinal product reimbursement policy***

There are no specific provisions in place for the reimbursement of orphan medicinal products. All Portuguese citizens are covered by the National Health Service. The investment of the NHS in orphan medicinal products between January and December 2013 was around €75 million, which represents 7.7 % of the total consumption of medicines in hospitals. It should be noted that there was an increase of 19.4 % in this group of medicinal products, as compared to the same period of 2012<sup>426</sup>.

### **Specialised social services**

Raríssimas has now opened Casa dos Marcos, the first Resource Centre for Rare Diseases in Portugal, gathering social and healthcare services and planning to respond in the educational area as well. Casa dos Marcos has both residential services and ambulatory care and is establishing several partnerships, nationally and internationally, developing innovative projects in various domains. In fact, it has a unique model of assistance with a mix offer that includes services under contract with the State (a long-term care unit, a residential unit, an occupational activity centre and an autonomous residential unit) and private services (respite centre; rehabilitation centre; medical and non-medical consultations). It also includes an information and training centre and a research centre on rare diseases. Holiday camps for patients are also run. Casa dos Marcos costs about €10 million (global investment) and Raríssimas raised about €8 million from private companies.

## **1.23. ROMANIA**

### **Definition of a rare disease**

In Romania, stakeholders accept the EU definition of a rare disease (RD) laid down in Regulation EC n° 141/2000 on Orphan Medicinal Products, the Directive 2011/24/EU on Cross Border Healthcare as well as in the Council Recommendation on an action in the field of rare diseases of 8 June 2009. According to the EU definition a RD is defined as life-threatening or chronically debilitating condition that afflicts fewer than 5 in 10 000 persons in the general population.

### **National plan/strategy for rare diseases and related actions**

Since February 2008, there is an official RD status: RD are recognised by stakeholders in the field as a priority for health care in Romania. A partnership agreement was signed by the Romanian Ministry of Health and the country's National Alliance for Rare Diseases (RONARD) aimed at guiding and structuring the actions for the elaboration of a National Plan for RD.

Between 2008 – 2010, RONARD and representatives of Ministries of Health, Education, and Labour, as well as the National Medicine Agency, the Authority of People with Disabilities and the Child Welfare Authority worked together on rare diseases in a comprehensive manner, with different topics ranging from the assessment of the current situation of RD in Romania to the increase knowledge of the epidemiology of RD, recognition of the specificity of RD, the development of information for patients, healthcare professionals and

<sup>426</sup>[http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO\\_DO\\_MERCADO/OBSERVATORIO/ANALISE\\_MENSAL\\_MERCADO/ANALISE\\_MERCADO\\_MEDICAMENTOS\\_CHNM/2013/Rel\\_Medicamentos%20MeioHospitalar\\_dez13.pdf](http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/OBSERVATORIO/ANALISE_MENSAL_MERCADO/ANALISE_MERCADO_MEDICAMENTOS_CHNM/2013/Rel_Medicamentos%20MeioHospitalar_dez13.pdf)

the public, the improvement of access to medical care, timely and appropriate diagnosis, better treatment and access to required drugs, the identification of the specific needs of assistance for people with RD and the definition of institutional and legal framework in the field of RD.

On the debate and consultation process involving RONARD and stakeholders, several objectives and priority actions have been identified as relevant for the development of a draft of the NPRD launched in 2010. The draft was posted on the Romanian Prader Willi Association website for online public comments and reactions. Moreover, the draft of NPRD was sent to European Commission in order to harmonise and share the strategic vision in accordance with the recommendations delineated by the Council of EU Recommendation on action in the field of RD. The plan was structured based on general objectives, such as:

1. Develop an institutional framework;
2. Develop services for the diagnosis, treatment, rehabilitation and prophylaxis of RD;
3. Improve access to the appropriate medication and technology;
4. Improve access to the information in the field of RD;
5. Develop human resources;
6. Stimulate the research in the field of RD;
7. Empowerment of patient organizations;
8. Develop national and European partnerships in the field of RD.

By the end of 2012 the inclusion of the NPRD in the National Public Health Strategy was the next step concerning the implementation and monitoring of the plan by the end of 2013. At the end of 2013, the National Council for RD (NCRD) was created by the Ministry of Health (MoH) through a Ministerial Order (1215/2013).

In 2013 RONARD continued its active work in the development of the NPRD. The main activities of the RONARD in 2013 were the following:

- RONARD organised the Rare Diseases Day (RDD) Campaign and during the National Conference for Rare Diseases on 2<sup>nd</sup> of March 2013, at the end of the RDD campaign it was signed a new partnership agreement<sup>427</sup> with Ministry of Health Romania to create the institutional framework for the implementation of the National Plan for Rare Diseases (National Council for Rare Diseases). It is an interdisciplinary scientific body without a legal personality, working as an advisor of the Ministry of Health, providing specialised expertise both from its own team, as well as from specialised teams in different areas, developing criteria for designating centres of expertise in the management of rare diseases, defining evaluation process and identify the Centre of Expertise in Romania, communicating with RONARD and other institutional partners and define priority actions to ensure continuity of care for patients with rare diseases: information, diagnosis, treatment or specific therapies, counselling and patient and family education, training and integration specialists in the community;
- The second Europlan National Conference<sup>428</sup> was organised under the auspices of Ministry of Health of Romania in Bucharest, on 24-25 May 2013. The Conference aimed at facilitating dialogue, participation and involvement of all stakeholders in the field of rare diseases in Romania (patients, professionals, authorities, politicians, industry, media, etc.) in order to address solutions that need to be taken to update the proposals of the National Plan for Rare Diseases (NPRD).
- A Resolution of the Europlan Conference has been agreed by all the stakeholders involved in rare diseases field in Romania around the main objectives and future activities for rare diseases in 2013 and the following NPRD for the period: 2014-2020.

The economic context had a negative impact on public funds allocated to NPRD in 2013.

Rare cancers are mentioned in the NPRD in Romania and future actions will be included for the period 2014-2020.

Emergency cards have not yet been developed in Romania.

### Centres of expertise

So far a number of centres of expertise are functioning in Romania, but they are not officially recognised / labelled as centres of expertise. Expertise has been developed around the medical Universities and National Institutes for Health and currently many rare diseases are diagnosed, treated and followed-up.

NCRD (National Council for Rare Diseases) started to develop a policy concerning Centres of Expertise for RD. A procedure for the designation and evaluation of centres of expertise is under development using the EUCERD Recommendations on Quality Criteria for Centres of Expertise adapted to the situation in Romania.

<sup>427</sup> [http://www.ms.gov.ro/documente/ordin%20boli%20rare\\_823\\_1638.pdf](http://www.ms.gov.ro/documente/ordin%20boli%20rare_823_1638.pdf)

<sup>428</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-romania.pdf>

NCRD will select the criteria, define the policy in the country and organise the national competition for expertise centres. The number of total national/regional centres of expertise is still debateable based on population size and geographic distribution. Following the competition the Centres of Expertise designated will participate in the future European Reference Network.

At the moment, expert medical care is provided by many different centres all over the country, including: National Institutes of Oncology (Trestioreanu – Bucharest and Chiricuta - Cluj Napoca), Institute of Cerebrovascular diseases (Bucharest), Heart Institute (Cluj), National Institute of Endocrinology (Parhon - Bucharest), National Institute for Mother and Child (Alfred Rusescu - Bucharest), National Institute for Research and Development Victor Babes (Bucharest), Fundeni Clinical Institute (Bucharest), and many others. In addition, in major Romanian medical centres (Bucharest, Iasi, Constanta, Cluj, Timisoara, Targu Mures) there is a programme in place for the diagnosis of foetal anomalies which also aims to improve healthcare during pregnancy and diagnosis of possible genetic disorders.

A network for Pulmonary Hypertension (PHT) has been composed, including the following ~~following~~ institutes: Institute of Cardiovascular Diseases "CC Iliescu"(Bucharest), Pneumology Hospital (Iasi), Hospital "Victor Babes" (Timisoara), Heart Institute (Cluj) Institute of Cardiovascular Diseases and Transplantation - Pediatric Cardiology Clinic (Targu Mures), Children's Emergency Hospital "Louis Turcanu (Timisoara), Heart Centre - Cardiovascular Surgery Clinic (Cluj), Department of Paediatric Cardiology (Bucharest).

Since 2011 a Pilot Reference Centre for Rare Diseases "NoRo" was opened in Zalau, made possible through the project "Norwegian - Romanian (NoRo) Partnership for Progress in Rare Diseases" (2009- 2011) with financial support from the Norwegian Cooperation Programme for sustainable economic development in Romania. The centre offers information concerning RD and through the helpline they refer patients to the specialists involved in the field.

### **Registries**

Since 2013 NCRD deals with the issue of a national registry for RD but no public financial resources have been allocated so far. At the moment, NCRD selects the common data elements for Rd databases and extends the work by ensuring that the dataset are defined in the same way, using the same standards and same terms. Also, NCRD is considering appropriate EU standardised databases in order to find how to harmonise, share and exchange information. In addition, NCRD establishes baseline measures for data safety and protection. National registries and databases can be used to plan and manage services in the field of RD.

So far some registries are in place managed by Academia, clinicians or patient organisations (Romanian biliary atresia registry and Romanian cystic fibrosis patient registry, both having national coverage). There are more patients' registries in the field of RD but they do not fulfil all the requirements for a registry (National Registry of Haemophilia, the National Registry of Primary Immunodeficiency, the National Registry of Infant Diabetes Mellitus, the National Registry of Thalassaemia, the National Registry for Pulmonary Hypertension, the National Registry for Hyperparathyroidism, the National Registry for Acromegaly, and the National Registry of Neuromuscular Diseases; The National Registry of congenital Hypothyroidism and National Registry of Neuroendocrine tumours are still under development).

Romania contributes to the following European registries: EBAR (European Biliary Atresia Registry), EUROCARE CF (European Cystic Fibrosis Registry) and EUTOS (European Treatment and Outcome Study for Chronic Myeloid Leukaemia).

### **Neonatal screening policy**

In 2013, according to the national health policy a mandatory newborn screening program was available for two diseases, phenylketonuria (PKU) and congenital hypothyroidism (CHT), with the goal of screening all infants born in the country. The screening is performed in 4 public medical centres throughout the country (Bucharest, Iasi, Cluj-Napoca and Timisoara). The current health policy improved the management of screening for PKU and CHT at local level, reaching 80% coverage for newborns.

In the last two years, efforts were made via the Health Programme at local level in order to generalise and improve the organisation of neonatal screening for these two disorders, as well as to introduce screening for other (rare) diseases for which some form of treatment is available. Newborn screening tests for other diseases are provided by private clinics / laboratories at full cost or can be carried out in the framework of research programmes (e.g., hearing loss).

However, despite the screening programme, some tests are not available nationwide due to logistic and resource problems and no additional RD have been added to the panel of diseases tested in 2013.

Also, in 2013, Romania continued to join in efforts aimed for the preparation of European guidelines on diagnostic tests or population screening (EUNENBS: European Network of Experts on Newborn Screening) respecting national decisions and competences.

### **Genetic testing**

Genetic testing in Romania is available through public or private Medical Genetic Clinics but it is not covered in the National Programme for Rare Diseases. Usually, genetic testing is performed in University Medical Centres (Bucharest, Cluj, Craiova, Iasi, Oradea, Targu-Mures and Timisoara). Physicians specialising in Medical Genetics only are allowed to provide genetic counselling and pre- and postnatal testing.

Services include molecular and cytogenetic analysis such as sexual chromatin, conventional karyotype and interphase and metaphase FISH techniques, and DNA tests (MLPA, QF-PCR, arrayCGH, targeted sequencing). Genetic testing is carried out before birth (via amniocentesis or chorionic villus samples and, recently, non-invasive prenatal testing using cfDNA in maternal blood for the detection of fetal chromosomal abnormality) and after birth.

The current policy for prenatal screening and diagnosis in Romania includes a national programme for all pregnant women over age 35 at conception offering tests free of charge on a limited budget. Biochemical screening, ultrasound and CVS/amniocentesis are performed in 6 public medical centres throughout the country. Prenatal screening/diagnosis is also offered to all pregnant women independently of maternal age with costs eligible to be covered by national health insurance. At this time, some prenatal testing procedures are invasive and performed for the most common clinically significant foetal aneuploidies. Prenatal diagnosis is also used to determine whether a foetus has a rare monogenic disorder. Usually, for a foetus at increased risk for rare monogenic diseases, CVS/amniocentesis and DNA isolation are performed in many public or private clinics. Then the DNA samples are sent abroad for molecular diagnosis of rare monogenic diseases (sequencing for entire gene or selected exons).

All genetic laboratories, public or private, are accredited at national level according to SR EN ISO 15189 :2013 (international standard for medical laboratories).

Patients are referred for genetic testing by a physician (i.e. obstetrician, paediatrician, medical geneticist, haematologist and oncologist). Usually the results of genetic tests are interpreted by a medical geneticist who can also offer the genetic counselling. In Romania the health insurance does not cover the costs of genetic tests. But some genetic tests are free of charge for children who are enrolled in national health programme for birth defects. Other times, the patients could be enrolled in research programmes or non-profit humanitarian programmes, so that genetic tests are available for free.

Romania, as is the case of other European countries, cannot provide genetic tests for all disorders: other specific tests unavailable nationally are available abroad. Form S2 for Health Care Abroad/E112 offers is used in these cases. Diagnostic tests are registered as available in Romania for 31 genes and an estimated 55 diseases in the Orphanet database<sup>429</sup>.

There are no national practice guidelines for genetic testing yet, but guidelines are in progress. Professional organisations (Romanian Society of Medical Genetics) and other NGOs are working to complete this task using their experience and European recommendations.

### **National alliances of patient organisations and patient representation**

RONARD – Romanian National Alliance for RD is the main organiser of the activities in the field of RD in Romania. The activity of the National Alliance is not supported by the National Authorities.

At the end of 2013, the National Council for RD was created by the Ministry of Health (MoH) through a Ministerial Order (1215/2013) and 3 representatives of the RONARD are full members in the executive committee of the council. The council, as an advisory group for MoH in the field of RD is playing an important support role in the consultation and implementation of the NPRD.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activity in Romania***

Since 2004 there is a dedicated Orphanet team in Romania, currently hosted by “Gr T Popa” University of Medicine and Pharmacy, Iasi. This team was designated as the official Orphanet team for Romania by the Ministry of Health in 2010. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. An Orphanet country site was launched in 2012.

<sup>429</sup> Data extracted from Orphanet (January 2014)

There is no provision to fund our Orphanet national team within the NPRD. The Orphanet Romania Team has an active representative in the National Committee for Rare Diseases. The Orphanet Romania Team organised an event for Rare Disease Day in Iasi and also, have presented Orphanet in different meetings (at local and national level).

#### **Official information centre for rare diseases**

The Romanian Prader Willi Association has established a centre for information for rare genetic disorders in 2005 which is accredited by the Ministry of Work for its activity. RONARD and the Romanian Association for Rare Cancers are also accredited for providing information and counseling for patients with RD and rare cancers in Romania. Their activity is funded through projects. Through the NoRo project a virtual platform for rare diseases has been developed: [www.edubolirare.ro](http://www.edubolirare.ro), both for information and authorised training sessions for different professionals, including personal assistants.

The NoRo Centre for RD has videoconference facilities which can be used for provision of information, counseling and training of patients, parents and professionals.

In October 2013, RONARD has also launched an online platform for the development of organisational capacity of patients' organisations in Romania: [www.aspac.ro](http://www.aspac.ro).

#### **Help line**

The Romanian Prader Willi Association – RPWA – manages the NoRo helpline (080 080 1111). In 2011 the helpline was improved by introducing Orphacodes in the call information management software. In addition, a caller profile analysis was carried out, together with the other members of the European Network of Help Lines for Rare Diseases. Legal attestation has been granted assuring that the service operates according to the Romanian legislation of data protection and privacy. The helpline is part of the European Network of Helplines organised by Eurordis, together with the helpline provided by the Romanian Association for Myasthenia Gravis. At the end of 2013, RPWA has initiated a restructuration of the NoRo HelpLine in order to develop the network of professionals that support the activity at national level.

#### **Other sources of information on rare diseases**

The site <http://bolirare.ro/> provides some information on rare and genetic diseases, in the Romanian language.

The Romanian Prader Willi Association also produces the publication "Rare People and Rare Diseases" for patients and the public.

Leaflets with information concerning major genetic disorders are available for patients and parents in some Medical Genetics Centres all over the country.

Other sources of information include lectures by specialists in the field of RD.

#### **Guidelines**

Before 2013, clinical practice guidelines have been produced for every medical specialty including RD but several of them are at national level (e.g., diagnosis and follow-up in Oncology, Pulmonary Hypertension or Hereditary Angioedema).

In Romania the following translated or elaborated RD guidelines were launched in 2013:

- The Romanian Prader Willi Association translated and printed "A medical alert for Prader Willi Syndrome";
- In cooperation with Romanian Society for Human Genetics and many other professionals a book entitled "Medical Alert in Rare Genetic Diseases, an emergency guideline for 18 rare diseases clusters" was re-published. The book's first edition (including 98 different RD) was elaborated during the implementation of NoRo project.

#### **Training and education initiatives**

In Romania, Universities of Medicine and Pharmacy all over the country included in their curricula relevant topics on RD incorporating them in the basic medical training for the undergraduate students. In addition, RD are included in optional/ facultative lectures covering rare diseases for medical students, as well as post graduate lectures on Medical/ Clinical Genetics are organised in major university centres.

The Romanian Society of Medical Genetics provided continued education for medical doctors and other health professionals, organising training courses every year from 2007 until now.

The Romanian Prader Willi Association has developed the [www.edubolirare.ro](http://www.edubolirare.ro), a platform for rare diseases, and the training courses are adapted to the needs of different professional working in the field of rare

diseases. The training courses are authorised and accredited by the Ministry of Education and Ministry of Work but, also, by National Physicians' Collegium when the training is addressed to medical doctors.

In November 2013 the 2<sup>nd</sup> rare diseases training course for medical journalists in Romania and also a course for parents and personal assistants was debuted in December 2013.

Other training courses have been provided through our workshops organised in different conferences during 2013.

### **National rare disease events in 2013**

The Romanian National Alliance for Rare Diseases has marked Rare Disease Day with many events since 2008, with the support of Eurordis and the Romanian Society for Human Genetics. The alliance coordinates efforts and collects the information about the campaign events organised by the member organisations. To mark Rare Disease Day a march for rare diseases took place on 28 February 2013 in Zalau and a workshop on European Reference Networks and Centres of Expertise in Romania for rare diseases, organised by the National Alliance for Rare Diseases Romania, was also organised the week before on 21 February 2013. In addition to these events the first National Conference on Rare Diseases was organised on 2 March 2013 in partnership with the Romanian Society of Medical Genetics and the National Alliance for Rare Diseases with the aim of bringing together different professionals in the field to exchange information on rare diseases.

The Romanian Europlan conference<sup>430</sup> was held on 24-25 May 2013 in Bucharest to facilitate an open dialogue between all stakeholders (patients, professionals, authorities, politicians, industry, media). This event was organised by ANBRaRo under the patronage of the Ministry of Health. The conference rendered support from the Ministry of Health of Romania, who are motivated to carry forth the National Plan for Rare Diseases in the near future. In addition to updating the national plan for Romania, the conference also discussed establishing relevant procedures for assessing the Centres of Expertise as well as finalising the procedure for appointing the National Committee for Rare Diseases and working groups. The process of reimbursement of orphan drugs in Romania was also analysed and alternative strategies to facilitate access to orphan medication were examined. A push towards rare disease research and the identification of possible sources of funding were considered. In conclusion, the outlook for adoption of the long-awaited National Plan for Rare Diseases in Romania looks promising.

In addition a Campaign for rare cancers and CML was organised in September 2013.

### **Hosted rare disease events in 2013**

No reported events.

### **Research activities and E-Rare partnership**

#### ***National research activities***

There is no specific research programme for RD in Romania. Research projects aimed to RD are included in the same group with other topics research projects. In 2013 there were few calls for research projects but not rare disease specific. There are currently no other fund-raising initiatives for RD research in Romania.

### **Participation in European research projects**

Romanian team(s) participate/participated in 1 FP7 rare disease related project.

#### ***E-Rare***

Romania joined the E-Rare consortium in 2012.

#### ***IRDiRC***

Romanian funding agencies have not yet committed financing to the IRDiRC.

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

No specific activity reported.

#### ***Orphan medicinal product incentives***

No specific activity reported.

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<sup>430</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-romania.pdf>



### **Orphan medicinal product availability**

From 1 January 2007, date at which Romania became an EU Member State, all medicinal products were required to obtain new authorisations according to EU standards: this created significant delay in the importation of certain orphan medicinal products. As a consequence of the creation of the National Plan for Rare Diseases, the Ministry of Public Health enlarged coverage of orphan medicinal products from July 2008 onwards in their health programme.

The list of orphan medicinal products available/commercialised in Romania and free of charge through the National Health Programme is available on the website of the Romanian National Medicines' Agency<sup>431</sup> and includes: Aldurazyme, Atriance, Busilvex, Carbaglu, Cystadane, Diacomit, Elapraxe, Evoltra, Exjade, Fabrazyme, Firazyf, Gliolan, Glivec, Increlex, Inovelon, Litak, Lysodren, Myozyme, Naglazyme, Nexavar, Onsenal, Orfadin, Pedeia, PhotoBarr, Prialt, Replagal, Revatio, Revlimid, Savene, Siklos, Soliris, Somavert, Sprycel, Sutent, Tasigna, Thalidomide Pharmion, Thelin, Torisel, Tracleer, Trisenox, Ventavis, Volibris, Wilzin, Xagrid, Xyrem, Yondelis, Zavesca.

### **Orphan medicinal product pricing policy**

There is national debate for regulation in this area.

### **Orphan medicinal product reimbursement policy**

The National Programme for Rare Diseases provides for the reimbursement of 47 orphan medicinal products in Romania.

### **Other initiatives to improve access to orphan medicinal products**

In Romania there are several ways of accessing orphan medicinal products via Order N° 962/2006 for approval of the application of art. 699, paragraph (1) of Law N° 95/2006 including: compassionate use of drugs for a certain patient (in the case where the drug already has marketing authorisation); compassionate use of drugs for a group of patients with an invalidating disease, either chronic or serious, or a disease considered to be life-threatening (the provision of a centrally authorised product); the off-label use of drugs. However, the public payer will not always reimburse the orphan medicinal product provided.

Many companies (i.e. Genzyme, Novartis) use humanitarian programs, sponsorship or partnership with medical societies in order to provide the orphan medicinal products, like Tasigna, Evoltra, Fabryzyme, Myozyme, and others. This way was a successful manner to give access of the patients to some orphan medicinal products. Other ways include the enrolment of patients in clinical trials for orphan medicinal products. Doctors have to prescribe the compassionate / off-label drugs and follow-up the patients.

### **Other therapies for rare diseases**

The NoRo Centre offers to patients with rare diseases access to therapies such as: medical evaluation, groups of support, psychological counseling, behaviour therapy, speech therapy, physical therapy, massage, sensorial therapy, hydro - kinetic – electric therapy, ergo-therapy, weight management, educational and occupational therapy. The NoRo Centre is accredited for specialised social services by the Ministry of Work and also for medical services from Ministry of Health; it is authorised for training by Ministry of Education and for research capacity by National Agency for Scientific Research. It is a resource centre and could be part of the patients' pathway and network of the future centres of expertise in Romania, ensuring continuity of care while implementing quality standards of services. It is the main goal of ExpertRARE – a project developed by Romanian Prader Willi Association and co-funded by a grant from Switzerland through the Swiss Contribution to the enlarged European Union.

### **Orphan devices**

No information reported yet.

### **Specialised social services**

The NoRo Centre was established by Romanian Prader Willi Association in 2011 with Norwegian funding through Norwegian Cooperation Program and it is working for 1 year and a half, supported partly by the local and national authorities. The service includes training courses, information and guidance services, and provision of information about social services, documentation and research. Daily support therapies, medical and

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<sup>431</sup> <http://www.anm.ro/ /Lista%20medicamentelor%20orfane%20valide%20in%20Romania.xls>

psychological consultations are also provided by NoRo centre. This service also aims to create a bridge between patients/families and all the stakeholders involved in patient care, such as medical services, rehabilitation and Therapeutic services, social services and social support authorities, education professionals and other professionals directly working with RD patients.

It is funded by the Local Council Zalau and County Council Salaj and other projects for the development of the services. It is mentioned on the map Specialized Social Services developed by Eurordis in the EUCERD Joint Action for Rare Diseases ([www.eurordis.org](http://www.eurordis.org); [www.eucerd.eu](http://www.eucerd.eu); ). The guidelines for specialised social services produced in the Joint Action started to be translated and will be available on RONARD website in June 2014.

## RARE DISEASE ACTIVITIES IN 2013 IN ROMANIA

### National plan/strategy for rare diseases and related actions

By the end of 2012 the inclusion of the National Plan for Rare Diseases in the National Public Health Strategy was the next step concerning the implementation and monitoring of the plan by the end of 2013. At the end of 2013, the National Council for RD (NCRD) was created by the Ministry of Health (MoH) through a Ministerial Order (1215/2013).

In 2013 RONARD continued its active work in the development of the NPRD. The main activities of the RONARD in 2013 were the following:

- RONARD organised the Rare Diseases Day (RDD) Campaign and during the National Conference for Rare Diseases on 2<sup>nd</sup> of March 2013, at the end of the RDD campaign it was signed a new partnership agreement<sup>432</sup> with Ministry of Health Romania to create the institutional framework for the implementation of the National Plan for Rare Diseases (National Council for Rare Diseases). It is an interdisciplinary scientific body without a legal personality, working as an advisor of the Ministry of Health, providing specialised expertise both from its own team, as well as from specialised teams in different areas, developing criteria for designating centres of expertise in the management of rare diseases, defining evaluation process and identify the Centre of Expertise in Romania, communicating with RONARD and other institutional partners and define priority actions to ensure continuity of care for patients with rare diseases: information, diagnosis, treatment or specific therapies, counselling and patient and family education, training and integration specialists in the community;
- The second Europlan National Conference<sup>433</sup> was organised under the auspices of Ministry of Health of Romania in Bucharest, on 24-25 May 2013. The Conference aimed at facilitating dialogue, participation and involvement of all stakeholders in the field of rare diseases in Romania (patients, professionals, authorities, politicians, industry, media, etc.) in order to address solutions that need to be taken to update the proposals of the National Plan for Rare Diseases (NPRD).
- that need to be taken to update the proposals of the National Plan for Rare Diseases (NPRD).
- A Resolution of the Europlan Conference has been agreed by all the stakeholders involved in rare diseases field in Romania around the main objectives and future activities for rare diseases in 2013 and the following NPRD for the period: 2014-2020.

Due to the complexity of political and socio-economic situation at the national level, no budget has been allocated for the NPRD in 2013 but it is expected financial support through budgetary integration on MoH.

Rare cancers are mentioned in the NPRD in Romania and future actions will be included for the period 2014-2020.

### Centres of expertise

The NCRD (National Council of Rare Diseases) started to develop a policy concerning Centres of Expertise for RD. A procedure for the designation and evaluation of centres of expertise is under development using the EUCERD Recommendations on Quality Criteria for Centres of Expertise adapted to the situation in Romania. NCRD will select the criteria, define the policy in the country and organise the national competition for

<sup>432</sup> [http://www.ms.gov.ro/documente/ordin%20boli%20rare\\_823\\_1638.pdf](http://www.ms.gov.ro/documente/ordin%20boli%20rare_823_1638.pdf)

<sup>433</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-romania.pdf>

expertise centres. The number of total national/regional centres of expertise is still debateable based on population size and geographic distribution. Following the competition the Centres of Expertise designated will participate in the future European Reference Network.

### **Registries**

Since 2013 NCRD deals with the issue of a national registry for RD but no public financial resources have been allocated so far. At the moment, NCRD selects the common data elements for Rd databases and extends the work by ensuring that the dataset are defined in the same way, using the same standards and same terms. Also, NCRD is considering appropriate EU standardised databases in order to find how to harmonise, share and exchange information. In addition, NCRD establishes baseline measures for data safety and protection. National registries and databases can be use to plan and manage services in the field of RD.

### **Neonatal screening policy**

In 2013, according to the national health policy a mandatory newborn screening program was available for two diseases, phenylketonuria (PKU) and congenital hypothyroidism (CHT), with the goal of screening all infants born in the country. The screening is performed in 4 public medical centres throughout the country (Bucharest, Iasi, Cluj-Napoca and Timisoara). The current health policy improved the management of screening for PKU and CHT at local level, reaching 80% coverage for newborns.

In the last two years, efforts were made via the Health Programme at local level in order to generalise and improve the organisation of neonatal screening for these two disorders, as well as to introduce screening for other (rare) diseases for which some form of treatment is available. Newborn screening tests for other diseases are provided by private clinics / laboratories at full cost or can be carried out in the framework of research programmes (e.g., hearing loss).

However, despite the screening programme, some tests are not available nationwide due to logistic and resource problems and no additional RD have been added to the panel of diseases tested in 2013.

Also, in 2013, Romania continued to join in efforts aimed for the preparation of European guidelines on diagnostic tests or population screening (EUNENBS: European Network of Experts on Newborn Screening) respecting national decisions and competences.

### **National alliances of patient organisations and patient representation**

At the end of 2013, the National Council for RD (NCRD) was created by the Ministry of Health (MoH) through a Ministerial Order (1215/2013) and 3 representatives of the RONARD are full members in the executive committee of the council. The council, as an advisory group for MoH in the field of RD is playing an important support role in the consultation and implementation of the NPRD.

### **Sources of information on rare diseases and national help lines**

#### ***Official information centre for rare diseases***

In October 2013, RONARD has also launched an online platform for the development of organisational capacity of patients' organisations in Romania: [www.aspac.ro](http://www.aspac.ro).

#### ***Help line***

At the end of 2013, The Romanian Prader Willi Association has initiated a restructuration of the NoRo HelpLine in order to develop the network of professionals that support the activity at national level.

### **Guidelines**

Before 2013, clinical practice guidelines have been produced for every medical specialty including RD but several of them are at national level (e.g., diagnosis and follow-up in Oncology, Pulmonary Hypertension or Hereditary Angioedema).

In Romania the following translated or elaborated RD guidelines were launched in 2013:

- The Romanian Prader Willi Association translated and printed "A medical alert for Prader Willi Syndrome";
- In cooperation with Romanian Society for Human Genetics and many other professionals a book entitled "Medical Alert in Rare Genetic Diseases, an emergency guideline for 18 rare diseases clusters" was re-published. The book's first edition (including 98 different RD) was elaborated during the implementation of NoRo project.

### **Training and education initiatives**

In November 2013 the 2<sup>nd</sup> rare diseases training course for medical journalists in Romania and also a course for parents and personal assistants was debuted in December 2013.

Other training courses have been provided through our workshops organised in different conferences during 2013.

### **National rare disease events in 2013**

The Romanian National Alliance for Rare Diseases has marked Rare Disease Day with many events since 2008, with the support of Eurordis and the Romanian Society for Human Genetics. The alliance coordinates efforts and collects the information about the campaign events organised by the member organisations. To mark Rare Disease Day a march for rare diseases took place on 28 February 2013 in Zalau and a workshop on European Reference Networks and Centres of Expertise in Romania for rare diseases, organised by the National Alliance for Rare Diseases Romania, was also organised the week before on 21 February 2013. In addition to these events the first National Conference on Rare Diseases was organised on 2 March 2013 in partnership with the Romanian Society of Medical Genetics and the National Alliance for Rare Diseases with the aim of bringing together different professionals in the field to exchange information on rare diseases.

The Romanian Europlan conference<sup>434</sup> was held on 24-25 May 2013 in Bucharest to facilitate an open dialogue between all stakeholders (patients, professionals, authorities, politicians, industry, media). This event was organised by ANBRaRo under the patronage of the Ministry of Health. The conference rendered support from the Ministry of Health of Romania, who are motivated to carry forth the National Plan for Rare Diseases in the near future. In addition to updating the national plan for Romania, the conference also discussed establishing relevant procedures for assessing the Centres of Expertise as well as finalising the procedure for appointing the National Committee for Rare Diseases and working groups. The process of reimbursement of orphan drugs in Romania was also analysed and alternative strategies to facilitate access to orphan medication were examined. A push towards rare disease research and the identification of possible sources of funding were considered. In conclusion, the outlook for adoption of the long-awaited National Plan for Rare Diseases in Romania looks promising.

In addition a Campaign for rare cancers and CML was organised in September 2013.

### **Other therapies for rare diseases**

The NoRo Centre offers to patients with rare diseases access to therapies such as: medical evaluation, groups of support, psychological counseling, behaviour therapy, speech therapy, physical therapy, massage, sensorial therapy, hydro - kinetic – electric therapy, ergo-therapy, weight management, educational and occupational therapy. The NoRo Centre is accredited for specialised social services by the Ministry of Work and also for medical services from Ministry of Health; it is authorised for training by Ministry of Education and for research capacity by National Agency for Scientific Research. It is a resource centre and could be part of the patients' pathway and network of the future centres of expertise in Romania, ensuring continuity of care while implementing quality standards of services. It is the main goal of ExpertRARE – a project developed by Romanian Prader Willi Association and co-funded by a grant from Switzerland through the Swiss Contribution to the enlarged European Union.

## **1.24. SLOVAK REPUBLIC**

### **Definition of a rare disease**

Stakeholders in Slovak Republic accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### **National plan/strategy for rare diseases and related actions**

A working group was established in January 2011 at the Ministry of Health to work on a strategy for improving health care for patients with rare diseases. This strategy includes the basic concepts for the plan and was

<sup>434</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-romania.pdf>

adopted by the Government of the Slovak Republic on 24 October 2012. However, no funding has been allocated for the Plan as of yet.

### Centres of expertise

There is currently no official policy concerning centres of expertise for rare diseases: no official centres of expertise for rare diseases in Slovak Republic exist. Health care for several rare diseases is centralised mainly at the University hospitals (as for example Children's University Hospitals in Bratislava or Banská Bystrica) or specialised hospitals (as for example National Institute for Cardiovascular diseases, National Institute for rheumatic diseases, National Cancer Institute), Departments of Clinical Genetics (12 in the country), the Centre for metabolic diseases (1 in the country), and in several specialised outpatient clinics for metabolism or few types of rare diseases, as well as in cooperation with some research laboratories of Slovak Academy of Science.

### Registries

At present, there is no national committee dedicated to deal with registries and no national rare disease registry; however the future National Plan for Rare Diseases will look at ways of patient data collecting. National health registries are financed by Ministry of Health of the Slovak Republic. The National Health Information Center (NCZI) is the operator of most national health registries. Of these the following registries are for rare diseases: the National registry for congenital disorders (established in 2011), the National registry for congenital heart defects (established in 1992), the National cancer registry (established in 1976 including rare cancers), the National child diabetes mellitus and neonatal diabetes registry (established in 1986).

The NCZI provides data for the new registry focused at the monogenic forms of diabetes. The registry has been launched in 2008 based upon the data produced by the DIABGENE Laboratory at the Institute of Experimental Endocrinology, Slovak Academy of Sciences. In 2011 the National juvenile hypertension registry was established as sub register of cardiovascular registry.

During 2013 the Slovak Society of Medical Genetics together with the NCZI worked on reporting congenital anomalies (including ORPHA, OMIM, codes), so as to use this for future information about rare disease patients.

There are also several disease-specific registries managed outside of the NCZI (i.e. clinical registry of haemophilia). Slovak patients are registered also in international registries as REaDy – REgister of muscular dystrophies (<http://ready.registry.cz/>). Currently, the database registers a total of 51 patients from Slovakia.. Up November 2013 Slovakia is involved in the European Cystic Fibrosis Society Patients Registry.

The use of Orphacodes to code rare diseases is being considered.

The Slovak Republic contributes to the EUROCARE CF and RARECARE registry.

### Neonatal screening policy

Neonatal screening (NBS) policy has been officially established by the Ministry of Health in the Slovak Republic. Screening is in place since 1985 for congenital hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, and cystic fibrosis. Screening is provided in one central National Newborn Screening Centre, in coordination with three regional Recall Centres providing definitive diagnostic procedures and continuous management of confirmed cases. MS/MS technology has been introduced into selective screening. In addition to the screened diseases every newborn/infant is screened for hearing disorders, hip dislocation and the majority of newborns (more than 90%) are screened immediately after birth by means of USG for somatic malformations (CNS, cardiology, obstructive uropathy, etc.) although this is not an official governmental policy. In 2012 a document on newborn screening was adopted, expanding the panel of screened diseases from 4 to 13, to include hyperphenylalaninemia (HPA), leucinosis (MSUD), Medium Chain Acyl Co A Dehydrogenase Deficiency (MCAD), Long Chain Acyl Co A Dehydrogenase Deficiency (LCHAD), VLCAD, Carnitin Palmitoyl Transferase I. Deficiency (CPT I), Carnitin Palmitoyl Transferase II. Deficiency (CPT II), Carnitin Acylcarnitin Translocase Deficiency (CACT), glutaric aciduria type I (GAI), and isovaleric aciduria(IVA). In the year 2013 the expanded newborn screening was launched<sup>435</sup>.

The National Newborn Screening Centre is a member of EUNENBS (European Union Network of Experts on Newborn Screening).

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<sup>435</sup> Dluholucký S./Knapková M. Newborn Screening in Slovakia – From 1985 Till Today  
<http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/afpuc-2013-0006/afpuc-2013-0006.xml?format=INT>

### **Genetic testing**

As a small country, the Slovak Republic does not have a large number of laboratories for genetic testing. Genetic testing is organised by the Departments of Clinical Genetics (12 in the country), specialised genetic outpatient clinics or specialised Departments of Clinical Oncogenetics (2 in the country). There are 5 bigger and several smaller DNA laboratories which perform or provide molecular diagnostics for around 350 monogenic mendelian disorders. There are currently no reference laboratories in Slovak Republic.

The Slovak Republic has also participated in elaboration of several international “Best Practice Guidelines”, e.g. “Molecular Genetic Diagnosis of Maturity – onset Diabetes of the Young”.

Specific provisions for the reimbursement of tests are not yet in place and genetic testing for non-medical reasons is paid for by the person requesting the test. Slovak Society of Medical Genetics and health insurance companies are now developing new system of reimbursement of genetic testing .Genetic testing also takes place abroad, mainly in the Czech Republic.

Diagnostic tests are registered in the Orphanet database for 49 genes and an estimated 103 diseases<sup>436</sup>.

### **National alliances of patient organisations and patient representation**

The Slovak Rare Disease Alliance<sup>437</sup> (Slovak RD Alliance) was established at their first constitutive meeting held in Bratislava in Slovakia on 12 December 2011 and was composed of 12 patient organisations out of the 17 related to rare diseases in the country at that time. In 2013, 16 rare disease organisations plus one voluntary group of patients form the Slovak RD Alliance.

The Slovak RD Alliance is leads the activities in the field of rare diseases in Slovakia and thus was the main organiser of the EUROPLAN National Conference on the Rare diseases day in February 2013. The fundamental challenge for the Slovak RD Alliance is to raise public awareness about rare diseases. The representatives of the Slovak RD Alliance are actively involved in the Working group for rare diseases at the Ministry of Health and in 2013 participated in the formation of National Plan for Rare Diseases. The RD Alliance also publishes a newsletter MINORIT (quarterly).

There are no public funding schemes for patient organisations in Slovak Republic. Some patient organisations are members of the NR OZP SR (National Disability Council in Slovak Republic).

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in the Slovak Republic***

Since 2006 there is a dedicated Orphanet team in the Slovak Republic, hosted before 2010 by the Institute of Molecular Physiology and Genetics in Bratislava. In 2010, in the context of the Joint Action Orphanet Europe, the Ministry of Health designated the 2<sup>nd</sup> Department of Paediatrics of the University Children’s Hospital Bratislava as the official Orphanet team for Slovak Republic. This team is engaged in collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team launched in 2011 the Orphanet Slovakia national website<sup>438</sup>. Part of the Orphanet Encyclopedia has also been translated to Slovak language and this initial set rare disease descriptions is now available on the Orphanet Slovakia website. In the year 2013 the Slovak Orphanet team was partner of the EUROPLAN National Conference held on the Rare Disease Day (2<sup>nd</sup> Slovak Rare Disease Conference<sup>439</sup> In April 2014 the Slovak Orphan team organised the 2<sup>nd</sup> Slovak Rare Disease Conference.

#### ***Official information centre for rare diseases***

There is no official information centre for rare diseases other than Orphanet in Slovak Republic.

#### ***Help line***

There is currently no dedicated help line for rare diseases at the moment.

#### ***Other sources of information on rare diseases***

Information sources on rare diseases are mostly run by non-governmental patient’s organisations with a few projects supported by the state and municipality. One well developed information source is internet page of Slovak RD Alliance. More used sources of information for professionals in clinical genetics are the websites

<sup>436</sup> Data extracted from the Orphanet database in January 2014.

<sup>437</sup> <http://www.sazch.sk/> [www.zriedkave-choroby.sk](http://www.zriedkave-choroby.sk)

<sup>438</sup> <http://www.orpha.net/national/SK-SK/index/%C3%BAvod/> [www.zriedkave-choroby.sk](http://www.zriedkave-choroby.sk)

<sup>439</sup> <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/issue-files/afpuc.2013.60.issue-supplementum8.xml>

OMIM (Online Mendelian Inheritance in Man), GeneTests, and many other web sites for another medical specialities.

### Guidelines

Good practice guidelines have been developed for cystic fibrosis, maturity-onset diabetes of the young, Wilson disease and haemophilia, as well as for new born screening. Some molecular genetics laboratories in Slovakia have been participating in the EMQN programme and EQA KRAS programme. The Slovak Republic participated in elaboration of the international Best Practice Guidelines for Molecular Genetic Diagnosis of Maturity-onset Diabetes of the Young. National guidelines for genetic testing were developed and adopted by the Slovak Society of Medical Genetics (SSLG) in June 2012. SSLG, oncogenetics laboratories and Association of Health Insurance Companies developed guideline for diagnostics and clinical management of HBOC.

### Training and education initiatives

Currently, there are no training or education initiatives organised systematically in the field of rare diseases.

### National rare disease events 2013

The main activity of the National Rare Disease Day 2013 in Slovakia was the EUROPLAN National Conference (27-28 February 2013)<sup>440</sup>. This second edition was organised by the Slovak RD Alliance in cooperation with the EUCERD representative and under auspices of the Chair of Health Care Committee National Council of the Slovak Republic and member of Parliament of the Slovak Republic - Richard Raši, MD., PhD, MPH., Ministry of Health of the Slovak Republic - Dr. Zuzana Zvolenská and EURORDIS.

The special website dedicated to Rare Disease Day was launched by Slovak RD Alliance ([www.zriedkave-choroby.sk](http://www.zriedkave-choroby.sk)) which is regularly updated mainly with information and news regarding activities run by Slovak RD Alliance on Rare Disease Day.

On 27 of February there was a press conference, where the representative of Health Care Committee National Council of the Slovak Republic: Richard Raši MD, the representative of EURORDIS Dorica Dan, the representative of professionals Anna Hlavatá MD from University Children's Hospital, the representative of EUCERD Slovakia Frantisek Cisarik MD and the press conference host from Slovak RD Alliance and DebRA SR Beata Ramljaková took part. After the press conference the speakers moved to the Ministry of Health, where together with others involved, the first meeting of the Working Group for Rare Diseases was held. The EUCERD representative from the Czech Republic Milan Macek gave a talk about the experience with the health care for rare disease patients in the Czech Republic. The representatives of the Slovak RD Alliance gave the official translation<sup>441</sup> of the National strategy into English to the representatives of the Ministry of Health. On the next day the Forum of Experts with 164 guests and 16 talks was held. The Conference was divided into three main parts, according the guideline for EUROPLAN conferences. In the first one, the starting points for the creation and formation of the National plan were explained and an update on the legislative status given. Then an update on Orphanet activities was given and professionals were encouraged to register their services. The availability of orphan medicinal products from the regulatory point of view as well as from the point of view of the health insurance company was discussed. In the next part experience with the newborn screening policy was presented. The issue of registries for rare diseases was also tackled. Finally the Slovak RD Alliance presented its activities and importance of active participation in the creation of the National Plan. Representatives of the patient organisations presented their experience with the specialised social services provided. The national scientific journal Acta Facultatis Pharmaceuticae Universitatis Comenianae published the proceedings<sup>442</sup>. The conference report is available online<sup>443</sup>.

On 24 April 2013, the 2<sup>nd</sup> Slovak Rare Disease Conference was held in Bratislava. One of the aims was to reflect on the creation of a national network of expert centres for rare diseases. A number of scientific lectures with emphasis on therapeutic approaches were also given.

Izakovic's Memorial is an annual conference organised in Slovak Republic by the Slovak Society of Medical Genetics, related to genetic and rare diseases.

### Hosted rare disease events 2013

No reported events.

<sup>440</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-slovakia.pdf>

<sup>441</sup> [http://www.europlanproject.eu/newsite\\_986989/Resources/docs/NATIONALPLANS\\_SL\\_nationalStrategySlovakiaEng.pdf](http://www.europlanproject.eu/newsite_986989/Resources/docs/NATIONALPLANS_SL_nationalStrategySlovakiaEng.pdf)

<sup>442</sup> <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/issue-files/afpuc.2013.60.issue-supplementum8.xml>

<sup>443</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-slovakia.pdf>

## **Research activities and E-Rare partnership**

### ***National research activities***

Currently there are no specific programmes for rare disease research in Slovak Republic.

### ***Participation in European research projects***

There are currently no teams from Slovakia participating in FP7 rare disease related projects.

### ***E-Rare***

Slovak Republic is not currently a partner of the E-Rare Project.

### ***IRDIRC***

Slovak funding agencies do not currently commit funding to the IRDiRC.

## **Orphan medicinal products**

### ***Orphan medicinal product committee***

Also in the year 2013 the Slovak Republic did not have a national orphan medicinal product committee, and a representative at the COMP neither in EUnetHTA. The Slovak Ministry of Health is responsible for system of pricing and reimbursement of all drugs as well as orphan medicinal products.

### ***Orphan medicinal product incentives***

To attract orphan medicinal products manufactures to launch the Slovak market better information about the patients with rare diseases is needed to be able to estimate the real need in this relatively small country. Formation of national strategy/plan might help to solve this problem.

### ***Orphan medicinal product market availability situation***

SUKL, the State Institute for Drug Control, is the regulatory body in the Slovak Republic responsible for the regulation and surveillance of human medicinal products and medical devices, including orphan medicinal products. The data about the adverse events is submitted to the European database of suspected adverse drug reactions.

The reimbursement level is set in a national process named “categorisation”. The “categorisation committee”, established at the Ministry of Health, is responsible for pricing and reimbursement.

All orphan medicinal products registered at EU level are available in the Slovak Republic. However since 2011 changes in the national legislation make it difficult for OMP to be launched on the Slovak market. This is reflected in the fact that since this change only one drug launched the Slovak market (2012 - Tobi Podhaler). Thus OMP are available on individual basis via an administratively and time demanding process. First the physician has to submit a special application on a patient named basis at the Ministry of Health, afterwards individual negotiation between marketing authorisation holder and the Insurance company starts.

Directly available on the Slovak market at the end of 2013 were 22 orphan medicinal products: Myozyme, Aldurazyme (since June 2013 not OMP anymore), Naglazyme, Zavesca, Kuvan, Ventavis, Revolade (not OMP anymore), Nplate, Firazyf, Volibris, Tracleer, Revatio, Incelex, Litak, Nexavar, Sprycel, Tassigna, Torisel, Revlimid, Lysodren, Vidaza, Inovelon, Exjade, Tobi podhaler. The information about the amount of OMP distributed at patient named-basis is not public (it is the subject of the individual contract between the marketing authorisation holder and the insurance company); data concerning this issue was presented at the EUROPLAN conference in February 2013<sup>444</sup> A systemic approach is lacking.

### ***Orphan medicinal product pricing policy***

No specific information reported.

### ***Orphan medicinal product reimbursement policy***

At the end of the year 2011 Slovak Ministry of Health introduced a monthly update of “categorisation list”, thus increasing the possibilities for all pharmaceutical companies to launch their product, however this is not the case of orphan medicinal product pharmaceutical companies, which have problems to meet the criteria for categorisation (Act No 36/2011 in the Collection of Laws of the Slovak Republic). The criteria for categorization are applicable only for high prevalent diseases.

<sup>444</sup>Foltánová, T. / Mazák J. Orphan drugs in EU, <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/afpuc-2013-0005/afpuc-2013-0005.xml?format=INT>



At the end of 2013 out of the 22 orphan medicinal products, 6 orphan medicinal products require patients' participation towards costs (Myozyme plc ifo 10x50 mg, plc ifo 25x50 mg, Tobi podhaler plv icd 224x28 mg, Firazyr sol inj 1x3ml, Inovelon tbl flm 50x200 mg, tbl flm 50x400 mg). The highest copayment was for Tobi podhaler plv icd (€497, which means 20.61% of the total price). The average copayment is 1.51% of the total price (0.87 – 20.61% ).The orphan medicinal products are distributed mainly through pharmacies as well as on a centre basis, depending on the reimbursement category which is also set in the "categorisation list".

#### **Other initiatives to improve access to orphan medicinal products**

Thanks to the participation in the REaDy – REgister of muscular dystrophies, 2 patients with Duchenne muscular dystrophy were involved in the clinical trial. Because of unavailability of Centres of expertise, the treatment was given in Czech Republic, in Brno.

#### **Orphan devices**

No specific information reported.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Specialised social services**

Care services, both government-run and private, are available in Slovak Republic and partial or full reimbursement is available (depending on certain criteria). Therapeutic programmes such as spa stays are available and paid mainly through private health insurance. However the definition of rare disease patient per se is not included in the indication list for such stays.

## **RARE DISEASE ACTIVITIES IN 2013 IN THE SLOVAK REPUBLIC**

#### **Registries**

During 2013 the Slovak Society of Medical Genetics together with the NCZI worked on reporting congenital anomalies (including ORPHA, OMIM, codes), so as to use this for future information about rare disease patients.

The use of Orphacodes to code rare diseases is being considered.

#### **National alliances of patient organisations and patient representation**

The Slovak RD Alliance is leads the activities in the field of rare diseases in Slovakia and thus was the main organiser of the EUROPLAN National Conference on the Rare diseases day in February 2013. The fundamental challenge for the Slovak RD Alliance is to raise public awareness about rare diseases. The representatives of the Slovak RD Alliance are actively involved in the Working group for rare diseases at the Ministry of Health and in 2013 participated in the formation of National Plan for Rare Diseases.

#### **Sources of information on rare diseases and national help lines**

##### **Orphanet activities in the Slovak Republic**

Since 2006 there is a dedicated Orphanet team in the Slovak Republic, hosted before 2010 by the Institute of Molecular Physiology and Genetics in Bratislava. In 2010, in the context of the Joint Action Orphanet Europe, the Ministry of Health designated the 2<sup>nd</sup> Department of Paediatrics of the University Children's Hospital Bratislava as the official Orphanet team for Slovak Republic. This team is engaged in collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team launched in 2011 the Orphanet Slovakia national website<sup>445</sup>. Part of the Orphanet Encyclopedia has also been translated to Slovak language and this initial set rare disease descriptions is now available on the Orphanet Slovakia website. In the year 2013 the Slovak Orphanet team was partner of the EUROPLAN National Conference held on the Rare

<sup>445</sup> <http://www.orpha.net/national/SK-SK/index/%C3%BAvod/> [www.zriedkave-choroby.sk](http://www.zriedkave-choroby.sk)

Disease Day (2<sup>nd</sup> Slovak Rare Disease Conference<sup>446</sup> In April 2014 the Slovak Orphan team organised the 2<sup>nd</sup> Slovak Rare Disease Conference.

### National rare disease events 2013

The main activity of the National Rare Disease Day 2013 in Slovakia was the EUROPLAN National Conference (27-28 February 2013). This second edition was organised by the Slovak RD Alliance in cooperation with the EUCERD representative and under auspices of the Chair of Health Care Committee National Council of the Slovak Republic and member of Parliament of the Slovak Republic - Richard Raši, MD., PhD, MPH., Ministry of Health of the Slovak Republic - Dr. Zuzana Zvolenská and EURORDIS.

The special website dedicated to Rare Disease Day was launched by Slovak RD Alliance ([www.zriedkave-choroby.sk](http://www.zriedkave-choroby.sk)) is regularly updated mainly with information and news regarding activities run by Slovak RD Alliance on Rare Disease Day.

On 27 of February there was a press conference, where the representative of Health Care Committee National Council of the Slovak Republic: Richard Raši MD, the representative of EURORDIS Dorica Dan, the representative of professionals Anna Hlavatá MD from University Children's Hospital, the representative of EUCERD Slovakia Frantisek Cisarik MD and the press conference host from Slovak RD Alliance and DebRA SR Beata Ramljaková took part. After the press conference the speakers moved to the Ministry of Health, where together with others involved, the first meeting of the Working Group for Rare Diseases was held. The EUCERD representative from the Czech Republic Milan Macek gave a talk about the experience with the health care for rare disease patients in the Czech Republic. The representatives of the Slovak RD Alliance gave the official translation<sup>447</sup> of the National strategy into English to the representatives of the Ministry of Health. On the next day the Forum of Experts with 164 guests and 16 talks was held. The Conference was divided into three main parts, according the guideline for EUROPLAN conferences. In the first one, the starting points for the creation and formation of the National plan were explained and an update on the legislative status given. Then an update on Orphanet activities was given and professionals were encouraged to register their services. The availability of orphan medicinal products from the regulatory point of view as well as from the point of view of the health insurance company was discussed. In the next part experience with the newborn screening policy was presented. The issue of registries for rare diseases was also tackled. Finally the Slovak RD Alliance presented its activities and importance of active participation in the creation of the National Plan. Representatives of the patient organisations presented their experience with the specialised social services provided. The national scientific journal Acta Facultatis Pharmaceuticae Universitatis Comenianae published the proceedings<sup>448</sup>. The conference report is available online<sup>449</sup>.

On 24 April 2013, the 2<sup>nd</sup> Slovak Rare Disease Conference was held in Bratislava. One of the aims was to reflect on the creation of a national network of expert centres for rare diseases. A number of scientific lectures with emphasis on therapeutic approaches were also given.

Izakovic's Memorial is an annual conference organised in Slovak Republic by the Slovak Society of Medical Genetics, related to genetic and rare diseases.

## 1.25. SLOVENIA

### Definition of a rare disease

Stakeholders in Slovenia accept the European Regulation on Orphan Medicinal Products definition of a prevalence of not more than 5 in 10 000 individuals. The same definition is also accepted in The Work Plan for Rare Diseases.

### National plan/strategy for rare diseases and related actions

In 2012 a national plan for rare diseases was accepted by the Health Council and the next steps will be to elaborate an action plan and its implementation, as well as to identify funding. The Work Plan for Rare

<sup>446</sup> <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/issue-files/afpuc.2013.60.issue-supplementum8.xml>

<sup>447</sup> [http://www.europlanproject.eu/newsite\\_986989/Resources/docs/NATIONALPLANS\\_SL\\_nationalStrategySlovakiaEng.pdf](http://www.europlanproject.eu/newsite_986989/Resources/docs/NATIONALPLANS_SL_nationalStrategySlovakiaEng.pdf)

<sup>448</sup> <http://www.degruyter.com/view/j/afpuc.2013.60.issue-supplementum8/issue-files/afpuc.2013.60.issue-supplementum8.xml>

<sup>449</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-slovakia.pdf>

Diseases<sup>450</sup> is designed to serve as a roadmap until 2020 and is qualified as “... an opportunity for better coordination of efforts of all partners involved, establishing health care that will be comprehensive, accessible, timely and patient-focused”. The major objectives of the plan centre around the identification and monitoring of rare diseases; improving early diagnosis and access to appropriate medical treatments; mechanisms to improve an integrated approach to rare diseases; and improving access to information for patients, the general public, and professionals. Amongst identified actions include the establishment of a national registry for rare diseases; establishment of national reference centres integrated with international networks; examining cross-border cooperation for genetic testing and other services; introducing a system of evidence-based clinical guidelines; defining orphan drug policy and developing decision guidelines for competent authorities; identifying additional funding sources for orphan drugs; establishing an umbrella organisation of patient groups; and establishing a national centre for rare diseases in the country.

The Center of Undiagnosed Rare Diseases (CURD) and Center for Mendelian genomics (CMG) have been introduced at the Clinical Institute of Medical Genetics (CIMG), UMCL. CURD serves as a central referral point of patients which need further diagnostic (genetic) evaluation for professionals. The CMG serves as a national and regional center for clinical application of next generation sequencing in clinical practice; medical procedures in this Centre are already covered within the public health system.

CIMG leads the SIGN (Slovenian Italian Genetic Network) crossborder initiative which aims at improvement to the access to diagnosis, therapy and rehabilitation of patients with genetic disorders in the region.

Cancers are separate working area in Slovenia and have not been included in work in the RD field.

Emergency cards for patients with congenital adrenal hyperplasia have been available for the past 25 years.

### **Centres of expertise**

There are no official centres of expertise in Slovenia, but the majority of patients with rare diseases in Slovenia are evaluated centrally at the University Medical Centre Ljubljana (UMCL) where there is an efficient system for the referral of genetic, endocrine, metabolic, and neurodegenerative disorders, amongst others. In addition to this, there is a Centre for Fabry disease in Slovenj Gradec. The establishment of centres of expertise is foreseen in the national plan for rare diseases.

### **Registries**

There is currently no national registry for rare diseases in Slovenia. A new Healthcare Databases Act, which sanctions the establishment of national registries, is under preparation, and the inclusion of registries in the area of rare diseases is expected. There is a plan to establish a national register for rare diseases.

Slovenia contributes to the EUROCARE CF European registry and RARECARE registry.

### **Neonatal screening policy**

Neonatal screening is available for phenylketonuria and congenital hypothyroidism. A screening policy is also in place for hearing impairments and developmental dislocation of the hip.

### **Genetic testing**

Genetic testing is offered to patients when there is an indication to perform such tests recognised by a medical specialist. While there are no formally established reference centres in Slovenia, the Institute of Medical Genetics at the University Medical Centre in Ljubljana is the tertiary institution in this area. There are no specific national guidelines regulating genetic testing, those that are deemed necessary are financed by the Health Insurance Institute of Slovenia.

Genetic testing is offered through few specialised laboratories and a tertiary laboratory at the Clinical institute of Medical Genetics (CIMG), UMCL. CIMG offers genetic testing for most of the currently known monogenic genetic disorders, offers panel as well as exome DNA testing in the clinical setting.

Genetic testing abroad is possible, however resources are limited.

Genetic tests are registered for 62 genes and an estimated 72 diseases in the Orphanet database<sup>451</sup>.

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<sup>450</sup> [http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke\\_bolezni\\_2012\\_-\\_nacrt\\_dela/Nacrt\\_dela\\_na\\_podrocju\\_redkih\\_bolezni.pdf](http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf)

<sup>451</sup> Data extracted from Orphanet in January 2014.

### **National alliances of patient organisations and patient representation**

There is currently no national alliance of rare disease patient organisations in Slovenia. Patient organisations are financed through different sources: this may include funding from the government/public sector and the private sector (private sponsorships and donations). The Ministry of Health financially supports some programmes within patient organisations through calls for project proposals: the aims of these calls vary.

The role of patient organisations is recognised in national plan. Patient organisation representatives are usually consulted concerning legislative proposals and in some cases are included in the process of drafting legislation. Patient organisation representatives do not usually receive financial support in order to attend these meetings.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Slovenia***

Since 2006 there is a dedicated Orphanet team in Slovenia, currently hosted by the Institute of Medical Genetics at the University Medical Centre Ljubljana. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was designated by the Ministry of Health in 2010 as the official Orphanet team in Slovenia. The team launched in 2011 the Orphanet Slovenia national website<sup>452</sup>. Currently the Orphanet national team receives no funds through national plan. There are plans to include national Orphanet in financing.

#### ***Official information centre for rare diseases***

There is no official information centre for rare diseases in Slovenia other than Orphanet at the moment. Establishment of national contact point for patients and professionals to get some extensive information on rare diseases diagnosis and treatment is foreseen in 2014. The Centre for Undiagnosed Rare Diseases is organised as a medical service and financed through genetic program allocated to CIMG.

#### ***Help line***

There is currently no information help line for rare diseases in Slovenia; it is foreseen though within the national information contact point.

#### ***Other sources of information on rare diseases***

Information on rare diseases is available on some institutions' web sites, and web sites run by patient organisations.

### **Guidelines**

The national clinical guidelines are available for the 4 inborn errors of metabolism which are treated with enzyme replacement therapy (Fabry disease, Pompe disease, MPS II and VI). Slovenia has not elaborated emergency guidelines for rare diseases; however they are roughly summarised in the chapter concerning inborn metabolic diseases in a new text book of Paediatrics<sup>453</sup>, issued in 2013.

### **Training and education initiatives**

No specific activity reported.

### **National rare disease events in 2013**

The Association of patients with blood diseases organised a meeting on rare disease day in February 2013.

### **Hosted rare disease events in 2013**

The 10th Balkan Congress of Human Genetics and 2nd Alps Adria Meeting on Human Genetics (10-12 October 2013, Bled) was organised.

### **Research activities and E-Rare partnership**

#### ***National research activities***

The Slovenian Research Agency is a government body which awards grants for research. Although not specifically aimed at rare diseases, in the past rare disease topics have been given research grants.

<sup>452</sup> <http://www.orpha.net/national/SI-SL/index/domov/>

<sup>453</sup> <http://www.dzs.si/artikel/9789610202943+++1/pediatrija-?folderId=10232173>

### **Participation in European projects**

Research teams in Slovenia have participated/participate in 8 FP7 rare disease related projects.

#### **E-Rare**

Slovenia is not currently a partner of the E-Rare project.

#### **IRDIRC**

Slovenian funding agencies have not yet committed funding to the IRDiRC.

### **Orphan medicinal products**

#### **Orphan medicinal product committee**

In Slovenia, orphan medicinal products are included in public funding in the same manner as any other drug. A decision on their financing from public funds is adopted by a commission of experts in the field of medicine and pharmacy within the Health Insurance Institute of Slovenia. Additionally a Strategic Council for Drugs operates within the Ministry of Health. It is responsible for policy and funding availability of medicinal products - particularly expensive drugs, including orphan medicinal products. In 2012 The Health Insurance Institute of Slovenia put on positive hospital list both orphan medicinal products: clofarabine (Evoltra) and busulfan (Busilvex) that were in 2011 covered by additional funding. The Strategic Council for Drugs in 2012 provided additional government budget funds of 794.537,00 € to finance two orphan medicinal products: eculizumab (Soliris) for 2 patients and idrusulfase (Elaprase) for 1 patient.

#### **Orphan medicinal product incentives**

In Slovenia, there are several measures concerning national incentives for orphan medicinal products according to the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*, including "reduced fees for marketing authorisation procedure (if the centralised procedure was not followed)<sup>454</sup>."

#### **Orphan medicinal product market availability situation<sup>455</sup>**

The orphan medicinal products launched on the market up to the end of 2013 were: Adcetris, Afintor, Arzerra, Busilvex, Cayston, Cystadane, Dacogen, Diacomit, Elaprase, Evoltra, Exjade, Fabrazyme\*, Firazyr, Glivec\*, Jakavi, , Litak, Lysodren, Mozobil, Myozyme, Naglazyme, Nexavar, Nplate, Pedea, Peyona, Replagal\*, Revatio, Revlimid, Revolade, Savene, Signifor, Soliris, Somavert\*, Sprycel, Sutent\*, Tasigna\*, Tepadina, Thalidomide, Tobi Podhaler, Torisel, Tracleer\*, Ventavis\*, Vidaza, Volibris, Votubia Vpriv\*, Wilzin, Xyrem\*, Yondelis, Zavesca.

#### **Orphan medicinal product pricing policy**

Pricing of orphan medicinal products is subject to the same procedure as other medicinal products, which are financed from public funds. Determination of maximum prices is the responsibility of the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP), whereas the Health Insurance Institute of Slovenia negotiates prices that are lower than those set by JAZMP. The latter sets the maximum prices taking into account those set in a selection of EU countries (Germany, France and Austria).

#### **Orphan medicinal product reimbursement policy**

In Slovenia, one of the criteria for including a drug among those covered by health insurance is an "ethical criteria" which applies in particular to severe and rare diseases: this has a positive influence on the accessibility of drugs for rare diseases patients.

All orphan medicinal products are covered mainly by compulsory health insurance and some partly by complementary health insurance, without the need for any co-payment by the patient.

The expenditure for orphan medicinal products increased by 44,9 % from 2010 to 2012, whereas total expenditure for other drugs was in 2012 lower in comparison to 2010 due to systematic price regulation.

#### **Other initiatives to improve access to orphan medicinal products**

In Slovenia, there are several measures concerning national incentives for orphan medicinal products according to the *Inventory of Community and Member States' incentive measures to aid the research, marketing,*

<sup>454</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (p19)

<sup>455</sup> (\*): medicinal products available in 2013 which are no longer included in Register of designated Orphan Medicinal Products at EU level.

development and availability of orphan medicinal products, including “permission to use medicines labelled in any EU language with stickers in Slovenian language; [and] negotiation on drug prices.”<sup>456</sup>”

#### **Other therapies for rare diseases**

In Slovenia other therapies for rare diseases are also available, for example: implantation of subdermal pump for treatment of epilepsy, surgical corrections of rare inborn heart defects, cranial synostosis, inborn facial defects and transplantation of hematopoietic stem cells.

#### **Orphan devices**

No specific information reported.

#### **Specialised social services**

Some respite care services are available in Slovenia for patients with disabilities, and are provided by governmental and non-governmental organisations with either government or private financing. Some services are available in Slovenia for patients with disabilities. Therapeutic recreational programmes are available for patients with disabilities in Slovenia, and are provided by governmental and non-governmental organisations with government and private financing. Services are in place promoting the social integration of patients with disabilities in the workplace: most activities are provided through government institutions.

## **RARE DISEASE ACTIVITIES IN 2013 IN SLOVENIA**

#### **National plan/strategy for rare diseases and related actions**

In 2012 a national plan for rare diseases was accepted by the Health Council and the next steps will be to elaborate an action plan and its implementation, as well as to identify funding. The Work Plan for Rare Diseases<sup>457</sup> is designed to serve as a roadmap until 2020 and is qualified as “... an opportunity for better coordination of efforts of all partners involved, establishing health care that will be comprehensive, accessible, timely and patient-focused”.

The Center of Undiagnosed Rare Diseases (CURD) and Center for Mendelian genomics (CMG) have been introduced at the Clinical Institute of Medical Genetics (CIMG), UMCL. CURD serves as a central referral point of patients which need further diagnostic (genetic) evaluation for professionals. The CMG serves as a national and regional center for clinical application of next generation sequencing in clinical practice; medical procedures in this Centre are already covered within the public health system.

CIMG leads the SIGN (Slovenian Italian Genetic Network) crossborder initiative which aims at improvement to the access to diagnosis, therapy and rehabilitation of patients with genetic disorders in the region.

#### **Centres of expertise**

The establishment of centres of expertise is foreseen in the national plan for rare diseases.

#### **Registries**

A new Healthcare Databases Act, which sanctions the establishment of national registries, is under preparation, and the inclusion of registries in the area of rare diseases is expected. There is a plan to establish a national register for rare diseases.

#### **Sources of information on rare diseases and national help lines**

##### **Orphanet activities in Slovenia**

Currently the Orphanet national team receives no funds through national plan. There are plans to include national Orphanet in financing.

<sup>456</sup> *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products* (2005 revision) (p19)

<sup>457</sup> [http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke\\_bolezni\\_2012\\_-\\_nacrt\\_dela/Nacrt\\_dela\\_na\\_podroczju\\_redkih\\_bolezni.pdf](http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podroczju_redkih_bolezni.pdf)

### **Official information centre for rare diseases**

Establishment of national contact point for patients and professionals to get some extensive information on rare diseases diagnosis and treatment is foreseen in 2014. The Centre for Undiagnosed Rare Diseases is organised as a medical service and financed through genetic program allocated to CIMG.

### **Help line**

There is currently no information help line for rare diseases in Slovenia; it is foreseen though within the national information contact point.

### **Guidelines**

Slovenia has not elaborated emergency guidelines for rare diseases; however they are roughly summarised in the chapter concerning inborn metabolic diseases in a new text book of Paediatrics<sup>458</sup>, issued in 2013.

### **National rare disease events in 2013**

The Association of patients with blood diseases organised a meeting on rare disease day in February 2013.

### **Hosted rare disease events in 2013**

The 10th Balkan Congress of Human Genetics and 2nd Alps Adria Meeting on Human Genetics (10-12 October 2013, Bled) was organised.

## **1.26. SPAIN**

### **Definition of a rare disease**

Spain accepts the definition of the "Community Action Programme on Rare Diseases (1999-2003)" of a rare, minority, orphan or uncommon diseases as a life-threatening or chronically debilitating diseases with a prevalence of less than 5 cases per 10 000 inhabitants.

### **National plan/strategies for rare diseases and related actions**

The first national initiative taken in relation to rare diseases was the creation of the Toxic Oil Syndrome Research Centre (Centro de Investigación sobre el Síndrome del Aceite Tóxico, CISAT), of the Carlos III Health Institute (Instituto de Salud Carlos III, ISCIII), in 1996. The CISAT, became the Toxic Oil Syndrome and Rare Diseases Research Centre (Centro de Investigación del Síndrome del Aceite Tóxico y Enfermedades Raras, CISATER) by Ministerial Order of 27 December 2001. One of the initiatives undertaken by the CISATER led to the creation of the first Spanish Rare Diseases Information System (Sistema de Información de Enfermedades Raras de España, SIERE). In 2003, the Carlos III Health Institute created, the Institute of Rare Disease Research (IIER) to be worth at the structure of Health system<sup>459</sup>. The tasks assigned to the aforementioned centre were those of maintaining and supporting the development of research and of implementing a National Research Programme in that field.

In 2012, the ISCIII has reinforced the Institute of Rare Diseases Research (IIER) with a new Human Genetic Brand, which is developing rare diseases research initiatives in iPCs development, searching new orphan drugs and looking for new diagnosis tests.

In 2006, the Centre for Biomedical Network Research on Rare Diseases (CIBERER) was created in order to act as a reference, coordinate and foster research on rare diseases in Spain. The CIBERER is one of the nine consortia of research created by the ISCIII to encourage the research of excellence in biomedicine and sciences inside the NHS. The CIBERER is oriented towards the development and implementation of cooperative research in the field of rare diseases, favouring basic, clinical and epidemiological biomedical research, placing special emphasis on transferring the research from the laboratory to the patient's bedside and scientifically responding to the questions that arise from the interaction between physician and patient<sup>460</sup>.

<sup>458</sup> <http://www.dzs.si/artikel/9789610202943+++1/pediatrica-?folderId=10232173>

<sup>459</sup> <http://www.boe.es/boe/dias/2003/11/14/pdfs/A40101-40103.pdf>

<sup>460</sup> <http://www.boe.es/boe/dias/2011/02/22/pdfs/BOE-A-2011-3539.pdf>

A centre for rare diseases in Burgos, Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias de Burgos (CREER) -“State Reference Centre for Rare Diseases Patients and their Families”)- was inaugurated on 30 September 2009 by the Spanish Ministry of Health, Social Services and Equality. This centre has the following missions, amongst others: coordination, research, innovation, professional training, dissemination of information and awareness raising and support to other Spanish organisations. CREER can accommodate up to 60 people distributed in 12 family flats and additional day care places with the aim of providing integral care following the recommendations of the EU. CREER will also play an important role anticipating respite programmes for the families, promoting the mutual knowledge and exchange of experiences between patients and families and providing information training concerning welfare policy, as well as social and health care. All areas are coordinated to feed into one another: new knowledge is applied to improve care and quality of life of people with rare diseases and their families.

### ***Rare Diseases Strategy of the Spanish National Health System (2009)***

In 2008 the Spanish Senate launched an official declaration after reaching a general agreement by all political parties where a strong recommendation regarding rare diseases actions was addressed to the Government of Spain. At the beginning of 2008, the Ministry of Health began to work on a National Strategy on Rare Diseases creating two committees (a Technical Committee made up of 15 scientific societies and 3 patient organisations and an Institutional Committee made up of the representatives appointed by the Health Departments of the Autonomous Communities”) which developed the contents of the Strategy. The Rare Diseases Strategy of the Spanish National Health System was approved by the Interterritorial Council of the Spanish NHS on 3 June 2009<sup>461</sup>. The elements defined in the Spanish strategy allow for the fulfilment of the recommendations established by the European Council Recommendation on an Action in the Field of Rare Diseases.

The Strategy is structured into three parts. The first part, ‘General aspects’, includes the justification, the purposes of the Strategy (its mission, principles, the values it inspires), the definition of rare diseases and their situation in Spain.. Finally, it sets out the strategy development methodology. The second part, ‘Development of strategic lines’, sets out the objectives and recommendations. The participants of the Strategy decided, by consensus, to establish the following strategic lines: information on rare diseases, prevention and early detection, healthcare, therapies, integrated health and social care, research and education/training. The third part, Monitoring and Evaluation, sets out the process that makes it possible to monitor the proposed actions. The strategic lines are broken down into 13 general and 37 specific objectives, with their respective technical recommendations and monitoring and evaluation indicators. Given the decentralised health administration of Spain in the Regional Governments (the Strategy will act as a framework and a set of recommendations for the different regions, which will in turn be in charge of implementation. Funds were allocated through a call for proposals opened to the Regional Governments in order to facilitate the implementation of the Strategy. The Strategy for Rare Diseases as well as any other related measures or actions aimed at rare diseases are included in the Spanish National Health Budget.

The first strategy’s assessment focused mainly on the implementation of the Strategy over the first two years, although it is too soon to measure health results, this process helped to update recommendations and objectives after consultation with the Stakeholders.

The main achievements have been, amongst others: the establishment of the National Registry for Rare Diseases, availability of an inventory of services and tests of prenatal diagnosis and derivation protocols for pregnant women at risk or foetal RD, to raise awareness and recognition of rare diseases, and to promote socio-health care and research for children under three with rare diseases. Moreover, the evaluation has also showed that it is necessary to implement actions aimed at collecting and disseminating information and resources available on rare diseases, to increase training of primary care professionals on suspected diagnosis of rare diseases and to establish adequate criteria for referral, to improve the availability of basic health information to the teaching staff that attends children with rare diseases, to develop initiatives of joint coordination and planning for the adaptation of jobs and for the management of the reintegration and continued employment of family members of persons affected by rare diseases, to carry out initiatives to facilitate keeping persons with rare diseases in their surroundings such as home care services, home hospitalisation, day centres, and so on, to develop integration activities in the community (leisure activities) for those with rare diseases, and to promote participation of patients associations in participation-decision bodies in the area of health of the Regional Governments.

The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government expects to raise knowledge and awareness for rare conditions,

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<sup>461</sup><http://www.msc.es/organizacion/sns/planCalidadSNS/docs/RareDiseases.pdf>



and establish stronger ties of mutual support. The operation focused on the health, research and social perspective of rare diseases<sup>462</sup>.

During 2013 updating update of the objectives and recommendations of the strategy on rare diseases of the NHS was carried out by all the stakeholders reaching an agreement. It is currently pending approval by the Interterritorial Council of the NHS.

One of the activities proposed for the year 2013 was the creation of a map of expert units in rare diseases to facilitate access to the information of the activity carried out in different hospitals in Spain in relation to the RD; to facilitate access to information for citizens, decision-makers and health professionals to establish networks.

The work procedure has been developed in the framework of the strategy on rare diseases of the NHS and was approved by the Interterritorial Council of the SNS on 21 March 2013.

The Interterritorial Council of the NHS approved on 21 March 2013 a common procedure for the good practices (BBPP) identification in the NHS. An ad hoc group was created in the framework of the strategy on rare diseases of the NHS to adapt the common criteria and the assessment tool approved by the CISNS to the field of rare diseases and to evaluate all experience collected. 69 experiences proposals were collected and evaluated for the evaluation group and 8 of them obtained the good practice title and stamp.

A campaign to raise awareness concerning RD was defined by the Ministry of Health and was published on the Internet on 21 October and lasted until 3 November. The Ministry of Health planned a total of 5.092.650 spots that appeared in the main sites of digital newspapers and sites of television.

A specific training course on disabilities in rare diseases for professional evaluators was organised. This course was coordinated by the CREER.

In October 2013 the Ministry of Health, Social Services and Equality organized a scientific meeting "Conocer la rareza, mejorar nuestras vidas. Presente y retos futuros de las enfermedades raras: traslación clínica de la investigación".

Also among the actions of awareness-raising, to understand the characteristics of these diseases, improve the situation of affected families and promote networks of collaboration and mutual support, the international day of families of 2013 was devoted to relatives of persons with rare diseases.

In October 2013 the Ministry of Health, Social Services and Equality signed a collaboration agreement with the President of RTVE Corporation to broadcast the Telethon of the Spanish year of the rare diseases. This event took place on 2 March 2014 and the income will be allocated to research for rare diseases.

### **Regional initiatives**

Before the launch of the Rare Diseases Strategy of the Spanish National Health System in 2009, some regional initiatives had already been put in place. The Regional Government of Andalusia created a genetics plan, (*Plan de Genética de Andalucía 2006-2010*), which, in turn, led to the creation of the *Plan de Atención a Personas Afectadas por ER 2008-2012*, a plan concerning care for people affected by rare diseases.

The Extremadura Autonomous Community approved in December 2010 its Plan Integral de Enfermedades Raras 2010-2014 based on general recommendations from Europe and the Spanish National Strategy. The Health Department of the Regional Government of Catalonia approved an Order for the creation of an Advisory Commission on rare diseases in 2009, with the aim of enhancing the implementation of specific health policies aimed at these pathologies, some of which are already included in Catalonia's different existing master plans (on integrated health and social care, mental health, oncology, etc.).

Also, the Regional Government of País Vasco has developed a *Plan de acción de la estrategia de enfermedades raras en la comunidad* in 2011 and this region has approved an Order for the creation of an Advisory Commission on Rare Diseases in 2012.

All regions have been collaborating in the National RD Registry. They contributed to the standardisation of procedures and methods and also in the development of the pilot study. At the end of 2013 they began with the collection of cases from 2010-2012.

### **Centres of expertise**

The legal base for designating reference centres, departments and units (RCDUs) in Spain is the Spanish National Health Service (SNS) Cohesion and Quality Act (16/2003). It sets out the legal framework for coordination and cooperation between public health authorities in the exercise of their respective functions and defines reference services that require the centralization of cases in a small number of centres for their

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<sup>462</sup> <http://www.msc.es/gabinete/notasPrensa.do?id=2611>

best management and to guarantee equitable access to high-quality, safe and efficient health care for patients affected by conditions that require highly specialised care.

In Spain, Royal Decree 1302/2006 establishes the procedure and principles for the designation and accreditation of the Reference Centres, Departments and Units (CSUR) of the Spanish NHS. It defines the characteristics to be met by diseases or groups of diseases in order to have a designated CSUR:

- a. Diseases that for their adequate care require preventive, diagnostic and therapeutic techniques, technologies and procedures of a *high level of expertise* requiring experience in their use, which can only be acquired and maintained through certain volumes of activity;
- b. Diseases that require *high technology* for their prevention, diagnosis or treatment and for which, in view of their cost-effectiveness and the available resources, the concentration of a minimum number of cases is required;
- c. *Rare diseases* which, because of their low prevalence, require a concentration of cases for their adequate care, which does not imply the ongoing care of the patient in the reference centre, service or unit, but rather that the latter can act as a support for diagnostic confirmation, the definition of therapeutic strategies and follow-up strategies and as an adviser for the clinical units that usually treat those patients.

The entire procedure for the designation of CSUR is formulated through the CSUR Designation Committee from the Spanish NHS, that was set up in 2006 and it is composed of the representatives from the different Regional Governments, the Ministry of Health, Social Services and Equity, National Transplant Organisation (ONT) and the Healthcare Technologies Assessment Agency and which reports and submits proposals to the Interterritorial Council. The tasks of the Designation Committee are: to study the needs and propose the pathologies or the diagnostic or therapeutic techniques, technologies and procedures for which a CSUR needs to be designated; to propose the procedure for the designation and accreditation of a CSUR and to report on it; to assess the designation applications received and make designation proposals to the Interterritorial Council; to study and propose the renewal/revocation of the designation of CSUR; and to establish the procedure for the referral of users.

Given that it was difficult to deal with all the different areas of specialisation at the same time, work is underway with groups of experts, designated by the Autonomous Communities, the Scientific Societies and the Ministry of Health, Social Services and Equality. These groups are making a proposal of the diseases or procedures for which it is necessary to designate CSUR and the criteria to be met by these in order to be designated as of reference. Since July 2007, the Interterritorial Council has agreed to 46 pathologies or procedures for which it is necessary to designate CSUR in the Spanish NHS, as well as, the criteria that these shall meet to be designated as reference.

Among these pathologies and procedures, all of them of low-prevalence, there are some concerning rare diseases such as the following:

- Reconstruction of the outer ear
- Congenital glaucoma and glaucoma in childhood
- Congenital disorders of eye development (alterations of the eyeball and eyelids)
- Extraocular Tumours during Childhood (Rhabdomyosarcoma)
- Intraocular Tumours during Childhood (Retinoblastoma)
- Penetrating keratoplasty in children
- Children's transplants (kidney, intestine, liver, heart, lung)
- Allogenic transplant in children from hematopoietic parents
- Child Orthopaedics: Orthopaedic treatment in neuromuscular diseases (cerebral palsy, myelomeningocele), congenital malformations (congenital short femur, tibiofibular agenesis), bone dysplasia (imperfect osteogenesis) and great lengthening of members
- Comprehensive care of the neonate with congenital heart disease and children with complex congenital heart disease
- Family heart disease (includes hypertrophic cardiomyopathy).
- Hereditary ataxia and paraplegia
- Paediatric Arrhythmology and Electrophysiology
- Refractory Epilepsy
- Complex Paediatric Neurosurgery
- Metabolic congenital diseases
- Neuromuscular diseases and rare diseases of motoneuron different to ALS

- Genetic neurocutaneous syndromes (Facomatosis)
- Rare diseases that occur with disorders of movement.
- Amyotrophic lateral sclerosis
- Complex upsets of the autonomic nervous system

Once the criteria have been agreed a period of CSUR application is opened, and the Regional Governments can present their proposals through the Designation Committee. Once they have been admitted for processing, the audit and accreditation process starts. After the respective accreditation reports have been received, the Designation Committee studies them and submits its proposals for designation, or non-designation, to the Interterritorial Council. The Ministry of Health, Social Services and Equality, at the suggestion of the Designation Committee and with the prior consent of the Interterritorial Council, decides on the designation of the CSUR for a maximum period of 5 years. Before that period has terminated the designation is renewed, provided that the re-evaluation is satisfactory.

Some official centres of expertise for rare diseases have already been designated by this procedure. Up to now, the Interterritorial Council and the Ministry of Health, Social Services and Equality have agreed to designate 186 CSUR, in 44 centres in Spain, for 44 pathologies or procedures, including some related to rare diseases. Around 78 of these CSUR are related to rare diseases.

At the same time, work continues in other areas of specialisation to define all the diseases and procedures, among them those related to rare diseases, which should be carried out in CSUR. Since 2001, FEDER (The Spanish Federation for Rare Diseases) has been working in the CSUR project with regard to rare diseases, by providing professionals to participate in the groups of experts related to rare diseases.

They are currently in phase of accreditation of the Autonomous Region's proposals related to: Arritmology electrophysiology and paediatrics, Metabolic Congenital Diseases, Genetic neurocutaneous syndromes (Phakomatosis), rare diseases concerned with movement disorders and complex disorders of the autonomic nervous system.

Work is currently being carried out on the definition of the criteria for designation of centres, services and Reference Units of the National Health System for rare cancers and pulmonary hypertension.

Work is continuing on the identification of diseases and procedures for which there is a need a CSUR in the NHS, still expected to finish such identification in 2014.

All the information related to the project CSUR for the NHS is available on the website of the Ministry of Health, Social Services and Equality.

Reference services are monitored annually. An information system is in place to report on how the activities performed comply with the designation criteria and meet the procedure and result indicators that were included in the designation criteria. The definition of these procedures and result indicators by the corresponding expert groups and units and services designated (agreed by the Interterritorial Council) is very complex, due to the diversity of diseases and procedures, considering that every disease and procedure has its own information system.

Currently, the annual follow-up of 177 CSUR of the NHS is being carried out. These CSUR cover 35 diseases and procedures, and they have been operating during 2009-2013. Each year collected data and indicators are analysed by professionals from CSUR and expert groups in each area of expertise, and if required, appropriate improvements are introduced.

All information concerning the CSUR project is available for health professionals and patients in the Web of the Ministry of Health, Social Services and Equality (MSSSI).

During 2014 the MSSSI will be involved in the implementation of European Reference Networks (ERN) in the context of the Directive of Cross Border Health Care.

## Registries

The Spanish Network of Rare Diseases Research on Epidemiology (REpIER) was created in June 2003 and analysed the existing rare diseases registries in Spain as of 2005. It concluded that the identified registries did not fit the standard criteria for epidemiological surveillance except for those population based registries which were mainly focused on rare cancers. Most of the registries defined as rare diseases registries were hospital case series intended for clinical studies' development. In 2007 the ISCIII decided to start designing a rare diseases national registry at its Institute of Rare Diseases Research (IIER). A Spanish patient's registry for rare diseases including several and different approaches and programmes has been developed and is online as of 2009. The Institute of Rare Diseases Research (IIER), belonging to ISCIII, is currently in charge of this registry. The Spanish Rare Diseases Registries Research Network is a €2.4 million project financed by the Institute of Health Carlos III (ISCIII) for 2011-2014. This project involves all Health Departments of the Autonomous

Communities (regions) of Spain, the Institute of Rare Diseases Research (IIER) which acts as a coordinator and leader of the network, the Spanish Ministry of Health, the Spanish Centre of Reference of People and Families affected by RD (CREER<sup>463</sup>), six Spanish Medical Societies, four research networks, pharmaceutical and biotechnological organisations (ASEBIO<sup>464</sup> and FARMAINDUSTRIA<sup>465</sup>), and the Spanish Federation of RD (FEDER<sup>466</sup>) and its foundation (FEDER TELETHON FOUNDATION). The main objective is to develop the National and Regional Registry for rare diseases based on methods for both population-based registries and patient outcomes registries. Industry, patient's organisations, foundations and more than 6 medical societies have signed agreements with the ISCIII to contribute to this national registry and cooperate with the IIER.

At regional level, Extremadura has run a population-based registry on rare diseases since 2004. All regions except Galicia have been developing their own legal framework since 2011 in order to set up regional rare diseases population-based which can collaborate with SpainRDR.

Several RD patient registries are being integrated into the central repository of the National RD Registry. At the same time, a preliminary agreement has been reached between SpainRDR and REDECAN, the network of population-based for cancer registries in order to collaborate in the process of rare cancer registration. Currently, SpainRDR is collecting prevalence cases corresponding to the period 2010-2012. A standardized mapping of codifications between ICDs, Orphacodes, SNOMED and OMIM is used. Common Data Elements, Standardised Operating Procedures, ELSI rules and methods for statistical analysis and reporting have been already developed.

In Spain, there are several population based cancer registries which officially report to the International Agency of Research Cancer of the WHO. Since REPIER was put in place, a specific working group was set up for this particular group of rare diseases as well as for congenital malformations. Both groups are working in collaboration with European and international networks (including EUROCAT) and participate in several European projects.

Spain also contributes/contributed to the following European registries: EUROCAT, ERCUSYN, EUGINDAT-PIADATABASE, EIMD, ESID, EURO-WABB, MOLDIAG-PACA, AIR, SCNIR, EURO CARE CF, ENERCA, TREAT-NMD, NPDR and EUROMAC, BURQOL-RD, EPIRARE, RD-CONNECT, Rare-Bestpractices, EUROPLAN2, COST on ASD Early Detection.

### Neonatal screening policy

National neonatal screening is currently in place for phenylketonuria and hypothyroidism congenital hypothyroidism, phenylketonuria, cystic fibrosis, deficiency of acyl Coenzyme A deshydrogenada medium-chain (MCADD), deficiency of 3-Hydroxy acyl-CoA Dehydrogenase, long-chain (LCHADD), glutaric acidemia type I (GA-I) and sickle cell anemia.

The incorporation of this population program of neonatal screening into the basic common portfolio of NHS services will be accompanied by the development of:

- An information system of neonatal screening at regional and State level allow proper monitoring and evaluation of the population programme.
- A system of quality management that allows addressing homogeneously in all autonomous communities' screening processes, so it is essential to the elaboration of agreed protocols and their implementation in the NHS.

At the beginning of this process, on 18 December 2013 the CISNS adopted the document "Objectives and quality requirements of the Neonatal screening of metabolic diseases of the SNS program": in this document quality objectives are defined for each of the stages of the program and the necessary or recommended requirements for achieving them.

A working group with representatives from the Ministry of Health, and the Regional health services, reviewed scientific evidence and will produce a report and recommendations about population screening programs for the National Health System<sup>467</sup>.

Also, the Spanish Network of Agencies for Health Technology Assessment and Benefits of the National Health Service has developed several reports on effectiveness and cost-effectiveness of the neonatal screening programme for some rare diseases.

<sup>463</sup> [http://www.creenfermedadesraras.es/creer\\_06/index.htm](http://www.creenfermedadesraras.es/creer_06/index.htm)

<sup>464</sup> <http://www.asebio.com/es/index.cfm>

<sup>465</sup> [http://www.farmaindustria.es/Farma\\_Public/index.htm](http://www.farmaindustria.es/Farma_Public/index.htm)

<sup>466</sup> <http://www.enfermedades-raras.org/>

<sup>467</sup> A document on screening in general (neonatal and cancer screening) was elaborated in 2010 : "Documento marco sobre cribado poblacional" elaborated by the Comisión de Salud Pública del Consejo Interterritorial del SNS (2010) (Committee for Public Health of the Interterritorial Council of the National Health System) (2010)

### **Genetic testing**

The Spanish Law 14/2007 on Biomedical Research, which considers genetic testing in research and care, stipulates that when carrying out a genetic analysis for health purposes “the interested party must be guaranteed appropriate genetic counselling”. Since the early 1970s genetic counselling in Spain has been provided by specific hospital services, although in the case of inherited metabolic diseases that task was usually carried out by the actual paediatrician or by the diagnostic laboratory. Usually the genetic services offer cytogenetic, molecular genetic and biochemical genetic tests (in the case of inherited metabolic diseases) as well as genetic counselling. These services are provided by health professionals: medical staff, highly qualified non-medical staff, nursing staff and laboratory technicians; and the genetic counselling is usually done by highly qualified staff. The basic training of these health professionals varies, and they may well come from different specialties.

In Spain, genetic diagnostics and counselling are disciplines which, initially, were associated with activities in hospital environments. In the Spanish NHS those activities are currently carried out by different professionals who have been trained and who have acquired experience in these areas.

As regards patients’ access to genetic testing and counselling, in Spain “referral of patients for genetic testing is nearly exclusive of hospitals and specialised care. It can also be performed for clinical reasons or as part of a research protocol”, according to the conclusions of a study carried out by the Institute for Prospective Technological Studies (IPTS).

The Spanish Law 14/2007 on Biomedical Research defines “genetic testing” as the “procedure to detect the presence or absence of, or change in, one or more segments of genetic material, including indirect tests for the detection of a gene product or other specific metabolite that is primarily indicative of a specific genetic change”. It is estimated that tests are currently available for more than 1000 genetic diseases. Nevertheless, their clinical use has been limited for several reasons. At times there are no external quality assessment services and at others insufficient data is available for their interpretation and validation. But the protocols and guidelines of best practices applicable to each case must always be taken into account, as must the legislative framework in which the genetic testing must be performed, whether for research or in the health system (Spanish Law 14/2007 on Biomedical Research).

At the present time, the MSSSI is working together with Regional Governments and Scientific Societies defining the genetic portfolio of services for the NHS and HTA agencies which are involved in the description of the Spanish map of genetic test offered by the NHS.

Genetic tests for 1635 genes and an estimated 1855 diseases are registered in the Orphanet database<sup>468</sup>.

### **National alliances of patient organisations and patient representation**

FEDER, the Spanish Rare Disease Federation, was established in 1999 as a non-governmental organisation (NGO). Currently, FEDER with its 190 members is recognised as an umbrella organisation for the 3 million people with rare diseases in Spain and their families. Several services to patients have been developed, funded by public and private, national and regional funds. FEDER has been very active in advocating for an Action Plan in different National Conferences (2005, 2006), as well as participating in the Technical Committee of the Ministry of Health, Social Services and Equality for the development of the National Strategy for Rare Diseases. Apart from this, FEDER is active at European level, present on the EURORDIS board and participating in many European projects at national level. FEDER is a member of the Spanish Committee of Disabled (CERMI) and the Spanish Patients’ Forum and is usually represented at regional level at the Health Councils. Support for patient organisations is provided by private and public (Labour Ministry and Ministry of Health) funds and organisations for patients with disabilities are also supported by the IMSERSO (Ministry of Health, Social Services and Equality).

FEDER has developed several specific agreements with CREER in order to improve the collaboration and the empowerment of FEDER patient’s organisation and has also signed a Framework Agreement with CIBERER. On the other hand, FEDER and the ISCIII have signed a new agreement to promote and collaborate with the IIER in the development of RD patient registries. In the same way, the ISCIII has signed an agreement with the patient organizations of people with intellectual disability (FEAPS) and with the Spanish Association of Professionals working with the Autistic Spectrum Disorders (AETAPI) aimed to improve the diagnosis, RD registries and training of professionals working with this important group of people affected by RD.

In 2012, FEDER organised the collection of used mobile phones to go towards fundraising for rare diseases.

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<sup>468</sup> Data extracted from Orphanet in January 2014.

Other National alliances that in the Technical Committee of the Ministry of Health, Social Services and Equality for the development of the National Strategy for Rare Diseases are the Federación Española de Enfermedades Neuromusculares (Spanish Federation of Neuromuscular Diseases), and la Federación Española de Fenilcetonuria y Otros Trastornos del Metabolismo (Spanish Federation of Phenylketonuria and Other Methabolic Disorders).

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Spain***

Since 2002, there is a dedicated Orphanet team in Spain, currently hosted by CIBERER. This team is in charge of collecting data on rare diseases related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was designated by the Ministry for Health, Social Policy and Equality in 2010 as the Orphanet team in Spain. The Orphanet portal is available in Spanish and the national team maintains a national Orphanet Spain website<sup>469</sup> in Spanish providing extra socio-educational documentation. CIBERER, from the ISCIII; supports the translation into Spanish of the Orphanet website content and contributes to the site with national data.

#### ***Official information centre for rare diseases***

There is no official information centre on rare diseases in Spain but there is a special Unit at the Ministry of Health to answer citizens' questions and to address the 200 rare disease related questions they receive each year. Other services are provided by Orphanet Spain which is supported by the Institute of Health Carlos III.

#### ***Help line***

FEDER's Service of Information and Orientation (SIO) provides a phone and internet helpline which receives support from the Ministry of Health. The help line is coordinated with specific rare disease info services and provides information on rare diseases, patient management of the disease, experts and consultations, obtaining a diagnosis, access to medicinal products, clinical trials, genetic tests, rehabilitation, publications, guidelines for creating a patient organisation, and information on financial support and respite care. FEDER's help line also provides information to callers from Spanish speaking countries. It also acts as a contact point for experience exchange amongst patients with the same pathology or pathology group. The help line belongs to the European Help Lines Network, led by EURORDIS.

#### ***Other sources of information on rare diseases***

Other sources of information were developed by rare diseases research networks such as REPIER, INERGEN, GIM; ORGEN, REDEMETH, REC-GEN, etc. They are in different stages of development and some have been recently closed or their information is being transferred to the national registry website. CIBERER also runs a website with information regarding its main lines of research.

FEDER maintains a website with information on rare diseases and certain documentation and runs a specialised helpline for patients and their families and social services professionals, the Information and Support Service (SIO) which has received more than 34 462 consultations since 2001, when it was established with the support of the former Social Affairs Ministry. Social, legal, psychological support as well as training is provided to individual patients, associations, professionals (and others) by specialised staff (e.g. five social workers and a biologist). There are two related services: Psychology Service (attended by 3 psychologists) and a legal consultancy attended by 1 lawyer. CREER is working with FEDER and the IIER on a new system to improve the coordination of different competences for providing several types of information on rare diseases. The System of Information for Patients (FEDER Help line) is thus also improved.

FEDER also promotes social and sanitary studies on rare diseases such as the 2009 "Estudio ENSERio "Estudio sobre situación de las Necesidades Sociosanitarias de las personas con Enfermedades Raras en España" FEDER, followed up in 2012 by the "Estudio ENSERio 2 "Por un modelo sanitario para la Atención a las personas con Enfermedades Raras en las Comunidades Autónomas".

#### **Guidelines**

Since 2000, *IMSERSO* (the main Spanish Institution in charge of providing social support for disable patients and families) has also been collaborating with FEDER in order to develop guides for rare diseases families, i.e. Amyotrophic Lateral Sclerosis, Achondroplasia, Familial Spastic Paraparesis and Aniridia, amongst others.

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<sup>469</sup> <http://www.orphanet-espana.es>

*GuíaSalud*<sup>470</sup> is a programme which is supported by the Ministry of Health. Since its first steps in mid-2002 until now, it has been immersed in framework changes within the quality of the NHS Plan. The measures were described in the Quality Plan of 2007, which implicated important changes to objectives, introducing into the work portfolio the development of products, based on scientific evidence, to assist health professionals in decision-making. Several guidelines for specific rare diseases have been developed by GuíaSalud, i.e. related to congenital abnormalities or skin care in epidermolysis bullosa and related to congenital hypothyroidism.

CIBERER also collaborates, along with the Spanish Orphanet team, in the revision and transplantation of GP guidelines on rare diseases.

There is also a Health Technology Assessment Agencies network that develops reports concerning specific rare diseases since 2006 (i.e. ataxias, inborn errors of metabolism or genetic tests).

CIBERER has developed a programme aimed at facilitating information to all those interested through guides and brochures on specific illnesses and/or through scientific lectures meant for patients. CIBERER has produced nearly 150 clinical guides on rare diseases since 2007 intended for nurses, general practitioners and clinical specialists. This research centre also organises therapeutic conferences, workshops and seminars in cooperation with other bodies such as patients' associations. CIBERER is committed to ensuring excellence amongst their scientific laboratories. Most of them are already accredited and some others are in the process of obtaining the best level of standard quality through external validation processes.

An online protocol for the primary care of patients with rare diseases was presented on 18 July 2010 at the national congress of the Spanish Society of Family and Community Medicine (SEMFyC) in Valencia. The protocol, *Protocolo Dice de Atención Primaria de Enfermedades Raras (DICE-APER)* was created by SEMFyC's working group on Clinical Genetics and Rare Diseases<sup>471</sup>, in collaboration with the Institute of Rare Diseases Research Institute, ISCIII, FEDER and CREER. The specific objectives of the protocol are to facilitate the diagnostic process, provide information to patients, improve coordination between primary care and specialised care physicians and render epidemiological data.

The Ethics Committee of the Institute of Rare Diseases Research (IIER) has published a series of guideline documents regarding registries, biobanks, and neonatal screening<sup>472</sup>. Originally published as separate articles in the Spanish Health Ministry publication *Revista Española de Salud Pública*<sup>473</sup>, the Ethics Committee has now grouped the guidelines into one document, entitled *Ethical Guidelines for Biomedical Research*, which it has made available in both Spanish and English languages. The guidelines address issues pertaining to creation, organisation, management, consent, privacy, post-mortem data, and ownership, within the context of existing ethical principles and norms, legal provisions, and international practices.

### **Training and education initiatives**

Since 2007 the CIBERER holds an annual scientific meeting where the principal investigators and pre-doctoral/postdoctoral researchers present their recent results in the field of the biology, pathophysiology, clinical research and therapies, and epidemiology in the field of rare diseases.

The Universidad Internacional de Andalucía (UNIA) and the Universidad Pablo de Olavide de Sevilla (UPO) in collaboration with the CIBERER, offers an official Master in 'Rare Disease Diagnosis and Therapy' since 2010. In 2012 and 2013 this course was held again. The IIER has been the as responsible of the training in RD epidemiology in the fourth editions of this Official Master. On the other hand, the IIER has been developing their own training strategy addressed to primary health care workers and physicians in collaboration with the Spanish Society of Primary and Family Medicine. Two different rounds of training courses have been developed during 2013. Finally, the IIER has launched its own on-line training course addressed to those professionals working in the SpainRDR network. It has been followed by more than 60 people and the same online course will be opened to other professionals using the new distant learning ISCIII platform.

Other initiatives led by CIBERER are the organisation of training courses on rare diseases.

In 2010 The Ministry of Health, Social Policy and Equality funded 10 projects related to the training and education on rare diseases carried out in different Spanish Regions in 2011 also 10 projects were funded, 3 of them related to training and education.

Each year FEDER and CREER organise a training school aimed at empowering rare disease patients groups.

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<sup>470</sup> <http://www.guiasalud.es/home.asp>

<sup>471</sup> <http://dice-aper.semfyc.es/web/index.php>

<sup>472</sup> [http://www.isciii.es/htdocs/publicaciones/documentos/IIER\\_Guias\\_eticas\\_INGLES.pdf](http://www.isciii.es/htdocs/publicaciones/documentos/IIER_Guias_eticas_INGLES.pdf)

<sup>473</sup> [http://www.msps.es/biblioPublic/publicaciones/recursos\\_propios/resp/home.htm](http://www.msps.es/biblioPublic/publicaciones/recursos_propios/resp/home.htm)

### **National rare disease events in 2013**

FEDER has organised various national conferences on rare diseases and regional conferences. Many other rare disease specific patient associations hold their annual meetings where some time is dedicated to comment on general questions concerning rare diseases. Some Medical and Scientific Societies include round table discussions and conferences related to rare diseases in their annual meetings.

Every year, the Spanish Federation of rare diseases (FEDER) celebrates Rare Disease Day, with hundreds of patient organisations organising a wealth of events.

The Spanish Ministry of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government raised knowledge and awareness for rare conditions, and established stronger ties of mutual support. The operation focused on the health, research and social perspective of rare diseases<sup>474</sup>.

In October 2013 the Ministry of Health, Social Services and Equality organized a scientific meeting "Conocer la rareza, mejorar nuestras vidas. Presente y retos futuros de las enfermedades raras: traslación clínica de la investigación".

Also among the actions of awareness-raising, to understand the characteristics of these diseases, improve the situation of affected families and promote networks of collaboration and mutual support, the international day of families of 2013 was devoted to relatives of persons with rare diseases.

The 5th CIBERER Meeting "Investigar es Avanzar" was held on 27 February 2013 in Madrid to celebrate Rare Disease Day 2013. The main objective of the meeting was to present CIBERER's research activities and scientific advances in rare diseases to the general public. Over 150 people attended the event and counted with the participation of researchers and patient organisation representatives.

The SpainRDR network held its national meeting with the presence of more than 100 participants including the Advisory Board of this network formed by external and well recognized experts in the RD field

CIBERER carried out many activities in the framework of the Spanish Year of Rare Diseases, among which the following could be highlighted as an example, due to their size or international dimension:

- 5<sup>th</sup> Edition of CIBERER's Meeting "Investigar es Avanzar", 27 February, Madrid.
- DNA-Day CIBERER Workshop, 25-26 April, Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz, Madrid
- International Symposium on Mitochondrial diseases, 20-21 May, Fundación Ramón Areces, Madrid.
- International Symposium on Diagnostic Challenges in Intellectual Disabilities by array CGH and Next Generation Sequencing, 3-4 October, Hospital Clínic, Barcelona.

### **Hosted rare disease events in 2013**

Amongst the events announced in *OrphaNews* were: International Congress of Inborn Errors of Metabolism (3-6 September 2013, Barcelona), 1st World Conference on Congenital Disorders of Glycosylation (1-2 September 2013, Barcelona), International Symposium on Urea Cycle Disorders (UCD) (1-2 September 2013, Barcelona), 18th Update in the management of gaucher disease and other Lysosomal disorders (13-16 May 2013, Zaragoza).

### **Research activities and E-Rare partnership**

#### **National research activities**

In Spain, research related to rare diseases is included in the "Plan Nacional de Investigación Científica" (National Plan for Scientific Research), "Desarrollo e Innovación Tecnológica" (Development and Technological Innovation) (2008 – 2011), and specifically within the "Acción Estratégica en Salud" (Strategic Action on Health [Research]), in which rare diseases constitute one of the most important research subjects. In September 2007, the outlines of the National R&D&I Plan were presented. According to the Ministry of Education and Science, the Public Central Administration increased its investment at a rate of 16% per year starting in 2008 and up to a total expenditure of 2.2% of GDP in 2011, in line with European Union recommendations. This estimate includes the business sector, which will finance 55% of the total investment.

The most relevant government initiative for research on rare diseases was the creation by ISCIII in 2006, of the Biomedical Research Network on Rare Diseases (CIBERER) in order to act as a research performing body on rare diseases in Spain. CIBERER is a centre orientated towards the development and implementation of cooperative research in the field of rare diseases, performing basic, clinical and epidemiological biomedical research, placing special emphasis on transferring the research from the laboratory to the patient's bedside and scientifically responding to the questions that arise from the interaction between physician and patient.

<sup>474</sup> <http://www.msc.es/gabinete/notasPrensa.do?id=2611>



This network acts as a public consortium of 29 institutions; the network has more than 700 professionals integrating 60 research groups and is mainly funded by the Institute of Health Carlos III and is attached to it. The aims of CIBERER are: to improve the resources available for researching rare diseases and rare disease treatments, to promote the integration between basic and clinical biomedical research groups in order to aid collaboration between the laboratory with the clinical setting, to develop cooperative investigational projects that allow for the exploration of new scientific hypotheses and technological developments, to demonstrate the value of rare disease research, and to establish collaborative efforts with the pharmaceutical and biotechnological industry.

Since the Rare Diseases Strategy of the Spanish National Health System began, rare diseases have been considered as a priority research area of the Fund for Health Research (FIS) and the Strategic Action in Health (AES) for 2008-2009. Rare diseases are also taken into account in the area of "additional performances" contemplating the strengthening of both basic research and clinical trials or the development of orphan medicinal products.

On 1 February 2013 the Council of Ministers approved the State Plan for Scientific Research, Technology and Innovation 2013-2016, which represents the instrument intended to develop and finance the activities of the Central Government in R&D to enable the achievement of the objectives and priorities included in the Spanish Strategy for Science, Technology and Innovation 2013-2020.

The State Plan determined as one of its programmatic activities the Strategic Action in Health 2013-2016 (AES), which main aim is to promote the health and welfare of citizens, and is structured as a space for interaction, integrating a synergistic and complementary set of instrumental performances, which results contribute to the consolidation of the NHS as a world leader in terms of its scientific, technological and innovation capabilities. Contributing thus to adapt to Europe, preparing for what would be the 8th Framework Program or Horizon 2020.

In the corresponding calls for granting aid for the Strategic Action in Health, in the frame of the National R&D Plan 2008-2011 and under the Plan for Scientific Research, Technology and Innovation 2013-2016, Rare Diseases have been referred to as one of the priorities in an explicit way.

Other research initiatives in Orphan Drug research include those of the Spanish Technological Platform for Innovative Medicines of Farmaindustria and the European Innovative Medicines Initiative (IMI).

CIBERER and the National Center for Genome Analysis are collaborating in the massive sequencing and analysis of 279 exomes corresponding to 39 rare diseases and/or groups of pathologies, including mitochondrial, hereditary metabolic, neuromuscular, and sensorineural hearing loss disorders, in a bid to uncover the genetic cause of the conditions. Identification of the genetic basis for these diseases could open new diagnostic pathways. It is anticipated that the study is leading to the identification of the genetic defect in at least 50% of the cases studied.

#### ***Participation in European research projects***

Teams in Spain have participated/participate in 68 FP7 rare disease related projects, and 15 projects were coordinated by a team in Spain.

#### ***E-Rare***

Spain, represented by the Institute of Health Carlos III (ISCIII), is a partner of the E-Rare. Spain has participated in the two calls for proposals managed by the Fund for Health Research (FIS), the Public Health Agency for Health Research, which is part of the ISCIII. Spain participated in the 2007 and 2009 E-Rare transnational calls with a total of €3.25 million of initial funding committed to the project Spain. Spanish teams participate in 6 of the 13 funded projects/consortia selected following the 1<sup>st</sup> Joint Transnational Call, and in 6 of the 16 consortia/projects selected for funding in the 2<sup>nd</sup> Joint Transnational Call, with a total funding of around 580,000€. Spain participated in the 3<sup>rd</sup> Joint Transnational Call in 2011 and supports a Spanish team in one of the selected consortia. Spain participated in the 4<sup>th</sup> Joint Transnational Call in 2012: 3 teams from Spain participated in the Consortia funded through the call. Spain participated in the 5<sup>th</sup> Joint Transnational Call in 2013: 3 teams from Spain participated in 5 out of the 12 Consortia funded through the call.

#### ***IRDiRC***

The Carlos III Health Institute is a committed member of the IRDiRC and will be the funding agency for collaborative research projects awarded by IRDiRC to institutions with the facilities to carry out the project and legal and fiscal address placed in Spain. In 2011 the ISCIII launched a call of Collaborative Research Projects with an overall funding up to €10 million for 5 consecutive years aligned with the IRDiRC scientific objectives, funding level, policies and governance structure. Three proposals were selected for funding at national level:

TREAT-CMT, the Spanish consortium on Charcot-Marie-Tooth disease, with a multidisciplinary approach (coordinated by CIBERER), DRUGS4RARE, Drug repositioning for rare diseases (coordinated by the Parc Científic de Barcelona) and SPAIN-RDR, the Spanish Rare Diseases Registries Research Network (coordinated by the IIER). These three projects are national projects, evaluated by an international review panel within the scope of the IRDiRC, and targeting IRDiRC objectives, and were communicated to and recognised by its secretariat.

### **Orphan medicinal products**

The Spanish Agency of Medicines and Medical Devices (AEMPS) is the National Authority responsible for evaluating medicines before approval as well as for conducting a continuous supervision post authorisation of its benefits and risks in order to update the approved conditions of use of any medicine. In the case of orphan medicinal products designated at the European level, this evaluation process is undertaken by all national European agencies under coordination of the EMA, i.e. 'centralised procedure'.

### **Orphan medicinal product committee**

No specific activity reported.

### **Orphan medicinal product incentives**

There are specific scientific advice procedures in place at the AEMPS to give guidance and advice to any potential orphan medicinal product development. These procedures can be applied within the context of a centralised advice coordinated by the EMA or on a purely national basis.

Since 2007, there is an annual call for public financing of clinical trials of medicines with no commercial interest. In this call, medicines for rare diseases (either designated as orphan medicines or not) are one of the priorities, together with paediatrics, antibiotics and studies of major interest for the National Health System). In the scope of this call, proposals for studies concerning medicines for the treatment of rare diseases have an outstanding rate of success in obtaining full public financing.

In Spain, the 29/2006 Act on "Guarantees and Rational Use of Medicines and Medical Devices" states in Article 2, referring to supplying and dispensation guarantees of orphan medicinal products, that: "the Government, in order to ensure the supplying of medicines, will be able to adopt special actions in relation with their manufacture, importation, distribution and dispensation. In the case of "orphan medicinal products," (pursuant to the Regulation (EC) number 141/2000 "medicines without any commercial interest") the Government could adopt, besides the above mentioned, other actions related to the economic and fiscal policy of the so-called medicines".

Since June 2010, orphan medicinal product manufacturers have a reduced rebate of 4% (instead of 5%, and 7.5% in the case of products directly distributed to hospitals) on the VAT-exclusive public price of medicines financed by the National Health System if they are not included in the reference price system (Royal Decree 8/2010)<sup>475</sup>.

### **Orphan medicinal product market availability situation**

Access to orphan medicines is extensive in Spain, with all designated orphan medicines authorised at the European level also authorised by the Spanish authorities and included in National Health System coverage.

Almost all authorised orphan medicines are marketed in Spain (57 out of 78, representing 83%, of the drugs with European Market Authorisation).

### **Orphan medicinal product pricing policy**

Pricing of medicines and access to reimbursement are combined and managed by the Health Ministry's General Subdirectorate of Quality of Medicines and Health Products, part of the Directorate General of National Health Service and Pharmacy. This is common procedure for all prescription medicines. Actual hospital purchase prices are determined by the government of each autonomous community or negotiated individually between manufacturers and each hospital/group of hospitals<sup>476</sup>.

### **Orphan medicinal product reimbursement policy**

In Spain, when marketing authorisation is granted either by the EMA or AEMPS, the Ministry of Health, Social Services and Equality initiates a procedure to decide on reimbursement of this new product on the national reimbursement list. If a reimbursement status is approved, the pricing is decided simultaneously. Up till now all

<sup>475</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) pp 85-86

<sup>476</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) p 85

orphan medicinal products approved by the EMA are reimbursed in Spain in one of these categories: 1) for use only in hospitals (hospital Use: H) or 2) in a non-hospital environment, but prescribed only by a specialist doctor (hospital diagnostic: DH).

Currently, 57 orphan medicinal products are fully reimbursed by the National Health System. Nevertheless, in some Regional Governments, there are protocols and systems to follow the access of patients to the treatment under the National Health System coverage.

Moreover, a new law which improves the regulation of compassionate use (particularly for orphan medicinal products) and foreign medications legally distributed in other countries but not authorised in Spain came into force in 2009.

#### ***Other initiatives to improve access to orphan medicinal products***<sup>477</sup>

An authorisation procedure for access to non-authorized medicines is in place. The AEMPS authorises either individual access for specific patients (compassionate use) or access to groups of patients through a certain protocol (temporary authorisation of use). The procedure for granting this access has recently been improved (Royal Decree 1015/2009) in order to make it faster, through entirely telematic communication with the hospitals at the same time that it has been reinforced the follow up of safety information by the AEMPS and the information systems.

Compassionate use is available for medicines under investigation for patients with a chronic or life-threatening disease that are not able to be treated satisfactory with an authorised medicine (based on Regulation (EC) No 726/2004). In the case of authorisation for individualised access, the treating hospital needs to submit a separate application for an individual patient to the Spanish Medicines Agency accompanied by a dossier.

Temporary Use Authorisation is possible for medicines under investigation. The Spanish Medicines Agency is able to set up such an authorisation for medicines under investigation independent of a clinical trial in an advanced phase of clinical investigation as long as the use is for a significant group of patients. The Temporary Use Authorisation will include all the conditions and requirements for use.

Off-label use is based on Act 29/2006 for Guarantees and the Rational Use of Medicines and Healthcare Products, Art. 24. Off label use must be exceptional and limited to those situations with a lack of therapeutic alternatives for a patient. The physician must justify the need for the use of the orphan medicines and inform the patient about potential risks and benefits and obtain his/her written consent.

Medicines not authorised in Spain but in other countries (Royal Decree 1015/2009 of 19 June 2009 for the availability of medicines in special situations) can be authorised exceptionally by the Spanish Medicines Agency when no medicine is authorised (or authorised and not marketed) with the same composition or the available dosage does not allow an appropriate treatment, or when there is no authorised medicine that represents an adequate alternative for that patient available in Spain. Any application needs to be accompanied by the prescriber's clinical report that justifies the clinical need for treatment and the estimated treatment duration, the number of packages required, scientific documentation for using, patient's written consent and the sponsor's conformity, if necessary. The Spanish Medicines Agency will make protocols for using medicines not authorised in Spain when there is a need concerning a significant subpopulation of patients.

The payer for all three described situations is the National Health Service, but in some case the companies act as "sponsors".

#### **Other therapies for rare diseases**

No specific activity reported.

#### **Orphan devices**

No specific activity reported.

#### **Specialised social services**

Respite care is provided for rare disease patients considered as living in a situation of dependency. These services can take the form of nursing homes, day care centres, home care, remote assistance, or as a residential stay such as those offered for free at the Burgos' National Reference Centre for Rare Diseases. These services are either public or private and co-payment is often required. Patients suffering from a disability

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<sup>477</sup> Information from the EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner (2011), pp58-59

are eligible for government allowances for resort and spa stays with 20% to 50% of the total cost covered (this includes travel and stay as well as insurance costs).

## RARE DISEASE ACTIVITIES IN 2013 IN SPAIN

### National plan/strategies for rare diseases and related actions

The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government expects to raise knowledge and awareness for rare conditions, and establish stronger ties of mutual support. The operation focused on the health, research and social perspective of rare diseases<sup>478</sup>.

During 2013 the update of the objectives and recommendations of the strategy on rare diseases of the NHS was carried out by all the stakeholders reaching an agreement. It is currently pending approval by the Interterritorial Council of the NHS.

One of the activities proposed for the year 2013 was the creation of a map of expert units in rare diseases to facilitate access to the information of the activity carried out in different hospitals in Spain in relation to the RD; to facilitate access to information for citizens, decision-makers and health professionals to establish networks.

The work procedure has been developed in the framework of the strategy on rare diseases of the NHS and was approved by the Interterritorial Council of the SNS on 21 March 2013.

The Interterritorial Council of the NHS approved on 21 March 2013 a common procedure for the good practices (BBPP) identification in the NHS. An ad hoc group was created in the framework of the strategy on rare diseases of the NHS to adapt the common criteria and the assessment tool approved by the CISNS to the field of rare diseases and to evaluate all experience collected. 69 experiences proposals were collected and evaluated for the evaluation group and 8 of them obtained the good practice title and stamp.

A campaign to raise awareness concerning RD was defined by the Ministry of Health and was published on the Internet on 21 October and lasted until 3 November. The Ministry of Health planned a total of 5.092.650 spots that appeared in the main sites of digital newspapers and sites of television.

A specific training course on disabilities in rare diseases for professional evaluators was organised. This course was coordinated by the CREER.

Also among the actions of awareness-raising, to understand the characteristics of these diseases, improve the situation of affected families and promote networks of collaboration and mutual support, the international day of families of 2013 was devoted to relatives of persons with rare diseases.

In October 2013 the Ministry of Health, Social Services and Equality signed a collaboration agreement with the President of RTVE Corporation to broadcast the Telethon of the Spanish year of the rare diseases. This event took place on 2 March 2014 and the income will be allocated to research for rare diseases.

### Regional initiatives

All regions have been collaborating in the National RD Registry. They contributed to the standardisation of procedures and methods and also in the development of the pilot study. At the end of 2013, they began with the collection of cases from 2010-2012.

### Centres of expertise

In Spain, Royal Decree 1302/2006 establishes the procedure and principles for the designation and accreditation of the Reference Centres, Departments and Units (CSUR) of the Spanish NHS. Work continues in other areas of specialisation to define all the diseases and procedures, among them those related to rare diseases, which should be carried out in CSUR. Since 2001, FEDER (The Spanish Federation for Rare Diseases) has been working in the CSUR project with regard to rare diseases, by providing professionals to participate in the groups of experts related to rare diseases.

They are currently in phase of accreditation of the Autonomous Region's proposals related to: Arritmology electrophysiology and paediatrics, Metabolic Congenital Diseases, Genetic neurocutaneous

<sup>478</sup> <http://www.msc.es/gabinete/notasPrensa.do?id=2611>

syndromes (Phacomatosis), rare diseases concerned with movement disorders and complex disorders of the autonomic nervous system.

Work is currently being carried out on the definition of the criteria for designation of centres, services and Reference Units of the National Health System for rare cancers and pulmonary hypertension.

Work is continuing on the identification of diseases and procedures for which there is a need a CSUR in the NHS, still expected to finish such identification in 2014.

Reference services are monitored annually. An information system is in place to report on how the activities performed comply with the designation criteria and meet the procedure and result indicators that were included in the designation criteria. The definition of these procedures and result indicators by the corresponding expert groups and units and services designated (agreed by the Interterritorial Council) is very complex, due to the diversity of diseases and procedures, considering that every disease and procedure has its own information system.

Currently, the annual follow-up of 177 CSUR of the NHS is being carried out. These CSUR cover 35 diseases and procedures, and they have been operating during 2009-2013. Each year collected data and indicators are analysed by professionals from CSUR and expert groups in each area of expertise, and if required, appropriate improvements are introduced.

All information concerning the CSUR project is available for health professionals and patients in the Web of the Ministry of Health, Social Services and Equality (MSSSI).

During 2014 the MSSSI will be involved in the implementation of European Reference Networks (ERN) in the context of the Directive of Cross Border Health Care.

### Registries

The Spanish Rare Diseases Registries Research Network is a €2.4 million project financed by the Institute of Health Carlos III (ISCIII) for 2011-2014. This project involves all Health Departments of the Autonomous Communities (regions) of Spain, the Institute of Rare Diseases Research (IIER) which acts as a coordinator and leader of the network, the Spanish Ministry of Health, the Spanish Centre of Reference of People and Families affected by RD (CREER<sup>479</sup>), six Spanish Medical Societies, four research networks, pharmaceutical and biotechnological organisations (ASEBIO<sup>480</sup> and FARMAINDUSTRIA<sup>481</sup>), and the Spanish Federation of RD (FEDER<sup>482</sup>) and its foundation (FEDER TELETHON FOUNDATION). The main objective is to develop the National and Regional Registry for rare diseases based on methods for both population-based registries and patient outcomes registries. Industry, patient's organisations, foundations and more than 6 medical societies have signed agreements with the ISCIII to contribute to this national registry and cooperate with the IIER.

Several RD patient registries are being integrated into the central repository of the National RD Registry. At the same time, a preliminary agreement has been reached between SpainRDR and REDECAN, the network of population-based for cancer registries in order to collaborate in the process of rare cancer registration. Currently, SpainRDR is collecting prevalence cases corresponding to the period 2010-2012. A standardized mapping of codifications between ICDs, Orphacodes, SNOMED and OMIM is used. Common Data Elements, Standardised Operating Procedures, ELSI rules and methods for statistical analysis and reporting have been already developed.

### Neonatal screening policy

National neonatal screening is currently in place for phenylketonuria and hypothyroidism congenital hypothyroidism, phenylketonuria, cystic fibrosis, deficiency of acyl Coenzyme A deshydrogenada medium-chain (MCADD), deficiency of 3-Hydroxy acyl-CoA Dehydrogenase, long-chain (LCHADD), glutaric acidemia type I (GA-I) and sickle cell anaemia.

The incorporation of this population program of neonatal screening in basic common portfolio of NHS services will be accompanied by the development of:

- An information system of neonatal screening at regional and State level allow proper monitoring and evaluation of the population programme.
- A system of quality management that allows addressing homogeneously in all autonomous communities' screening processes, so it is essential to the elaboration of agreed protocols and their implementation in the NHS.

<sup>479</sup> [http://www.creenfermedadesraras.es/creer\\_06/index.htm](http://www.creenfermedadesraras.es/creer_06/index.htm)

<sup>480</sup> <http://www.asebio.com/es/index.cfm>

<sup>481</sup> [http://www.farmaindustria.es/Farma\\_Public/index.htm](http://www.farmaindustria.es/Farma_Public/index.htm)

<sup>482</sup> <http://www.enfermedades-raras.org/>

At the beginning of this process, on 18 December 2013 the CISNS adopted the document "Objectives and quality requirements of the Neonatal screening of metabolic diseases of the SNS program": in this document quality objectives are defined for each of the stages of the program and the necessary or recommended requirements for achieving them.

A working group with representatives from the Ministry of Health, and the Regional health services, reviewed scientific evidence and will produce a report and recommendations about population screening programs for the National Health System<sup>483</sup>.

Also, the Spanish Network of Agencies for Health Technology Assessment and Benefits of the National Health Service has developed several reports on effectiveness and cost-effectiveness of the neonatal screening program for some rare diseases<sup>484,485,486,487,488</sup>.

### Genetic testing

At the present time, the MSSSI is working together with Regional Governments and Scientific Societies defining the genetic portfolio of services for the NHS and HTA agencies which are involved in the description of the Spanish map of genetic test offered by the NHS.

### Sources of information on rare diseases and national help lines

#### **Official information centre for rare diseases**

There is no official information centre on rare diseases in Spain but there is a special Unit at the Ministry of Health to answer citizens' questions and to address the 200 rare disease related questions they receive each year. Other services are provided by Orphanet Spain which is supported by the Institute of Health Carlos III.

### Guidelines

The Ethics Committee of the Institute of Rare Diseases Research (IIER) has published a series of guideline documents regarding registries, biobanks, and neonatal screening<sup>489</sup>. Originally published as separate articles in the Spanish Health Ministry publication *Revista Española de Salud Pública*<sup>490</sup>, the Ethics Committee has now grouped the guidelines into one document, entitled *Ethical Guidelines for Biomedical Research*, which it has made available in both Spanish and English languages. The guidelines address issues pertaining to creation, organisation, management, consent, privacy, post-mortem data, and ownership, within the context of existing ethical principles and norms, legal provisions, and international practices.

### Training and education initiatives

The Universidad Internacional de Andalucía (UNIA) and the Universidad Pablo de Olavide de Sevilla (UPO) in collaboration with the CIBERER, offers an official Master in 'Rare Disease Diagnosis and Therapy' since 2010. In 2012 and 2013 this course was held again. The IIER has been the as responsible of the training in RD epidemiology in the fourth editions of this Official Master. On the other hand, the IIER has been developing their own training strategy addressed to primary health care workers and physicians in collaboration with the

<sup>483</sup> A document on screening in general (neonatal and cancer screening) was elaborated in 2010 : "Documento marco sobre cribado poblacional" elaborated by the Comisión de Salud Pública del Consejo Interterritorial del SNS (2010) (Committee for Public Health of the Interterritorial Council of the National Health System) (2010)

<sup>484</sup> Paz Valinas L. Cribado neonatal de la fibrosis quística. Eficacia/efectividad y protocolos de implementación. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Agencia de Evaluación de Tecnologías Sanitarias de Galicia; 2013. Informes de evaluación de tecnologías.

<sup>485</sup> Efectividad clínica del cribado neonatal de errores congénitos del metabolismo mediante espectrometría de masas en tandem. Parte I: enfermedad de la orina con olor a jarabe de arce, homocistinuria, acidemia glutárica tipo I, acidemia isovalérica y deficiencia de 3-hidroxil-CoA deshidrogenasa de cadena larga. – Margot Einoder Moreno, Gerardo Atienza Merino. – Santiago de Compostela: Agencia de Evaluación de Tecnologías Sanitarias de Galicia (avalía-t). Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013.

<sup>486</sup> Queiro Verdes T. Cribado neonatal de la anemia falciforme. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Agencia de Evaluación de Tecnologías Sanitarias de Galicia; 2013. Informes de evaluación de tecnologías sanitarias.

<sup>487</sup> Castilla I, Arvelo-Martín A, Valcárcel-Nazco C, Linertová R, Serrano-Aguilar P, Ruiz-Pons M, Posada M, Dulín-Íñiguez E, Espada M, Zubizarreta R. Coste-efectividad del cribado ampliado de errores congénitos del metabolismo mediante espectrometría de masas en tandem. Red Española de Evaluación de Tecnologías y Prestaciones del Sistema Nacional de Salud del Ministerio de Sanidad, Política Social e Igualdad. Servicio de Evaluación del Servicio Canario de la Salud; 2012. Informes de Evaluación de Tecnologías Sanitarias: SESCS Nº 2012/11.

<sup>488</sup> Seoane Mato D, Cantero Muñoz P, Atienza Merino G. Efectividad clínica del cribado neonatal de errores congénitos del metabolismo mediante espectrometría de masas en tandem. Parte II: acidemia metilmalónica, acidemia propiónica, tirosinemia tipo I. Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del SNS. Agencia de Evaluación de Tecnologías Sanitarias de Galicia; 2014. Informes de Evaluación de Tecnologías Sanitarias

<sup>489</sup> [http://www.iscii.es/htdocs/publicaciones/documentos/IIER\\_Guias\\_eticas\\_INGLES.pdf](http://www.iscii.es/htdocs/publicaciones/documentos/IIER_Guias_eticas_INGLES.pdf)

<sup>490</sup> [http://www.msps.es/biblioPublic/publicaciones/recursos\\_propios/resp/home.htm](http://www.msps.es/biblioPublic/publicaciones/recursos_propios/resp/home.htm)

Spanish Society of Primary and Family Medicine. Two different rounds of training courses have been developed during 2013. Finally, the IIER has launched its own on-line training course addressed to those professionals working in the SpainRDR network. It has been followed by more than 60 people and the same online course will be opened to other professionals using the new distant learning ISCIII platform.

### **National rare disease events in 2013**

FEDER has organised various national conferences on rare diseases and regional conferences. Many other rare disease specific patient associations hold their annual meetings where some time is dedicated to comment on general questions concerning rare diseases. Some Medical and Scientific Societies include round table discussions and conferences related to rare diseases in their annual meetings.

Every year, the Spanish Federation of rare diseases (FEDER) celebrates Rare Disease Day, with hundreds of patient organisations organising a wealth of events.

The Spanish Minister of Health, Social Services and Equality, declared 2013 the Spanish Year of Rare Diseases. With this initiative, the government raised knowledge and awareness for rare conditions, and established stronger ties of mutual support. The operation focused on the health, research and social perspective of rare diseases<sup>491</sup>.

In October 2013 the Ministry of Health, Social Services and Equality organized a scientific meeting "Conocer la rareza, mejorar nuestras vidas. Presente y retos futuros de las enfermedades raras: traslación clínica de la investigación".

Also among the actions of awareness-raising, to understand the characteristics of these diseases, improve the situation of affected families and promote networks of collaboration and mutual support, the international day of families of 2013 was devoted to relatives of persons with rare diseases.

The 5th CIBERER Meeting "Investigar es Avanzar" was held on 27 February 2013 in Madrid to celebrate Rare Disease Day 2013. The main objective of the meeting was to present CIBERER's research activities and scientific advances in rare diseases to the general public. Over 150 people attended the event and counted with the participation of researchers and patient organisation representatives.

The SpainRDR network held its national meeting with the presence of more than 100 participants including the Advisory Board of this network formed by external and well recognized experts in the RD field

CIBERER carried out many activities in the framework of the Spanish Year of Rare Diseases, among which the following could be highlighted as an example, due to their size or international dimension:

- 5<sup>th</sup> Edition of CIBERER's Meeting "Investigar es Avanzar", 27 February, Madrid.
- DNA-Day CIBERER Workshop, 25-26 April, Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz, Madrid
- International Symposium on Mitochondrial diseases, 20-21 May, Fundación Ramón Areces, Madrid.
- International Symposium on Diagnostic Challenges in Intellectual Disabilities by array CGH and Next Generation Sequencing, 3-4 October, Hospital Clínic, Barcelona.

### **Hosted rare disease events in 2013**

Amongst the events announced in *OrphaNews* were: International Congress of Inborn Errors of Metabolism (3-6 September 2013, Barcelona), 1st World Conference on Congenital Disorders of Glycosylation (1-2 September 2013, Barcelona), International Symposium on Urea Cycle Disorders (UCD) (1-2 September 2013, Barcelona), 18th Update in the management of gaucher disease and other Lysosomal disorders (13-16 May 2013, Zaragoza).

### **Research activities and E-Rare partnership**

#### ***National research activities***

On 1 February 2013 the Council of Ministers approved the State Plan for Scientific Research, Technology and Innovation 2013-2016, which represents the instrument intended to develop and finance the activities of the Central Government in R&D to enable the achievement of the objectives and priorities included in the Spanish Strategy for Science, Technology and Innovation 2013-2020.

The State Plan determined as one of its programmatic activities the Strategic Action in Health 2013-2016 (AES), which main aim is to promote the health and welfare of citizens, and is structured as a space for interaction, integrating a synergistic and complementary set of instrumental performances, which results contribute to the consolidation of the NHS as a world leader in terms of its scientific, technological and

<sup>491</sup> <http://www.msc.es/gabinete/notasPrensa.do?id=2611>

innovation capabilities. Contributing thus to adapt to Europe, preparing for what would be the 8th Framework Program or Horizon 2020.

In the corresponding calls for granting aid for the Strategic Action in Health, in the frame of the National R&D Plan 2008-2011 and under the Plan for Scientific Research, Technology and Innovation 2013-2016, Rare Diseases have been referred to as one of the priorities in an explicit way.

CIBERER and the National Center for Genome Analysis are collaborating in the massive sequencing and analysis of 279 exomes corresponding to 39 rare diseases and/or groups of pathologies, including mitochondrial, hereditary metabolic, neuromuscular, and sensorineural hearing loss disorders, in a bid to uncover the genetic cause of the conditions. Identification of the genetic basis for these diseases could open new diagnostic pathways. It is anticipated that the study is leading to the identification of the genetic defect in at least 50% of the cases studied.

#### **E-Rare**

Spain participated in the 5<sup>th</sup> Joint Transnational Call in 2013: 3 teams from Spain participated in 5 out of the 12 Consortia funded through the call.

## **1.27. SWEDEN**

### **Definition of a rare disease**

The Swedish definition of a rare disease is a disorder resulting in an extensive disability with a prevalence of no more than 1 in 10 000 inhabitants. The Swedish Medical Products Agency applies the European Regulation on Orphan Medicinal Products definition, a prevalence of no more than 5 in 10 000.

### **National plan for rare diseases and related actions**

In June 2010, the National Board of Health and Welfare presented a report concerning the organisation of national resources for rare diseases to the Ministry of Health and Social Affairs.

In June 2010, the Swedish Government decided to establish a national focal point for coordination in the field of rare diseases<sup>492</sup>, a €300,000/year project, with the main objective of coordinating rare disease efforts and disseminating knowledge and information within and between health services, NGOs and other stakeholders. The decision represented an important step towards a better use of the resources available for patients with rare diseases and the patients' relatives. The National Board of Health and Welfare was commissioned to establish this national focal point.

In November 2010, the Swedish National Conference on Rare Diseases<sup>493</sup> was held in Stockholm, to discuss a future national plan or strategy for rare diseases under the EUROPLAN project. The conference allowed stakeholders to meet to discuss a range of policy topics and helped put rare diseases on the national agenda, stimulating discussion concerning a national plan for rare diseases.

At the end of 2011 the National Board of Health and Welfare announced the new National Function for Rare Diseases (NFSD - *Nationella Funktionen för Sällsynta Diagnoser*). Their work includes the promoting of coherence and coordination of health care resources for people with rare diseases and to accomplish increased coordination with the social insurance, employment services, social services, NGOs and other actors. They also contribute to the dissemination of knowledge and information and to the exchange of good practice and experiences. NFSD started on 1 January 2012 and the assignment has been entrusted to the non-profit rare disease care facility Ågrenska. An inventory of available resources for people with rare diseases was one of the first tasks for the NFSD.

The Swedish Government decided in October 2011 to assign the National Board of Health and Welfare the task of developing a national strategy for rare diseases. The National Board of Health and Welfare have worked together with the NFSD and other stakeholders to develop the strategy. In October 2012, the Swedish national strategy for rare diseases was transmitted to the government. For the moment the financial implications have not been considered.

<sup>492</sup> <http://www.regeringen.se/sb/d/13214/a/148634>

<sup>493</sup> [http://download.EURORDIS.org/europlan/2 EUROPLAN Guidance Documents for the National Conference/FINAL%20Report Sweden%20EUROPLAN%20NC%202010.pdf](http://download.EURORDIS.org/europlan/2%20EUROPLAN%20Guidance%20Documents%20for%20the%20National%20Conference/FINAL%20Report%20Sweden%20EUROPLAN%20NC%202010.pdf)



On 26 November 2012, a EUROPLAN national conference<sup>494</sup> was held in Stockholm bringing together 140 stakeholders, to follow the elaboration of the national plan for rare diseases. The conference was organised by Rare Diseases Sweden and focused on how to transform the strategy proposed by the National Board of Health and Welfare into a concrete plan of action to improve care for rare diseases. Health care providers, policy makers and user representatives from across the country signed up to take part in the discussion about how to put the strategy into action.

In 2013, the plan had still not been adopted officially, but meetings of the NSFD were held concerning the plan and steps are being taken to implement some of the proposed measures, including the establishment of a number of centres of expertise.

### Centres of expertise

Sweden's health care system is decentralised and run by 21 county councils/regions. In accordance with a 1990 agreement with the Federation of County Councils, the National Board of Health and Welfare has issued a catalogue of providers of specialist care, which is intended to provide recommendations on reference points for local administrators. These centres providing expertise are mainly located at the seven university hospitals. During 2013 NFSD has collected information concerning these centres in Sweden. Criteria for centres of expertise have also been developed. At the university hospitals Centres for Rare Diseases (CSD) are under construction. There are currently two centres founded, at the university hospitals in Gothenburg and in Stockholm. The development and creation of CSDs at the remaining five university hospitals is ongoing. Within each CSD a number of centres of expertise will be established, each with responsibility for a diagnosis, a group of diagnosis or diagnostic group. At the end of 2013, there were 18 centres of expertise established at the two already founded CSDs.<sup>495</sup>

### Registries

There is a National Patient Registry funded by the National Board of Health and Welfare, including the International Classification of Diseases, Tenth Revision (ICD 10) based diagnoses for all in-patient and some out-patient visits (including day surgery and specialist psychiatric care) from both private and public health care providers. This registry is mainly used for statistics.

The centres of expertise, run by county councils/regions, have developed local quality registries to allow them to monitor activities and results. Currently there are approximately 20 registries for various rare diseases.

At the national level, around 70 National Quality Registries have been established<sup>496</sup> and are supported by the Swedish Association of Local Authorities and Regions (SALAR). All National Quality Registries contain individual-based data concerning diagnosis, treatment interventions and outcomes. These registries are primarily general and do not solely concern rare diseases, although patients with rare diseases may be included, as in, for example, the Swedish Dementia Registry. SALAR encourages managers of registries to apply for funding to become a National Quality Register in order to increase quality of health care on a national level as well as the accessibility of the registry.

During 2012 and 2013 a group including NFSD and Centre for Rare Diseases Stockholm worked together for the purpose of developing a national register of rare diseases. In 2013 an application of funding of a National Quality Register for Rare Diseases was sent in to SALAR, however funding was not granted. The work with a national register will be continued.

Sweden contributes to the EURO CARE CF, EUROCAT, SCNIR, and AIR European registries.

### Neonatal screening policy

For many years, a newborn screening programme has been in place for phenylketonuria, hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency and galactosemia in Sweden. However, since November 2010, the programme has been extended to twenty-four disorders. The required blood sample volume remains the same. The additional disorders screened are MCAD deficiency, LCHAD deficiency and other defects in TFP, VLCAD deficiency, dysfunction of the carnitine cycle molecules CPTI, CPTII and CACT, primary carnitine deficiency CUD, Isovaleric aciduria, methylmalonic aciduria MMA, glutaraciduria type I and 2, beta-ketothiolase deficiency, citrullinemia, argininosuccinate lyase deficiency (ASA), arginase deficiency, maple syrup urine disease (MSUD), tyrosinemia type 1, propionic acidemia and homocystinuria.

<sup>494</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-sweden.pdf>

<sup>495</sup> <http://www.nfsd.se/hitta-ratt/Samhallsaktorer/Halso---och-sjukvard/Kompetens-inom-omradet-sallsynta-diagnoser/Centrum-for-sallsynta-diagnoser-med-expertteam/>

<sup>496</sup> <http://www.kvalitetsregister.se/>

### Genetic testing

Genetic testing is mainly performed by the six clinical genetics units at the University Hospitals of Lund, Gothenburg, Linköping, Uppsala, Stockholm and Umeå<sup>497</sup>. Some molecular testing, mainly SNP-analysis for single polymorphisms, is done in medical biochemistry units or pathology units without special competence in clinical genetics. There are neither national reference laboratories nor any formal agreements between laboratories regarding co-operation and specialisation. There are no specific national guidelines for genetic testing issued by health authorities.

Genetic tests are reimbursed in the same way as all other medical tests. Laboratories must be authorised by the county councils in order to receive reimbursement (this applies for any laboratory service). There is no private sector of any significance. Genetic testing abroad is possible and is widely used, and there are not any specific regulations opposing this.

Diagnostic tests are registered as available in Sweden for 119 genes and an estimated 175 diseases in the Orphanet database<sup>498</sup>.

### National alliances of patient organisations and patient representation

Rare Diseases Sweden (*Riksförbundet Sällsynta diagnoser*) is a national alliance for rare disease patient organisations. The alliance aims to create a holistic view of the common problems associated with rare diagnoses to support small handicap groups, to ease the particular difficulties of patients with rare diagnoses and to promote and protect human rights. *Riksförbundet Sällsynta diagnoser* also provides funds to support the empowerment of patient organisations. The alliance represents about 50 different rare disease associations and has 12 000 individual members.

Patient organisations for rare diseases are mainly sponsored by private sponsors, but they may also receive public sponsorship for specific projects. Although the Swedish healthcare system emphasises both decentralisation and organisation at municipal, county and regional levels, new bills have been passed by the Parliament to support patient organisations and their activities. One bill supported a conference in November 2009 for members and non-members of *Riksförbundet Sällsynta diagnoser*. Another bill supports further development of a communication platform on the website [www.sallsyntadiagnoser.se](http://www.sallsyntadiagnoser.se) where a diagnosis database for members is available. This communication platform will also allow those concerned to reach both formal and non-formal contacts and get in contact directly via a web community and a web forum.

At present, there is no specific platform for the representation of or consultation with patient organisations in policy issues for rare diseases in Sweden.

### Sources of information on rare diseases and national help lines

#### **Orphanet activities**

Since 2006 the Karolinska Institute has hosted an Orphanet team in Sweden. During 2012 the Orphanet team was integrated with the Regional Centre of Rare Diseases, Karolinska University Hospital. The team collects data on services in Sweden related to rare diseases (for example, specialised clinics, medical laboratories with lists of diagnostics tests, ongoing research, registries, clinical trials, networks, technological platforms, patient organisations and emergency guidelines) for entry into the Orphanet international database. Since 2011, the team provides national information on the Orphanet Sweden website<sup>499</sup>, offering a national entry point to the Orphanet database in Swedish, giving medical professionals, patients, researchers and other interested parties free access to an encyclopedia and inventory of more than 3000 rare diseases, disease related gene description, orphan medical products and specialised services in Sweden and in 35 other countries. All data are reviewed by experts and abstracts are available in five languages. Orphanet Sweden started a close cooperation during 2012 with the recently installed National Function for Rare Diseases and the Swedish Information Centre for Rare Diseases to optimise the national information resources and became part of the Centre for Rare Diseases Stockholm at the Karolinska Institute in 2013.

#### **Official Information Centre for Rare Diseases**

Since 1999, the Swedish Rare Disease Database has been run by the Swedish Information Centre for Rare Diseases (*Informationscentrum för ovanliga diagnoser*) at the Sahlgrenska Academy of the University of Gothenburg. The Centre is financed by the National Board of Health and Welfare and is a national resource for patients, families and professionals. Apart from producing and maintaining the Rare Disease Database<sup>500</sup>, the

<sup>497</sup> <http://sfmg.se/externa-lankar>

<sup>498</sup> <http://www.orpha.net> Information extracted from the Orphanet database (January 2014).

<sup>499</sup> <http://www.orphanet.se/national/SE-SV/index/hemsida/>

<sup>500</sup> <http://www.socialstyrelsen.se/ovanligadiagnoser>

Centre offers assistance in information retrieval and works to increase awareness and knowledge about rare diseases. The Centre acts as a clearing house for all information related to rare diseases and for relevant national resources.

The Rare Disease Database of the National Board of Health and Welfare currently includes detailed and expert-validated information about 300 rare diseases. This material is freely accessible at the website of the National Board of Health and Welfare<sup>8</sup>. Each text in the database includes information on symptoms, occurrence, causes, genetics, diagnostics, treatment, national and regional resources, patient associations, courses for patients and for healthcare professionals, national medical specialists, national (and sometimes international) medical centres, social support, other sources of information, and research references.

The material can be printed out easily. There are also concise information sheets for every disease. All the texts in the database are updated on a regular basis. The material is being translated into English and currently more than 170 information texts can be accessed. The database has more than 1 million visitors per year.

### **Help line**

The Swedish Information Centre for Rare Diseases also serves as a public helpline by answering questions, mediating contacts and giving advice on where to find further assistance. Orphanet Sweden also provides information about national and international rare diseases resources.

### **Other sources of information on rare diseases**

*Ågrenska* contributes to the dissemination of information by providing information with a holistic perspective, including information on available social services and everyday consequences living with a rare disease. They also participate in maintaining the Nordic web resource [www.rarelink.org](http://www.rarelink.org) and the *Ågrenska* Academy was established in 2009 and provides streaming live cast lectures and conferences. Experiences and lecturers are documented and distributed on *Ågrenska*'s website.

There is a close cooperation between *Ågrenska* and Rare Diseases Sweden.

Updated information on orphan medicinal products has been published by *Läkemedelsindustriföreningen* (LIF)<sup>501</sup>, the trade association for research-based pharmaceutical industry in Sweden.

Rare Diseases Sweden (*Riksförbundet Sällsynta diagnoser*) has an online database with information on 75 rare diseases.

In 2013 NFSD launched a new website containing various information and links aimed for persons with rare diseases and professionals.<sup>502</sup>

### **Guidelines**

Professional networks between the University Hospitals of Sweden and within Medical Associations initiates and continuously develops best practices and guidelines for rare diseases. The Best practice clinical guidelines have been elaborated upon as a result of initiatives by *Ågrenska* and professional networks.

### **Training and education initiatives**

A number of courses are held on the initiative of patient organisations and knowledge centres for rare diseases.

*Ågrenska* offers families, adults and children the possibility to benefit from educational activities adapted to their needs. They also provide guidance regarding the availability of social services. In 2013 *Ågrenska* arranged 28 national family stays such as empowerment programmes, including two educational days for professionals and five empowerment programmes for adults (adult stays) with a rare disease.

The University hospital teams that provide care for certain rare diseases educate and inform patients and families during educational days about their specific diagnosis. Medical professionals and representatives from the social services are given specialist training. The Orphanet team also helps specialists in training about how to find validated information on rare diseases.

### **National rare disease events in 2013**

Rare Diseases Sweden organised a seminar ("Rare disorders without borders") to mark Rare Disease Day.

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<sup>501</sup> <http://www.lif.se/>

<sup>502</sup> <http://www.nfsd.se/>

### **Hosted rare diseases events in 2013**

The Nordic Council has funded a project that investigated possible areas for Nordic networking and cross-country cooperation in the field of rare diseases. One of these projects is arranging Nordic conferences.

### **Research activities and E-Rare partnership**

#### ***National research activities***

The Swedish Research Council (SRC) is a government agency under the Ministry of Education and Science. The agency evaluates and prioritises research in medicine, pharmacy, odontology and dental care sciences and decides on project grants in these fields. Project funding is based on quality criteria (bottom-up procedure) and not subject to prioritisation based on research area, with a few exceptions. SRC also makes decisions to provide financing for principal investigators in areas of research where directed support is of strategic value.<sup>503</sup> Rare diseases are thus funded through a yearly call for proposals for project grants; however, there is no dedicated budget for rare diseases. Instead, applications dealing with rare diseases compete with other applications on the basis of the quality of the proposal and not subject to prioritisation of research areas, with a few exceptions. Approximately 80 research projects on rare diseases were funded by SRC.

Medical research on rare diseases is also supported by a number of private foundations. However, these grants are not specifically dedicated to rare diseases.

Research on rare diseases is performed at many universities and university hospitals. This research is supported by grants from the government as well as from non-governmental foundations. Clinical research concerning rare diseases is partly supported by county councils/regions and clinical trials are partly sponsored by orphan drug companies. Some 50 national hospital units and 30 university departments involved in research activities are registered in the Orphanet database.

The Swedish Cancer Society and the Childhood Cancer Foundation are examples of a non-profit organisation which contributes to the funding of cancer research (including rare cancer), information-sharing and supporting activities which aim to improve cancer treatment and care. Research projects are funded following the same policy as that of the SRC.

It is impossible to separate support for rare disease research from support for orphan medicinal product development, as these research efforts are often mixed. In all likelihood, however, probably very little money directly supports orphan drug development.

An example of a centre performing research on rare disorders is Mun-H-Centre. Their activities focus on oral health and orofacial functions such as eating, speech, facial expression and saliva control in rare diseases. Since 1996, data on oral health and orofacial function have been collected through structured parental and clinical observations and registered in a database. Selected data from the database is presented at the Mun-H-Centre website<sup>504</sup> and the information is updated regularly.

The Family programme and Respite service at *Ågrenska* provides the opportunity to meet a large number of children with rare diseases. During family stays using an assessment form (validated by University of Gothenburg, Institute of Psychology), *Ågrenska* performs systematic observations of the children in their school, pre-school and leisure activities, and the results are put together in a database.

#### ***National participation in European research projects***

Teams from Sweden participate/participated in 58 rare disease related FP7 projects, and 8 projects are coordinated by a team based in Sweden.

#### ***E-Rare***

Sweden is not currently a partner of the E-Rare project.

#### ***IRDiRC***

Swedish funding agencies have not yet committed funding to the IRDiRC. However, the progress of the consortium activity programme is followed by Orphanet Sweden and the National Board of Health and Welfare.

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<sup>503</sup> Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (pp20-21).

<sup>504</sup> [www.mun-h-center.se](http://www.mun-h-center.se)

## **Orphan medicinal products**

### ***Orphan medicinal product committee***

A few Orphan medical product expert committees in Sweden have been formed on the initiative of the Swedish Society of Medicine and of local county councils, respectively.

### ***Orphan medicinal products incentives***

The Medical Products Agency (MPA)<sup>505</sup> is responsible for the regulation and surveillance of the development, manufacturing and marketing of medicinal products in Sweden. Regarding orphan medicinal products, centralised marketing authorization application to the European Medicines Agency (EMA) is mandatory. The applications are assessed by the Committee for Human Medicinal Products (CHMP) at the EMA and the decision, valid for the whole of the EU, is granted by the Commission.

The MPA can waive the fees for clinical trial applications and provide scientific advice for researchers, applicants and companies lacking support from the pharmaceutical industry. Concerning the provision of free of charge IMP by clinical trial sponsors, Swedish law allows exemptions: should an obligation to perform a trial after marketing have been a condition of the marketing authorisation being granted for an orphan drug. The same could apply for all clinical trials and IMPs, not just orphan drugs on the condition that the clinical trial is performed without the participation of the pharmaceutical industry or that the clinical trial is special importance to public health.

### ***Orphan medicinal product market availability situation***

According to the MPA, out of the 78 orphan medical products (OMPs) authorised by December 2012. The Dental and Pharmaceutical Benefits Agency had decided to reimburse the following 38 OMPs (some with restrictions): Fabrazyme\*\*, Replagal\*\*, Glivec\*\* (for CML), \*(withdrawn from registry of OMPs for remaining orphan designated conditions), Tracleer\*\*, Somavert, Zavesca (for Niemann-Pick's disease), Carbaglu, Aldurazyme, Ventavis, Onsenal (withdrawn register medicinal products human use), Wilzin, Xagrid, Orfadin, Prialt, Revatio, Nexavar, Sutent\*, Thelin (withdrawn register medicinal products human use), Exjade, Sprycel, Diacomit, Inovelon, Cystadane, Revlimid, Increlex, Tasigna, Thalidomide Celgene, Volibris, Firazyr, Ceplene, Mepact, Afinitor\*, Cayston, Nplate, Revolade\*, Esbriet, TOBI Podhaler, Votubia. The DPBB decided not to reimburse the following 21 OMPs: Busilvex, Litak, Lysodren, Pedeia, Xyrem\*, Naglazyme, Myozyme, Evoltra, Savene, Elaprase, Soliris, Atriance, Glilolan, Yondelis, Torisel, Kuvan, Vidaza, Mozobil, Ilaris\*, Arzerra, VPRIV<sup>506</sup>. Of note, Zavesca\*\* for treatment of Gaucher's disease has been removed from the list of reimbursed OMPs by the DPBB. Reimbursement information is lacking for a number of OMPs, some of which have been withdrawn from the market but the majority being products authorised late in 2011 and 2012. Several OMPs are marketed in Sweden without general reimbursement.

### ***Orphan medicinal product pricing policy***

The Dental and Pharmaceutical Benefits Agency whether a new medicinal product should be reimbursed for community use and approves its pharmacy purchase and selling price. Manufacturers of hospital-use drugs can negotiate directly with the county councils<sup>507</sup>.

### ***Orphan medicinal product reimbursement policy***

Reimbursement decisions are made by The Dental and Pharmaceutical Benefits Agency<sup>508</sup>, a government agency commissioned to make decisions on state subsidies for dental and pharmaceutical products. If a positive decision on reimbursement has been made by the agency, OMPs are fully reimbursed by social insurance in Sweden (there are no conditions specific to orphan drugs) and are available through hospital and community pharmacies when prescribed by a specialist physician or a general practitioner.

### ***Other initiatives to improve access to orphan medicinal products***

Compassionate use of OMPs/non-OMPs has been introduced in Sweden under the responsibility of the MPA. For OMPs not yet available in Sweden, the MPA can approve "named patient prescription" of a certain drug for a certain patient on a yearly basis: this procedure also applies for non-OMPs.

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<sup>505</sup> [www.mpa.se](http://www.mpa.se)

<sup>506</sup> \*The product has been withdrawn by the sponsor from the Registry of Orphan Medical Products, \*\*The product has been removed from the Registry of Orphan Medicinal Products since its 10 years of market exclusivity has expired. For Glivec the applies to the acute lymphatic leukaemia indication only.

<sup>507</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) p117

<sup>508</sup> [www.tlv.se](http://www.tlv.se)

### **Other therapies for rare diseases**

No specific information reported.

### **Orphan devices**

No specific information reported.

### **Specialised social services**

Ågrenska offers families, adults and children the possibility to benefit from programmes that provide guidance to patients regarding latest medical knowledge, available social services as well as educational and holistic activities adapted to their needs.

The Mo Gård Group coordinates measures for patients with communication disabilities, some of which are linked to rare diseases.

The Swedish Act concerning Support and Service for Persons with Certain Functional Impairments (*Lagen om stöd och service till vissa funktionshindrade* - LSS) is an entitlement law that ensures good living conditions for people with extensive and permanent functional impairment, ensuring that they receive the help they need in daily life and that they can influence the support and services they receive. This law is most relevant for rare diseases because in most cases, rare diseases entail functional impairment. Accordingly, municipality institutions provide fully reimbursed activities, such as respite care services, therapeutic recreational programmes and services aimed to promote the quality of life.<sup>509</sup>

## **RARE DISEASE ACTIVITIES IN 2013 IN SWEDEN**

### **National plan for rare diseases and related actions**

In 2013, the plan had still not been adopted officially, but meetings of the NSFD were held concerning the plan and steps are being taken to implement some of the proposed measures, including the establishment of a number of centres of expertise.

### **Centres of expertise**

During 2013 NFSD has collected information concerning these centres in Sweden. Criteria for centres of expertise have also been developed. At the university hospitals Centres for Rare Diseases (CSD) are under construction. There are currently two centres founded, at the university hospitals in Gothenburg and in Stockholm. The development and creation of CSDs at the remaining five university hospitals is ongoing. Within each CSD a number of centres of expertise will be established, each with responsibility for a diagnosis, a group of diagnosis or diagnostic group. At the end of 2013, there were 18 centres of expertise established at the two already founded CSDs.<sup>510</sup>

### **Registries**

During 2012 and 2013 a group including NFSD and Centre for Rare Diseases Stockholm worked together for the purpose of developing a national register of rare diseases. In 2013 an application of funding of a National Quality Register for Rare Diseases was sent in to SALAR, however funding was not granted. The work with a national register will be continued.

### **Sources of information on rare diseases and national help lines**

#### **Orphanet activities**

Orphanet Sweden started a close cooperation during 2012 with the recently installed National Function for Rare Diseases and the Swedish Information Centre for Rare Diseases to optimise the national information resources and became part of the Centre for Rare Diseases Stockholm at the Karolinska Institute in 2013.

<sup>509</sup> <http://www.vgregion.se/upload/HoH/Kansli/R%c3%a5d%20och%20st%c3%b6d/lss-engelska-hso-hoh.pdf>

<sup>510</sup> <http://www.nfsd.se/hitta-ratt/Samhallsaktorer/Halso---och-sjukvard/Kompetens-inom-området-sallsynta-diagnoser/Centrum-for-sallsynta-diagnoser-med-expertteam/>

### **Help line**

The Swedish Information Centre for Rare Diseases also serves as a public helpline by answering questions, mediating contacts and giving advice on where to find further assistance. Orphanet Sweden also provides information about national and international rare diseases resources.

### **Other sources of information on rare diseases**

In 2013 NFSD launched a new website containing various information and links aimed for persons with rare diseases and professionals.<sup>511</sup>

### **National rare disease events in 2013**

Rare Diseases Sweden organised a seminar (“Rare disorders without borders”) to mark Rare Disease Day.

## **1.28. UNITED KINGDOM**

### **Definition of a rare disease**

There is no official definition of a rare disease in the UK. NHS England is responsible for commissioning ‘specialised services’, as defined in the NHS Manual<sup>512</sup>. A large number of these services support people with rare diseases. Similar arrangements apply in the devolved administrations of Scotland, Wales and Northern Ireland.

### **National plan/strategies for rare diseases and related actions**

The government issued its UK Strategy for Rare Diseases in November 2013<sup>513</sup>. The strategy, signed by health ministers of all four countries of the United Kingdom, contains 51 commitments to patients with rare disease. These commitments are wide ranging and include diagnosis, information, healthcare, genomics, registries and research. Health systems and other organisations in the four countries will now develop plans to implement the commitments. A Stakeholder Forum has been established to monitor progress in implementing the strategy.

### **Centres of expertise**

#### **Current organisation of health care for rare diseases in the UK**

In the past, the basic concept in the National Health Service is not that of ‘rare diseases’ but rather that of ‘specialised services’. However, since 1 December 2012, whilst all aspects of specialised service provision remain under the control of the NHS, for the first time, rare diseases policy (including the development of the UK Plan for Rare Diseases) is now the responsibility of the genetics and genomics team in the Health Science and Bioethics Division of the Department of Health England.

The majority of services are commissioned by Clinical Commissioning Groups (CCGs) in partnership with general practice. A large proportion of the money is spent on services for conditions affecting large numbers of people. Services for rarer or more complex conditions, known as “specialised services” are subject to different commissioning arrangements. Specialised services are those with low patient numbers and which few clinicians are able to provide expertly, usually of relatively high cost to provide, requiring planning across larger populations to maintain quality and make treatment centres cost-effective.

Different arrangements exist in Scotland, Wales and Northern Ireland. NHS Wales has recently undergone reorganisation and since April 2010, 7 Local Health Boards are responsible for planning health services for their population. For specialised services, the Welsh Health Specialised Services Committee (WHSCSC) is responsible for the joint planning of Specialised and Tertiary Services on behalf of Local Health Boards in Wales. In Scotland, the National Services Division commissions nationally designated specialist services funded by top sliced funding from the Scottish Government Health Directorates: a service may receive designation if the service need is very low and that there is a clinical need for such a service. In Northern Ireland, the Health and Social Care Board along with 5 local commissioning groups commission services.

<sup>511</sup> <http://www.nfsd.se/>

<sup>512</sup> <http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf>

<sup>513</sup> <https://www.gov.uk/government/publications/rare-diseases-strategy>

Funds for care of patients with rare diseases are included in the current expenditure within the general NHS budget, most of which sits within the budget for specialised services commissioned by NHS England. NHS England's specialised commissioning budget is held nationally for all patients in England, with services planned at national level and contracts held against this budget by 10 local offices. There are budgets for the equivalent structures in Scotland, Wales and Northern Ireland.

Arrangements are in place enabling patients in Scotland, Wales and Northern Ireland to access designated centres although funding is provided by the relevant body in each country. Regional specialist services also exist for genetic diseases but these are funded separately. There is an annual call for applications for national commissioning and designation. Research and epidemiology are not funded under this system.

An article<sup>514</sup> appearing in the *Orphanet Journal of Rare Diseases* applies the Systematic Component of Variation (SCV) in order to look at access to highly specialised healthcare in England, generally affecting fewer than 500 people in England or involving services where *"fewer than 500 highly specialised procedures are undertaken each year"*. Concentrating specialised services in a few centres ensures a volume high enough to maintain excellence, although there is an obligation to ascertain that patients geographically far from such centres are not disadvantaged. The authors applied the Systematic Component of Variation, taking "access" (measured as "service use") in order to study access to highly specialised services, which, prior to April 2013, were commissioned by the National Specialised Commissioning Team (NSCT) in England. The results of this study suggest that *"...equity of access can usually be achieved at about five years after establishing a service, and this is not dependent, within the geography of England, on the number of centres designated"*.

### Registries

In the UK registries are kept for individual conditions and some groups of conditions, including congenital anomalies.

In England, a government-backed initiative will allow researchers unprecedented access to anonymised patient health records. The Clinical Practice Research Datalink (CPRD) is a new observational data and interventional research service of the National Health Service (NHS), jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is *"... designed to maximise the way anonymised NHS clinical data can be linked to enable many types of observational research and deliver research outputs that are beneficial to improving and safeguarding public health"*. Data confidentiality is a top priority for the new service and several mechanisms are in place to protect patient privacy. Access to patient data could help rare disease researchers advance knowledge and understanding of rare conditions.

The United Kingdom contributes/has contributed to the following European registries: EUROCAT, EIMD, TREAT-NMD, AIR, EUROCARE-CF, EURO-WABB, EUHASS, EUROPAC, SCNIR, European Prader-Willi database and EUROWILSON.

### Neonatal screening policy

Under current policy<sup>515</sup> in the United Kingdom, newborn screening is performed for five disorders using blood spot tests: phenylketonuria, congenital hypothyroidism, sickle-cell disorders (haemoglobinopathies), cystic fibrosis and medium chain acyl CoA dehydrogenase deficiency. There are some variations in the four countries of the UK.

Newborn screening is performed in England for phenylketonuria, congenital hypothyroidism, sickle cell disease, cystic fibrosis and medium-chain acyl-CoA dehydrogenase deficiency. Currently all babies in Scotland are offered screening for phenylketonuria, congenital hypothyroidism, cystic fibrosis, sickle cell disease and medium-chain acyl-CoA dehydrogenase deficiency. In Wales screening is offered for as part of routine care for hypothyroidism, cystic fibrosis, phenylketonuria and Duchenne Muscular Dystrophy (boys only). In Northern Ireland Universal screening of all infants at 5 days of age is offered for phenylketonuria, congenital hypothyroidism and cystic fibrosis; screening for homocystinuria and tyrosinaemia is also offered; and screening for medium chain acyl CoA dehydrogenase deficiency (MCADD) has been available from August 2009 and screening for sickle cell started in April 2010. An official list of screening policies is available <http://www.screening.nhs.uk/policydb.php>.

The National Health Service revised its screening programme standards in 2011 for sickle cell disease and thalassaemia: the revised screening standards provide new material relating to objectives and performance indicators and will take effect from April 2012.

<sup>514</sup> <http://www.ojrd.com/content/7/1/85/abstract>

<sup>515</sup> <http://www.screening.nhs.uk/programmes>



## Genetic testing

In the UK, genetic testing for rare inherited conditions for patients being managed by the National Health Service are usually provided by laboratories that are part of a Regional Genetics Centre. Each Regional Genetics Centre comprises a clinical service and laboratories (molecular, cytogenetics and biochemical) that are usually co-located. There are 23 regional Genetics Centres that are situated in tertiary hospitals. There are also a number of specialised laboratories that provide some genetic testing. For example there is a network of laboratories that provide genetic testing for haemophilia and other individual laboratories testing for specific rare conditions such as retinoblastoma or porphyrias.

Clinical genetics (clinical service and laboratory provision) are funded differently in each country of the UK. As noted above, In England specialised services are commissioned by NHS England. In Scotland there is a consortium arrangement, in Wales the Welsh Health Specialised Services Committee is responsible for the joint planning of Specialised and Tertiary Services on behalf of Local Health Boards in Wales, in Northern Ireland the Regional Medical Services Consortium informs the Health and Social Services Boards who commission genetic services.

All the molecular and cytogenetic laboratories across the whole of the UK which are part of a Regional Genetics Centre are members of the UK Genetic Testing Network (UKGTN – [www.ukgtn.nhs.uk](http://www.ukgtn.nhs.uk)). The focus for the UKGTN is to support equity of access to genetic testing services for patients being treated by the National Health Service for rare inherited conditions. The Network is a collaborative group of genetic testing laboratories, clinical geneticists, genetics commissioners and patient representatives.

The core functions of the UKGTN include:

- Approval of molecular, cytogenetic and specialist laboratories for membership where quality standards are met;
- Audit/review of testing provision in order to highlight any areas where there may be inequity of access to genetic testing and to review laboratory compliance in meeting national standards;
- Evaluation of new genetic tests for clinical utility and scientific validity to recommend new testing services for NHS funding through a process called the Gene Dossier process;
- Developing mechanisms to improve the commissioning of genetic services such as standard laboratory currencies;
- Maintaining a publicly available free online database of the member laboratories showing where national services are available and the providers of the tests listed in the NHS Directory of Genetic Testing. The database also provides access to approved gene dossiers and testing criteria;
- Advising NHS policy developers, the Department of Health, the National Specialised Commissioning Team and the National Institute for Health and Clinical Excellence (NICE) on new developments and provide a view on policies that impact on the provision of genetic testing services;
- Providing advice to genetics commissioners on new services and funding requirements.

The term “reference laboratories” is commonly used but it is often country specific and can also refer to different functions depending on the pathology discipline. In England there are two National Genetics Reference Laboratories based in Wessex and Manchester. These laboratories were funded by the Department of Health from 2002 to 2012 to support the UK genetic laboratory centres by bringing new technologies into service. The specific remit of the laboratories includes: technology development, assessment and validation; developing new quality management systems; developing reference and control reagents; developing information systems for genetics; and providing advice to government and other bodies.

The National Genetics Reference Laboratory in Manchester has developed particular expertise in health informatics and bioinformatics applied to genetic medicine. Its current work programme includes the support and development of databases and software tools used in genetic analyses, bioinformatics training for clinical scientists and developing best practice and support for clinical bioinformatics. It also participates in a number of UK and EU funded projects addressing health and bioinformatics issues in genetic medicine, including the GEN2PHEN<sup>516</sup> and EUCERD projects on clinical coding. UKGTN has also commissioned NGRL Manchester to develop a clinical genetics data set for use in the NHS and make recommendations to improve the laboratory information systems and their interoperability with NHS systems and other genetic centres.

When laboratories request UKGTN to evaluate a new test for inclusion on the NHS Directory of Genetic Disorders/Genes for Commissioning an integral component of the Gene Dossier requires the submitting laboratories to develop ‘testing criteria’ (TC). The TC identifies the key features of the disorder, indicates the types of referrers who would be expected to order the test and aims to ensure that a particular

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<sup>516</sup> [www.gen2phen.org](http://www.gen2phen.org)

genetic test is being used for the appropriate target population, i.e. those who are most likely to have the condition. TC can also have an educative role and are a helpful guidance tool. If a clinician is required to complete a TC form then they will get a succinct picture of what may well be a disease with which they are not familiar. TC are available from the UKGTN website by searching for testing services using the online database. Between 2004 and 2012 the UKGTN had evaluated 371 gene dossiers and made recommendation for 293 tests to be available for NHS service. During this time 312 testing criteria were developed. There are more testing criteria than Gene Dossiers approved because some TC have been developed for tests already provided by laboratories prior to the introduction of TC. A long term goal for the UKGTN is to draw up TC for all conditions available through the UKGTN including those that pre-date the development of TC in 2006. The Clinical Molecular Genetics Society also develops best practice guidelines which are available from their website. Individually laboratories may develop referral guidelines for local use.

There are no restrictions on either clinicians or laboratories sending samples abroad for testing however laboratories receiving samples are normally expected to comply with recognised accreditation standards and take part in external quality assessment.

Diagnostic tests are registered as available in the UK for 738 genes and an estimated 833 diseases in the Orphanet database<sup>517</sup>. Between 2004 and September 2012 the UKGTN has recommended tests for 604 disorders and 810 genes for NHS commissioning in addition to 11 panel tests using Next Generation Sequencing (with some of these panels testing over 100 conditions).

### **National alliances of patient organisations and patient representation**

The major alliances representing rare disease patient organisations in the UK are Rare Disease UK, the Specialised Healthcare Alliance (SHCA) and the Genetic Alliance UK<sup>518</sup> (formerly the Genetic Interest Group). Rare Disease UK was established in November 2008 as a joint initiative between Genetic Alliance UK and others in response to the unmet health care needs of families who currently struggle to get access to integrated care and support from the NHS.

#### Rare Disease UK

Rare Disease UK (RDUK)<sup>519</sup> is the national multi-stakeholder alliance for people with rare diseases and all who support them. Their membership of over 1,600 includes 250 patient groups, patients, clinicians, industry, academics and researchers. RDUK provides a unified voice for the rare disease community, capturing the experiences of patients and families and raising the profile of rare diseases across the UK.

RDUK has campaigned for the development and implementation of an effective strategy that is comprehensive and fully reflects the needs of the rare disease community in the UK.

RDUK is actively engaged with all four health departments and national health services in the UK. In England, RDUK is co-producing with NHS England a rare disease plan to implement the health care recommendations of the UK rare disease strategy in England.

#### Specialised Healthcare Alliance (SHCA)

The Specialised Healthcare Alliance (SHCA) was formed in 2003 to campaign on behalf of people with rare and complex conditions. It has now grown to over 100 patient-related organisations, supported by a far smaller number of corporate members. The SHCA focuses on the overarching policies and structures of specialised commissioning and has been closely involved with the development of specialised commissioning policy over the last decade. In particular, the Alliance has focused on aligning resource and expertise in the commissioning of specialised services, ensuring multidisciplinary input into the development of services and the need for better integration and planning of specialised care for patients, supported by care co-ordination and registries. The SHCA has run a number of workshops in partnership with the NHS in England and holds a conference every two years on the outlook for specialised services.

The Alliance partnered with NHS England to engage with the public on the scope for NHS England's five-year strategy for specialised services.

#### Genetic Alliance UK

Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. The Alliance is made up of over 170 patient organisations. The aim of the charity is

<sup>517</sup> Information extracted from the Orphanet database (January 2014).

<sup>518</sup> <http://www.geneticalliance.org.uk/>

<sup>519</sup> <http://www.raredisease.org.uk/>

to ensure that high quality services, information and support are provided to all who need them. Genetic Alliance UK actively supports research and innovation across the field of genetic medicine.

The organisation was founded in 1989 as the Genetic Interest Group and changed to its current name in 2010. In 2008 Genetic Alliance UK launched Rare Disease UK.

The Northern Ireland Rare Disease Partnership (NIRDP) was formally launched on Rare Disease Day 2012 with support from patients, families, health professionals and government representatives. A non-profit organisation, the NIRDP seeks to bring together rare disease patients and organisations with clinicians and other health professionals, researchers and producers of specialist medicines and equipment, health policy makers and academics to find “...practical ways of improving the quality of life, treatment and care for those with rare diseases in Northern Ireland”. The association works closely with the Patient Client Council, RDUK, DHSSPS, the Health and Social Care Board in Northern Ireland, the Public Health Agency in Northern Ireland, IPOSSI, and GRDO in the Republic of Ireland.

Patient organisations are officially recognised thanks to a strong government policy for public and patient involvement (PPI). Hospitals and health services are required to consult their patients about changes to the service and there are continuous surveys a patient experience and patient satisfaction in NHS hospitals. Patient opinion is not binding. In most cases patients’ representatives are eligible for reimbursement of expenses.

Amongst the sources of funding available for patient organisations, the government makes funding available to patient organisations through a system known as a Section 64 grant. Many patient organisations have also obtained funding from the National Lottery which is obliged by law to give a percentage of its profits to charitable organisations: activities such as capacity building, networking, dissemination of information, educational events, exchange of best practices, capacity building to improve patients’ integration in social environments and outreach to very isolated patients are all eligible for funding by these schemes. Some patient groups (e.g. those for Alström Syndrome and Ataxia-telangiectasia) receive NHS funding to provide support to clinics. This is a novel structure where the clinic is partnered by patient groups, hospitals and the NHS.

#### **Sources of information on rare diseases and national help lines**

##### ***Orphanet activity in the United Kingdom***

Since 2004 there is a dedicated Orphanet team for the United Kingdom (Orphanet UK) hosted at the University of Manchester. This team was officially designated by the Department of Health as the official Orphanet team in the United Kingdom in 2010.

Orphanet UK is in charge of collecting and validating data on rare disease related services (expert centres, medical laboratories, patient organisations, clinical trials, patient registries, mutation databases/biobanks and ongoing research), in the UK and in Ireland for entry into the Orphanet database. The Orphanet UK team maintains the Orphanet UK national website<sup>520</sup> that aims to be an interactive communication tool between the team and the rare disease community. The team represents Orphanet at many major national conferences and events such as workshops on rare diseases and the Rare Disease Day and it also participates regularly at the ESHG (European Society of Human Genetics) conference. Orphanet UK has established collaborations with Dyscerne (A Network of Centres of Expertise for Dymorpology), Rare Disease UK and Ataxia UK, a charity aiming to support everyone affected by ataxia and fund research into developing treatments. The team also works closely with the National Genetics Reference Laboratory (NGRL) Manchester and has established solid relations with other rare disease organisations such as the Genetic Alliance UK, the British Paediatric Surveillance Unit (BPSU) and the Myrovilitis Trust.

##### ***Official information centre for rare diseases***

There is no official information centre for rare diseases in the UK other than Orphanet.

##### ***Help line***

There is no official helpline specifically dedicated to rare diseases in the UK but there are national NHS helplines which differ slightly in each of the four countries. In England and Wales the helpline is known as NHS Direct, and in Scotland as NHS 24.

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<sup>520</sup> <http://www.orphanet.co.uk>

### **Other sources of information on rare diseases**

Information, advice and support are generally provided by patient organisations dealing with particular rare diseases. Some information is provided by NHS websites: <http://www.nhs.uk/>, <http://www.england.nhs.uk/> and <http://www.evidence.nhs.uk>.

Contact-a-Family is a key resource for rare diseases. It runs a help line and an online service putting patients in contact with other patients with the same disease (rare or non-rare) and support groups. Other larger patient organisations, both large and small are instrumental in providing information and support. Many run help lines providing general and technical information, provide written information and psychological support: these are funded through various means including donations, fundraising, pharmaceutical companies and grants for the government and other organisations. Many hospitals, especially in the nationally commissioned services also run help lines: these are funded using general health services funds.

UK-based charity Unique<sup>521</sup> has been gathering information on specific chromosome disorders for almost 25 years and since 2003 has been producing family-friendly, medically-verified, disorder-specific information leaflets (learn more.) To date, Unique has published over 125 guides on individual chromosomal disorders, which are available free of charge, and frequently in other languages including Dutch, French, German and Spanish. The Unique newsletter reports that for many families, the leaflets are the first concrete source of information obtained for a specific disorder. Now another new guide, entitled After Diagnosis: What Happens Next? The Early Years, targets parents of pre-school children (0 to 4 years) with a rare chromosome disorder and/or global developmental delay. This guide responds to questions relevant to parents of a newly-diagnosed infant everywhere, and also lists resources available in the United Kingdom for affected children and their families.

### **Guidelines**

Nowgen<sup>522</sup>, a centre of excellence in public engagement<sup>522</sup>, education and professional training in biomedicine, part of the NIHR Manchester Biomedical Research Centre, in collaboration with Dyscerne<sup>523</sup> has published a portfolio of management guidelines for rare diseases (Angelman syndrome, Kabuki syndrome, Noonan syndrome, Williams syndrome, 22q11 Deletion Syndrome, Achondroplasia, Neurofibromatosis Type 1 & Neurofibromatosis Type 2) using validated methodologies<sup>524</sup>.

A range of other guidelines for rare and very rare diseases are posted on the NHS England website or published in professional journals.

### **Training and education initiatives**

Nowgen's professional training team delivers a portfolio of training courses that are particularly relevant to healthcare professionals involved in the management and treatment of rare diseases. These include: Antenatal and Newborn Screening; Molecular Genetics for Genetic Counsellors; Molecular Genetics for Cytogeneticists and Bioinformatics for Clinical Geneticists. Many of these courses have included interactive sessions to inform delegates about Orphanet.

### **National rare disease events in 2013**

The UK based charity 'Jeans for Genes' holds an annual awareness day to raise funds for genetic disorders<sup>525</sup>.

Rare Disease UK and their member organisations planned a number of events to mark Rare Disease Day 2013 across the United Kingdom. This included a parliamentary reception at Westminster on 27 February 2013. The reception, hosted by Elizabeth Kendall MP, included speakers from RareDisease UK, Earl Howe and a number of academics in the field as well as patients. At the event, a new report entitled 'Rare Disease care coordination: delivering value, improving services'<sup>526</sup> was launched by Rare Disease UK. At the Scottish Parliament and Welsh Assembly receptions were hosted to launch two new reports from Rare Disease UK 'Experiences of Rare Diseases: Patients and Families in Wales'<sup>527</sup> and 'Experiences of Rare Diseases: Patients and Families in Scotland'<sup>528</sup> which investigate the experience of patients and families living with a rare

<sup>521</sup> <http://www.rarechromo.org/html/home.asp> and <http://www.rarechromo.org/html/LeafletProtocol.asp>

<sup>522</sup> [www.nowgen.org.uk](http://www.nowgen.org.uk)

<sup>523</sup> [www.dyscerne.org](http://www.dyscerne.org)

<sup>524</sup> [www.dyscerne.org/dysc/Guidelines](http://www.dyscerne.org/dysc/Guidelines) & <http://www.mangen.co.uk/professionals/clinical-services/useful-documents.aspx>.

<sup>525</sup> <http://www.jeansforgenes.com/about>

<sup>526</sup> <http://www.raredisease.org.uk/documents/RDUK-Care-Coordinator-Report.pdf>

<sup>527</sup> <http://www.raredisease.org.uk/documents/Research%20Report/rduk-walessurvey-report-2.pdf>

<sup>528</sup> <http://www.raredisease.org.uk/documents/Research%20Report/rduk-scotland-survey-report.pdf>

condition in these countries. A range of awareness raising events were also organised across Britain for the Day.

On 25 July 2013 a workshop was organised by the Department of Health to discuss the draft proposals of National Plan on Rare Diseases. The workshop engaged a wider range of stakeholders than the Rare Disease Stakeholder Forum which has been assisting the Department of Health to develop the National Plan. On 22 November 2013 the finalised Rare Disease Strategy was launched.

### **Hosted rare disease events in 2013**

OrphaNews announced the following rare disease events: Mitochondrial Disease: Translating biology into new treatments (2-4 October 2013, Cambridge), 8th International Prader-Willi Syndrome Conference (17-21 July 2013, Cambridge), 4th International DSD (Disorders of Sex Development) Symposium (7-9 June 2013, Glasgow).

### **Research activities and E-Rare partnership**

#### ***National research activities***

Rare diseases research has been supported in the UK. Government funding is mostly available through the Research Councils (e.g. the Medical Research Council) and the National Institute for Health Research (NIHR). Many of the NIHR-funded Biomedical Research Centres (BRCs) and Biomedical Research Units (BRUs) undertake translational health research into rare diseases, and in April 2012 a new round of BRCs and BRUs commenced with £800 million investment over 5 years. In addition, as announced in *the Strategy for UK Life Sciences*, the Department of Health is creating a new NIHR BioResource, to provide a national cohort of healthy volunteers, patients and their relatives who wish to participate in experimental medicine research, and are willing to provide clinical information and samples that will enable them to be recalled for specific studies. These studies will have the potential to rapidly advance the understanding of disease mechanisms, identify potential drug targets, and improve insight into the therapeutic potential and limitations of existing and emerging therapies. The BioResource is on track to be launched in early 2014, however it is already supporting translational research into rare diseases, which is one of its 4 themes of focus. On the basis of the research into rare diseases being undertaken in the NIHR, the Department of Health has confirmed NIHR's membership of the International Rare Disease Research Consortium (IRDiRC) this consortium.

There are several major funding charities, particularly for cancer and heart diseases, and a number of rare diseases charities fund research (such as the Muscular Dystrophy Campaign, the Cystic Fibrosis Trust, the Dystrophic Epidermolysis Association etc). Many products for rare diseases have been put through trials in the UK by major pharmaceutical companies (i.e. enzyme replacement therapies, drugs for pulmonary hypertension, etc).

In 2012, a new funding mechanism was created by global charitable foundation the Wellcome Trust. The Pathfinder Awards support academic-industry partnerships dedicated to early-stage applied research in the field of rare and neglected diseases. Open to international participation, the Pathfinder Awards seek to kick-start pilot research initiatives showing potential for developing innovative medicinal products for rare or neglected diseases. The first two awards were granted in 2012, both for rare diseases.

In 2012, the Medical Research Council awarded the University of Edinburgh's MRC Human Genetics Unit and the MRC Institute of Genetics and Molecular Medicine £60 million (€74.2 million) in funding over a five-year period to study illnesses and inherited disorders, including cystic fibrosis, retinitis pigmentosa, anophthalmia, and other rare conditions.

#### ***Participation in European research projects***

British teams participate or have participated in 134 rare disease related FP7 projects, and UK teams coordinated 30 projects.

#### ***E-Rare***

The UK is not currently a partner of the E-Rare project.

#### ***IRDiRC***

The National Institute for Health Research is a committed member of the IRDiRC.

### **Orphan medicinal products<sup>529</sup>**

The promotion of the development of orphan medicinal products in the UK takes place at a European, and not national, level: orphan medicinal products obtain Marketing Authorisation through the centralised procedure at the EMA. Orphan medicinal products obtain Marketing Authorisation through the centralised procedure at EMA. The body responsible for regulatory approval in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA): accessibility to medicinal products is generally determined by the National Institute for Clinical Excellence (NICE).

#### ***Orphan medicinal product committee***

From April 2013 NICE established a new committee to evaluate highly specialised technologies. This committee will take on the role of appraising drugs for ultra-rare conditions. The first product to go through this new procedure is eculizumab for atypical haemolytic uraemic syndrome.

#### ***Orphan medicinal product incentives***

No specific incentives reported.

#### ***Orphan medicinal product market availability situation***

No specific information has been provided concerning orphan medicinal products launched on the market in the United Kingdom.

#### ***Orphan medicinal product pricing policy***

Control of branded manufacturer prices for all medicines is regulated by the Pharmaceutical Price Regulation Scheme which is essentially a profit cap adjusted to the company's capital in the UK. Value-priced pricing will come into effect from 2014 for newly launched branded medicines<sup>530</sup>.

#### ***Orphan medicinal product reimbursement policy***

The NHS provides all medicines almost free of charge to all patients: there is a small co-payment ('prescription charge') for out-of-hospital drugs. However the elderly, children and those on low income (and other groups) are exempt from this charge. There is no prescription charge in Scotland and Wales.

Licensed drugs are paid for by the NHS in the UK. In England, decisions on non-specialised services are taken by relevant funding bodies at CCG level, not nationally, in the light of available funds. This has led to criticism that access to drugs can be a "postcode lottery" i.e. access varies widely depending on where an individual lives. For specialised services, including most drugs for people with rare diseases, NHS England sets access policies which apply equally across England, eliminating this variation. NICE is also able to oblige the NHS to make products available to patients within 90 days of its appraisal.

#### ***Other initiatives to improve access to orphan medicinal products<sup>531,532</sup>***

Orphan medicinal products, like other drugs, are distributed through hospital pharmacies and specialist centres. Home delivery is available for various products, for example enzyme replacement therapies.

Patients with rare diseases can receive unlicensed drugs; in such cases the doctor applies to the MHRA to import it on an individual named patient basis.

The National Institute for Health and Clinical Excellence (NICE) started to commission expert assessments for off-label medicine use from spring 2012<sup>533</sup>. These assessments do not constitute formal guidance, but rather provide "a summary of available evidence on selected unlicensed drugs to inform local decision-making". The National Health Service (NHS) in England receives some 1000 specific requests for off-label use annually. The announcement for the off-label product assessments has been met with approval from the rare disease community.

<sup>529</sup> Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

<sup>530</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Acces Issues, Donald Macarthur (2011) pp.86-7

<sup>531</sup> Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

<sup>532</sup> Written using information from the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) (p23).

<sup>533</sup> <http://www.nice.org.uk/newsroom/news/BetterInformationOnUnlicensedDrugS.jsp>

### **Other therapies for rare diseases**

No specific information reported.

### **Orphan devices**

No specific information reported.

### **Specialised social services**

Respite care services are available in most parts of the UK and are provided by the NHS and charitable organisations. Patient groups also organise holiday camps for children and adolescents. Reimbursement varies: all NHS services are free but charities may ask for a small co-payment in some cases. The provision of recreational programmes is patchy but it is difficult to obtain full information: schemes are usually run by individual patient organisations or by local authority social service departments. A small co-payment is usually expected. Services to integrate patients in daily life are the responsibility of local authority social services departments which are government financed.

## **RARE DISEASE ACTIVITIES IN 2013 IN THE UNITED KINGDOM**

### **National plan/strategies for rare diseases and related actions**

The government issued its UK Strategy for Rare disease in November 2013<sup>534</sup>. The strategy, signed by health ministers of all four countries of the United Kingdom, contains 51 commitments to patients with rare disease. These commitments are wide ranging and include diagnosis, information, healthcare, genomics, registries and research. Health systems and other organisations in the four countries will now develop plans to implement the commitments. A Stakeholder Forum has been established to monitor progress in implementing the strategy.

### **Registries**

In England, a government-backed initiative will allow researchers unprecedented access to anonymised patient health records. The Clinical Practice Research Datalink (CPRD) is a new observational data and interventional research service of the National Health Service (NHS), jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is “... designed to maximise the way anonymised NHS clinical data can be linked to enable many types of observational research and deliver research outputs that are beneficial to improving and safeguarding public health”. Data confidentiality is a top priority for the new service and several mechanisms are in place to protect patient privacy. Access to patient data could help rare disease researchers advance knowledge and understanding of rare conditions.

### **Orphan medicinal products<sup>535</sup>**

#### ***Orphan medicinal product committee***

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<sup>534</sup> <https://www.gov.uk/government/publications/rare-diseases-strategy>

<sup>535</sup> Written using information from KCE reports 112B : Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 (pp 62-66)

<sup>536</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Acces Issues, Donald Macarthur (2011) pp.86-7

## 2. OTHER EUROPEAN COUNTRIES

### 2.1. ICELAND

#### Definition of a rare disease

In Iceland a condition is defined as rare if it affects 2 or fewer individuals per 10 000.

#### National plan/strategy for rare diseases and related actions

In Iceland there is not yet a specific plan for rare diseases. In 2012, for the first time, Iceland was able to send a representative to a EUCERD meeting, which increased discussion and awareness of rare diseases in Iceland at the level of the Ministry, stakeholders and rehabilitation services. Representatives from these organisations now meet regularly with the purpose to increase awareness of rare diseases within the country. A plan for rare diseases is being defined by a working group with the cooperation of stakeholders. A strategy for disabilities was launched in 2012 and the plan is to revise this document in a few years and include a chapter on rare diseases within it. Currently, there is no specific funding in place for rare diseases.

#### Centres of expertise

Up to now, no centres in Iceland have been designated as national centres of expertise. However, since 1986 one national habilitation centre provides services for children and adolescents with conditions leading to disability, including rare diseases and syndromes. The same accounts for diagnostic and habilitation services for visually impaired and hearing impaired children and adults including those with rare diagnosis. These services are centralised at two national centres. Administrative databases designed to collect and store data on causes of disability (including rare diseases/syndromes) are developed at these three centres and updated regularly. The plan is to further enhance services for individuals with rare diseases at these centres.

#### Registries

In Iceland there is no formal national committee dedicated to dealing with registries but administrative databases (see above) are organised by directors of the individual national centres. In 2012, a centralised database on causes of deaf blindness (combined hearing and visual impairment) among Icelandic children and adults was established in cooperation of these three national centres servicing people with disabling conditions. These administrative databases are financed by the state. In addition, Icelandic teams contribute to the EUROCARE CF and RARECARE European registries.

#### Neonatal screening policy

There have not been any developments in the neonatal screening policy in 2012 nor have there been additions to the list of rare diseases tested. Since 1 January 2008 neonates in Iceland have been screened for 42 different rare diseases using tandem mass spectrometry.

#### Genetic testing

Genetic testing (as well as genetic counseling) in Iceland is centralised at the Department of Genetics and Molecular Biology of the National University Hospital of Iceland. Other than guidelines regarding the newborn screening, Iceland does not have national guidelines regarding genetic testing. Genetic testing abroad is possible as specimens are frequently sent abroad for advanced testing which is not possible to perform in Iceland. The patients pay only a small proportion of the total cost of genetic testing (universal health care system) but there are no specific provisions in place for patients with rare diseases.

#### National alliances of patient organisations and patient representation

In Iceland there is one patient organisation focusing on children with rare diseases and their families. The organisation is called "Unique children". In 2012, collaboration was initiated between representatives from the organisation "Unique children", the Ministry of Welfare and the national habilitation centre with the aim to increase awareness of rare diseases at all service levels in the country.



## **Sources of information on rare diseases and national help lines**

### ***Orphanet activities in Iceland***

There is no Orphanet team in Iceland.

### ***Official information centre for rare diseases***

In Iceland there is no official information centre for rare diseases. However, the patient organisation, Unique Children, provides information regarding rare diseases and the Nordic cooperation Rarelink (with its Icelandic link, [www.rarelink.is](http://www.rarelink.is)) provides information on hundreds of rare diseases (either in the Nordic languages or English). Rarelink also offers networking for people with rare diseases i.e. people can get information on others within the Nordic countries with the same diagnosis. The organisation Unique Children is not funded by the state but by donations and specific fundraising activities.

### ***Help line***

There is no rare disease specific helpline in Iceland.

### ***Other sources of information***

Iceland has taken part in Nordic activities regarding rare diseases during the past several years. In autumn 2011 the homepage [www.rarelink.is](http://www.rarelink.is) was launched and since 2012 information regarding several rare diseases and syndromes has been translated into the Icelandic language and published on this website.

### ***Guidelines***

Best practice guidelines for rare diseases have not been produced in Iceland.

### ***Training and education initiatives***

No specific activity reported.

### ***National rare disease events in 2013***

The organisation Unique Children celebrated the Rare Disease Day 2013. This year the organisation donated money to the Children's Hospital in Iceland and to Rjodur which is a centre offering respite care and rehabilitation services for chronically ill and disabled children.

### ***Hosted rare disease events in 2013***

No specific activity reported.

### ***Research activities and E-Rare partnership***

#### ***Research activities***

There are no specific programmes for rare diseases research in Iceland and there are not any fund-raising initiatives for rare diseases research in Iceland.

#### ***Participation in European research projects***

Teams in Iceland have participated in 31 rare disease related FP7 projects and 2 projects are coordinated in Iceland.

#### ***E-Rare partnership***

Iceland is currently not an E-Rare partner and has not yet participated in these calls.

### ***IRDiRC***

Icelandic funding agencies are not yet committed members of IRDiRC.

### ***Orphan medicinal products***

#### ***Orphan medicinal product committee***

In Iceland there is no orphan drug committee and there are no official plans to introduce one.

#### ***Orphan medicinal product incentives***

No specific information reported.

**Orphan medicinal product market availability situation**

No specific information reported.

**Orphan medicinal product pricing policy**

No specific information reported.

**Orphan medicinal product reimbursement policy**

No specific information reported.

**Other initiatives to improve access to orphan medicinal products**

No specific information reported.

**Orphan devices**

No specific information reported.

**Specialised social services**

A new information centre for children with rare disease and their families was opened in Autumn 2012. The centre is called Leiðarljós (Guiding Light) and offers parents of children with rare diseases nursing services, social support as well information regarding available services.

## RARE DISEASE ACTIVITIES IN 2013 IN ICELAND

**National plan/strategy for rare diseases and related actions**

In 2012, for the first time, Iceland was able to send a representative to a EUCERD meeting, which increased discussion and awareness of rare diseases in Iceland at the level of the Ministry, stakeholders and rehabilitation services. Representatives from these organisations now meet regularly with the purpose to increase awareness of rare diseases within the country. A plan for rare diseases is being defined by a working group with the cooperation of stakeholders. A strategy for disabilities was launched in 2012 and the plan is to revise this document in a few years and include a chapter on rare diseases within it. Currently, there is no specific funding in place for rare diseases.

**National rare disease events in 2013**

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**Specialised social services**

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## 2.2. ISRAEL

**Definition of a rare disease**

There are ongoing discussions in the Commission for rare diseases regarding the definition of rare diseases in Israel and the need for a legislation and regulation.

### **National plan/strategy for rare diseases and related actions**

There is currently no national plan for rare diseases in Israel. The costs related to these diseases are included in the national health care budget. There is no funding for action in the field of rare diseases. The Parliament lobby for rare diseases was founded in 2009 and met again in 2013; several laws have been submitted to the parliament but there is no legislation as of yet.

The costs related to rare diseases are included in the national health care budget.

### **Centres of expertise**

There is a Ministry of Health policy to develop centres of expertise for rare diseases. There are several centres in Israel recognised for providing expert services in the field of rare diseases including, the National Multidisciplinary Clinic for Prader Willi Syndrome, and the Hereditary Hemorrhagic Telangiectasia HHT Clinic.

### **Registries**

Several registries are maintained in Israel including a cystic fibrosis registry, SCNIR registry, trisomy 21 registry and a registry of genetic syndromes causing bone marrow failure. At the moment there is no governmental financing for these registries and no national committee dedicated to the issue of registries nor a rare disease registry.

Teams in Israel contribute to the EUROCARE CF and SCNIR European registries.

### **Neonatal screening policy**

In Israel, all newborns are screened for 9 rare metabolic diseases and 2 endocrine diseases. All activities related to these tests and quality control is carried out under the supervision of the Ministry of Health at the Sheba-Tel Haschomer governmental medical centre.

### **Genetic testing**

Genetic testing is under the supervision of the Ministry of Health and accreditation is obligatory. There is one private reference laboratory and in many cases the reference laboratories are abroad. There also are Guidelines published by the Medical Genetics Association for prenatal population genetic screening. From the beginning of 2013, the majority of the tests including SMA, Fragile X, Cystic fibrosis are provided for free. While genetic tests should be provided free there are still many challenges; chromosomal microarray are reimbursed for children with mental retardation and malformations and for prenatal testing of fetuses with malformations; mutation analysis and gene sequencing (in part) are reimbursed, although still there are many families who need to pay for genetic tests privately. Genetic testing abroad is possible and testing for any gene is available in private laboratories, but in most cases are not reimbursed and patients pay for these tests privately.

In the Orphanet database, 233 genes are tested in Israel for 258 diseases<sup>537</sup>. Private testing for any known disease-causing gene is available in private labs.

### **National alliances of patient organisations and patient representation**

There is no alliance for rare diseases, although there is a non-rare disease specific patient alliance in Israel who is taking action to promote various themes related to Rare Diseases. There are plans to establish an organisation for rare disease patients.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities***

The Orphanet Israel country coordinator is currently based at the Sheba Tel Haschomer Medical Centre. Orphanet Israel does not currently receive national or European funding. The representative collects data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) for entry into the Orphanet database. This activity is not systematic and is based on the free time of the representative. Orphanet has been officially recognised by the Israeli Ministry of Health; there is a need for funding in order to maintain the national website in a systematic matter. The Orphanet team maintains the Orphanet Israel national website<sup>538</sup> in Hebrew.

<sup>537</sup> Information extracted from the Orphanet database (January 2014).

<sup>538</sup> <http://www.orpha.net/national/IL-HE/index/%D7%93%D7%A3-%D7%94%D7%91%D7%99%D7%AA-%D7%A9%D7%9C-%D7%90%D7%95%D7%A8%D7%A4%D7%A0%D7%98-%D7%99%D7%A9%D7%A8%D7%90%D7%9C/>

### **Official information centre for rare diseases**

There is no official information centre for rare diseases; there is Health Ministry information website on general issues linked to the health insurance and national insurance.

### **Help line**

No specific information reported.

### **Other information on rare diseases**

There is some publicly open information on rare diseases in Israel available on the Community Genetics Department at the Ministry of Health Website and at the Israeli site at the Goldenhelix mutation database. Web-based information is available for a limited number of diseases and certain information is maintained using a state budget.

### **Guidelines**

No specific information reported.

### **Training and education initiatives**

No specific information reported.

### **National rare disease events in 2013**

A Rare Disease Day event was organised by the Orphanet coordinator at the Meir medical centre with support from the Clalit health insurance fund. A meeting on RASopathies was organised in June 2013.

### **Hosted rare disease events in 2013**

A Cardio-Facio-Cutaneous (CFC) meeting on strategies to study RASopathies and other rare diseases was organised on 24 June 2013 in Haifa.

### **Research activities and E-Rare partnership**

#### **National research activities**

There are fund-raising initiatives by specific patient organisations for various rare diseases such as familial dysautonomia, ALS, etc.

#### **Participation in European research projects**

Teams in Israel participate/have participated in 10 rare disease related FP7 projects.

#### **E-Rare**

Israel is part of the E-Rare consortium, represented by the CSO-MOH (Ministry of Health) and participated in the first two transnational calls in 2007 and 2009 (Israel is represented in three of the selected projects in the first two calls). Israel participated in the third call in the context of E-Rare2 in 2011 and funds Israeli teams participating in 4 of the selected consortia. Israel participated in the 4<sup>th</sup> Joint Transnational Call in 2012, with teams from Israel participating in 4 out of the 11 projects selected for funding. Israel participated in the 5<sup>th</sup> Joint Transnational Call in 2013, with teams from Israel participating in 3 out of the 12 projects selected for funding. Israel participated in the 6<sup>th</sup> joint transnational call in 2014 with teams from Israel participating in 4 projects.

#### **IRDiRC**

The CSO-MOH as member of the E-Rare Group of Funders joined the IRDiRC in 2012.

### **Orphan medicinal products**

Currently in Israel there is no agreed definition of an Orphan disease or drug. In addition, there is no special legislation regulating the development registration and payment for orphan medicinal product therapies. Thus these products and patients find themselves competing with general diseases, to their disadvantage.

#### **Orphan medicinal product committee**

There is currently no such committee. Attempts to reform the law and regulations have thus far not succeeded, but a draft law is currently going through the Parliament.

### **Orphan medicinal product incentives**

No specific information reported.

### **Orphan medicinal product market availability situation**

All new drugs (including orphan medicinal products) must be registered with the Ministry of Health. The pharmaceutical division has regulations regarding the registration of new drugs, similar to those of the EMA and FDA. There are 63 drugs for rare diseases available in Israel, including: Rilutek, Flolan, Novoseven, Replagal, Lyozyme, Elaprase, Incredlex, Soliris, Firazyr, Kuvan, Carbaglu, Orfadin, Naglazyme, Elelyso.

### **Orphan medicinal product pricing policy**

No specific information reported.

### **Orphan medicinal product reimbursement policy**

Hospitals and health insurance companies pay for the drugs which are registered in the national 'health basket'. Since 1995 the year of the national health insurance law the committee in charge of the 'health basket' meets once a year in order to decide which drugs and technologies will be financed by the government. The committee is composed of representatives of all the relevant stakeholders and interested parties. Since budgets are limited, this process of selection is always controversial. More products are proposed than are accepted and the process is complex and competitive. Nevertheless, some orphan medicinal products have been accepted in recent years (e.g. myozyme, elaprase, naglazyme, fabrazyme, replagal, Kuvan, carglumic acid, nitisinone and miglustat for Gaucher disease, cystagon, berinert).

### **Other initiatives to improve access to orphan medicinal products**

A "compassionate" procedure ("Form 29g") exists by which life-saving products may be given to individual patients on the responsibility of the treating physician, even if the drug is not registered, or is off-label, or is not included in the basket. However, obtaining such products and paying for them may be challenging

### **Other therapies for rare diseases**

No specific information reported.

### **Orphan devices**

A draft law on this subject has been proposed.

### **Specialised social services**

No specific information reported.

## **RARE DISEASE ACTIVITIES IN 2013 IN ISRAEL**

### **National plan/strategy for rare diseases and related actions**

The Parliament lobby for rare diseases was founded in 2009 and met again in 2013; several laws have been submitted to the parliament but there is no legislation as of yet.

### **Centres of expertise**

There is a Ministry of Health policy to develop centres of expertise for rare diseases.

### **Genetic testing**

Genetic testing is under the supervision of the Ministry of Health and accreditation is obligatory. There is one private reference laboratory and in many cases the reference laboratories are abroad. There also are Guidelines published by the Medical Genetics Association for prenatal population genetic screening. From the beginning of 2013, the majority of the tests including SMA, Fragile X, Cystic fibrosis are provided for free. While genetic tests should be provided free there are still many challenges; chromosomal microarray are reimbursed for children with mental retardation and malformations and for prenatal testing of fetuses with malformations;

mutation analysis and gene sequencing (in part) are reimbursed, although still there are many families who need to pay for genetic tests privately. Genetic testing abroad is possible and testing for any gene is available in private laboratories, but in most cases are not reimbursed and patients pay for these tests privately.

#### **National alliances of patient organisations and patient representation**

There are plans to establish an organisation for rare disease patients.

#### **National rare disease events in 2013**

A Rare Disease Day event was organised by the Orphanet coordinator at the Meir medical centre with support from the Clalit health insurance fund. A meeting on RASopathies was organised in June 2013.

#### **Hosted rare disease events in 2013**

A Cardio-Facio-Cutaneous (CFC) meeting on strategies to study RASopathies and other rare diseases was organised on 24 June 2013 in Haifa.

#### **E-Rare**

Israel participated in the 5<sup>th</sup> Joint Transnational Call in 2013, with teams from Israel participating in 3 out of the 12 projects selected for funding. Israel participated in the 6<sup>th</sup> joint transnational call in 2014 with teams from Israel participating in 4 projects.

## **2.3. NORWAY**

#### **Definition of a rare disease**

In Norway a medical disorder is considered rare when there are less than 100 known cases per million inhabitants. In Norway this corresponds to fewer than 500 known cases. Some medical disorders with a higher prevalence may also be considered rare if only a small number of people have been diagnosed or because of scarcity of knowledge among service providers.

#### **National plan/strategy for rare diseases and related actions**

There is ongoing political and practical activity in the field of rare disorders in Norway. Services for people with rare disorders and their families was an area of priority in the government's early plans of actions for the disabled (1990-1993 and 1994-1997). In the following years these action plans have been implemented, followed up and developed to meet current needs.

As users of long-term, coordinated health care and/or social services, patients are entitled to an Individual Plan, which is a personal overall plan for service provisions. Particularly relevant to rare disorders patients, and not conditional on any particular diagnosis or age, this plan will contain an outline of the objectives, resources and the services the patient requires. Despite the various resources available to rare disease patients in Norway, a study reveals that more specialist knowledge is needed, along with an "integrated approach" to health care.

In 2010 the Ministry of Health requested a report on how to reorganise the centres for rare disorders under one administration. The working group led by the Directorate of Health delivered the report<sup>539</sup> on 1 December 2010. In March 2012 the Ministry announced that the South-Eastern Norway Regional Health Authority (SE-RHF) should establish a national competence service for rare diagnosis and disabilities to administrate all the national services in this field today, except the services for dual sensory impairment (for which there is established a new national service at Northern Norway Regional Health Authority). The SE-RHF chose to establish a project in 2013, to organise the unit from 1 January 2014. During 2013, some tasks, responsibilities and resources were moved from the Norwegian Directorate of Health to this new central unit. One of these tasks is the national coordination of Orphanet.

<sup>539</sup> [http://www.helsedirektoratet.no/vp/multimedia/archive/00316/Revidert\\_rapport\\_Sa\\_316599a.pdf](http://www.helsedirektoratet.no/vp/multimedia/archive/00316/Revidert_rapport_Sa_316599a.pdf)

In addition to this the Regulation on “Approval of hospitals and national services”<sup>540</sup>, which includes centres of expertise for rare disorders, was enforced from the start of 2011: this Regulation imposes the same criteria and demands on centres of expertise for rare disorders as on other national centres of expertise. The document has been translated to English and published<sup>541</sup>.

## Centres of expertise

### **National competence service**

In Norway there are 10 different state-financed centres of expertise for people with rare and less known disorders. They provide services for more than 16 000 persons with more than 350 different rare disorders, which often lead to disability. As mentioned, these centres will be under one administration from 1 January 2014. In order for a service to be established for a rare disease, the condition must meet the criteria of being complex and compound, and there must be a need for multidisciplinary and cross-institutional services. These centres also facilitate the development and dissemination of expertise, and they provide forms of support unmet by standard services. The centres are administered under the South Eastern Norway Regional Health Authority as specialist health care services. The grants to the centres are earmarked to the RHA through the state budget. The centres report to the Regional Health Authority and to the Directorate for Health. See section 4, §4-5 and §4-6 in the above-mentioned regulation for requirements and responsibilities for the national competence services. §4-3 and §4-4 regulate requirements and responsibilities for national and multi-regional treatment services.

In 2013 a project was funded for the organisation of one administrative body for the units dealing with rare diseases, located at Oslo University Hospital. The services will be evaluated through annual and five-year reports.

There are several departments of medical genetics in Norway. Genetic counselling and genetic testing is available on demand as public health care services. In Norway many specialised health care services (e.g. surgery and specialised medical treatment) are centralised to one or a few units in addition to the Centre of Expertise. This is specified in the guide to the regulation mentioned above<sup>542</sup>.

### **Registries**

Each national resource centre has its own registry: they report to their respective Regional Health Authority, as well as to the Directorate of Health. Public Health Registries also exist (such as the medical birth registry, cause of death registry, national patient registry and social security registry). Norway contributes to the EURADRENAL, EUROCAT, EPR (European Porphyria Registry), HUE-MAN, SCNIR, RARECARE and EUROCARE European registries. The new administrative unit will continue the work to develop registries for rare disorders in Norway.

### **Neonatal screening policy**

Neonatal screening for phenylketonuria and congenital hypothyroidism, as well as newborn hearing screening, has been in place for several years. A report presented to The Norwegian Directorate of Health in March 2009, suggested an expansion to include biochemical screening for in total 23 different conditions. The Government concurred with the recommendations and sanctioned in October 2010 newborn screening for the following conditions: Propionic acidemia, Methylmalonic acidemia, Isovaleric acidemia, Holocarboxylase synthetase deficiency, Biotinidase deficiency,  $\beta$ -Ketothiolase deficiency, Glutaric acidemia type I, Medium-chain acyl-CoA dehydrogenase deficiency, Long-chain L-3-Hydroxy dehydrogenase deficiency, Trifunctional protein deficiency, Very long-chain acyl-CoA dehydrogenase deficiency, Carnitine uptake defect, Carnitine palmitoyltransferase I deficiency, Carnitine palmitoyltransferase II deficiency, Carnitine acylcarnitine translocase deficiency, Glutaric acidemia type II, Maple syrup urine disease, Homocystinuria, Phenylketonuria, Tyrosinemia type I, Congenital adrenal hyperplasia, Congenital hypothyroidism and Cystic fibrosis.

The expansion of the program was to be implemented following a revision of the legal regulation on genetic testing. The new regulation was sanctioned in December 2011 with effect from 1 January 2012. Under this regulation, prior to newborn screening, it is expected that the parents are well informed about tests, methods and possible consequences. Information brochures to parents were produced in close collaboration between The Directorate of Health and Oslo University Hospital before the program was launched on 1 March 2012. Screening is to be based on informed consent, and residual samples may be kept in a diagnostic bio bank

<sup>540</sup> <http://www.regjeringen.no/upload/HOD/SHA/forskrift-eng-270911.pdf>

<sup>541</sup> Unofficial translation: <http://www.regjeringen.no/upload/HOD/SHA/forskrift-eng-270911.pdf>

<sup>542</sup> <http://www.regjeringen.no/upload/HOD/SHA/VeiledernasjonaleTjenester01022013b.pdf>

for 6 years. Consent is also required for later use of demographic data, analytical results and information related to diagnostic follow-up and treatment. This information will be stored in a quality register for evaluation of the screening program. Parents can decline storage or use of remaining samples in research. In general, use of screening samples in research will require an approval from an ethical committee and a signed agreement from the parents.

### **Genetic testing**

The portal <http://www.genetikportal.no> gives an overview of the genetic tests/analysis available in Norway at any time. The portal is administered through Department of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway. When there is no test available in Norway, samples are sent to laboratories abroad.

Diagnostic tests are registered as available in Norway for 126 genes and an estimated 144 diseases in the Orphanet database<sup>543</sup>.

### **National alliances of patient organisations and patient representation**

There is currently no alliance of rare disease patient organisations in Norway, but the Norwegian Federation of Organisations of Disabled People (FFO) is recognised as the co-ordinating body for organisations of disabled people, including many rare disease patient organisations. The government contributes financially to many patients organisations. There must be at least 250 members in an organisation to qualify for government co-funding. The Directorate of Health initiated a project in 2009 (which has since been finalised) to bring together smaller organisations in order to qualify for financial support, as organisations with less than 250 members may merge with others in order to qualify for government financial support. The Norwegian Directorate for Children, Youth and Family Affairs (BUFdir) is now considering to change the regulations on governmental support to patient organisations, e.g. to make it possible for people with rare disorders and their family to establish organisations.

### **Sources of information on rare disorders and national help lines**

#### ***Orphanet activities in Norway***

Since 2006 the national coordinator for Orphanet in Norway was based at the Norwegian Directorate of Health before being handed over to the new competence service for rare disorders at Oslo University Hospital at the end of 2013. The coordinator is in charge of collecting data on rare disease related services for entry into the Orphanet database. The Orphanet Norway<sup>544</sup> national website in Norwegian is maintained by the coordinator.

#### ***Official information centres for rare diseases***

The centres of expertise develop and revise professionally reviewed information about the different syndromes for which they provide services<sup>545</sup>. This information is published on their websites and in paper copies, often available on site at the Centres from staff dedicated to informing patients and family members.

#### ***Help line***

Since 1999, the Norwegian Directorate of Health services a free help line for rare disorders (+47 800 41 710). To date, the help line has answered calls for about 850 different rare disorders. From 1 January 2014 the Norwegian National Advisory Unit on Rare Disorders maintains the free help line for rare disorders.

#### ***Other sources of information***

The Directorate's website makes publications concerning rare diseases available to the public. Norway is also part of Rarelink ([www.rarelink.no](http://www.rarelink.no)), a Nordic website which contains a compilation of links to information on rare disorders, published by organisations commissioned by the governments of Sweden, Finland, Denmark and Norway. Another important source of information is the Directorate's website<sup>546</sup> and the site for the project to establish a new national unit for administration of the centres of expertise<sup>547</sup>.

<sup>543</sup> Information extracted from the Orphanet database (January 2014).

<sup>544</sup> <http://www.orpha.net/national/NO-NO/index/kort-om-orphanet/>

<sup>545</sup> Accessible on these sites amongst others <http://www.sjeldnediagnoser.no/> and <http://www.frambu.no/>

<sup>546</sup> <http://www.helsedirektoratet.no/helse-og-omsorgstjenester/sjeldne-tilstander/Sider/default.aspx>

<sup>547</sup> <http://www.oslo-universitetssykehus.no/omoss/avdelinger/nasjonalt-kompetansetjeneste-for-sjeldne-diagnoser/Sider/enhet.aspx>



## **Guidelines**

The centres of expertise are involved in the preparation and implementation of guidelines and guides for rare disorders.

## **Training and education initiatives**

The national Centres of Expertise are involved in different educations and training, such as medical schools, odontology training, nursing schools etc. Some centres administrate web-based courses for specific diseases<sup>548</sup>.

## **National rare disease events in 2013**

There are meetings organised at all the resource centres, and annual contact meetings between each centre and their respective regional health authority. Conferences and congresses are organised on special occasions such as Rare Disease Day.

## **Hosted rare disease events in 2013**

A Nordic collaboration meeting for rare diseases was hosted by Norway in September 2013.

## **Research activities and E-Rare partnership**

### ***National research activities***

National centres of expertise are involved in a number of research projects on rare disorders.

### ***Participation in European research projects***

Teams in Norway participate/participated in 13 FP7 rare disease related projects and 3 projects are coordinated by a team in Norway.

### ***E-Rare partnership***

Norway is not currently a partner of the E-Rare project.

### ***IRDiRC***

Norwegian funding agencies have not yet committed funding to the IRDiRC.

## **Orphan medicinal products**

### ***Orphan medicinal product committee***

There is no orphan medicinal product committee in Norway.

### ***Orphan medicinal product incentives***

As an EFTA/EEA member, the EU orphan medicinal product regulation is fully implemented in the EEA agreement, including the orphan designation incentives. As yet no additional national program has been put in place for granting incentives specifically for the development of orphan medicinal products.

### ***Orphan medicinal product market availability situation***

By the end of December 2013, 52 orphan medicinal products were marketed in Norway. These drugs are: Adcetris, Arzerra, Atriance, Bosulif, Ceplene, Cystadane, Dacogen, Diacomit, Duodopa, Elaprased, Esbriet, Evoltra, Exjade, Firazyr, Gliolan, Iclusig, Inovelon, Jakavi, Kalydeco, Kuvan, Litak, Lysodren, Mepact, Mozobil, Myozyme, Nexavar, Nplate, Orfadin, Pedeia, Plenadren, Prialt, Revatio, Revlimid, Savene, Signifor, Soliris, Sprycel, Tassigna, Tepadina, Thalidomide Celgene, Tobi Podhaler, Torisel, Tracleer, Vidaza, Volibris, Votubia, Vpriv, Wilzin, Xagrid, Xaluprine, Yondelis and Zavesca. Other orphan products with an EEA marketing authorisation, but not yet marketed in Norway, can nevertheless be readily dispensed by the pharmacy when a doctor provides a specific medical prescription form.

### ***Orphan medicinal product pricing***

Norway has a structured system for pricing, and orphan medicinal products follow these overall principles.

### ***Orphan medicinal product reimbursement***

Norway has an extensive reimbursement system, and all residents are covered by the National Insurance Scheme. Orphan medicinal products follow these overall principles for general reimbursements, however

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<sup>548</sup> <http://www.sjeldnediagnoser.no/?k=sjeldnediagnoser/home&aid=10960>

special consideration can be made for chronic rare diseases (i.e. prevalence < 1/10,000) after individual application for reimbursement.

#### **Other therapies for rare diseases**

No information reported.

#### **Orphan devices**

The National Insurance Act<sup>549</sup> (folketrygdloven) gives rights for the use of assistive devices (orphan and common) for daily life activities and work.

#### **Specialised social services**

There are no special rights or specialised social services In Norway: all citizens have the same rights. As a user of long-term, coordinated health and/or social services in Norway, you are entitled to an Individual Plan (IP). The right to an IP is not conditional on a particular diagnosis or age, and is mentioned in several Norwegian acts. One service provider (coordinator) has the overall responsibility for each person's IP. To succeed as a coordinator it is essential to establish and maintain a relationship with the user based on trust and respect. An IP contains an outline of your objectives, your resources and the services you require. As a user you have the right to participate throughout the planning process.

National competence services (Centres of Expertise) offer residential training courses for patients, families and professionals. The courses include lectures, group discussions, consultations and joint activities. These courses are free of charge for patients and their families. Staff from the centres also visits people in their home environment, pass on information and hold guidance meetings, as well as making contributions to courses, conferences and seminars. Collaboration with local health services and staff ensures that people with a rare disorder and their families receive treatment, care and services appropriate to their needs within their local community.

Frambu<sup>550</sup> was established in 1954, with services to patients with polio, cerebral palsy, epilepsy etc., and offered services to 41 different rare diseases in 1991 : it now offers services for over 100 diseases to children, adolescents and adults. Frambu offers summer camps for four groups of around 50 children and adolescents each year, offering a chance to meet others in the peer's situation and build a network of friends and contacts. The centres of expertise for rare diseases provide these types of social services, which are meant to supplement generally available programmes.

## **2.4. SERBIA**



#### **Definition of a rare disease**

There is no official definition of a rare disease in Serbia although the generally accepted and used definition is that of the European Regulation on Orphan Medicinal Products : of a disease affecting no more than 5 in 10 000 persons.

#### **National plan/strategies for rare diseases and related actions**

There is currently no national plan for rare diseases in Serbia. A Republic Expert Committee for a Strategy on Rare Diseases has been established and a proposal for a strategy was developed in 2013 envisaging a number of actions over the years leading up to 2020 including: improvement of diagnostics and treatment, improving availability of orphan drugs, registration of rare disease patients, screening for rare diseases, and increasing the participation in patients' associations. The establishment of centres of expertise has been highlighted as a priority topic. The lack of coordination between different parts of public administration is a problem in the field of rare diseases. The Ministry of Health has yet to give their opinion of the proposals. It is hoped that a stakeholder task force will be established to define objectives, activities and next steps for the implementation of key areas of the proposed National Strategy.

<sup>549</sup> <http://www.lovdatab.no/all/hl-19970228-019.html>

<sup>550</sup> <http://www.frambu.no/>

Currently there is a policy to provide treatment for limited number of rare diseases and to define centres of expertise for rare diseases.

A Europlan conference, co-organised by the National Organisation for Rare Diseases of Serbia and the Institute for Molecular Genetics and Genetic Engineering of Belgrade University, under the auspices of the Ministry of Health and Eurordis, was held on 6-7 December 2013 in Belgrade bringing together 170 participants from all stakeholder groups. The conference also drew participation from surrounding countries. At the conference the proposal for a national rare disease strategy was presented and priority topics concerning the field of rare diseases were discussed. The conference report is available online for consultation<sup>551</sup>.

### **Centres of expertise**

The proposed strategy recommends that centres of expertise should be formed within existing institutions so that existing resources and expertise can be fully utilised. The Republic Expert Committee for Rare Diseases has already determined that 5 centres should be formed.

### **Registries**

There is currently no national registry for rare diseases, although there are national registries for individual rare diseases (cystic fibrosis, haemophilia and rare coagulopathies).

### **Neonatal screening policy**

Compulsory screening programmes are in place for phenylketonuria and congenital hypothyroidism.

### **Genetic testing**

Diagnostic tests are registered as available in Serbia 31 genes and an estimated 29 diseases in the Orphanet database<sup>552</sup>. Medical laboratories offering diagnostic services for rare diseases are mostly not accredited due to the high costs of the procedure and because accreditation is not officially required. Reimbursement is not possible for majority of genetic tests.

### **National alliances of patient organisations and patient representations**

The umbrella organisation the National Organisation of Rare Diseases in Serbia (NORBS<sup>553</sup>) groups 13 rare disease patient organisations in the country. NORBS organises Rare Disease Day events in Serbia and co-organised the 2013 Europlan conference to discuss a proposal for a national strategy for rare diseases.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activity in Serbia***

There is no official, rare disease specific information centre on rare diseases in Serbia other than Orphanet. Since 2006 there is a dedicated Orphanet team for Serbia that works on voluntary basis and it is currently hosted by the Institute for Molecular Genetics and Genetic Engineering of Belgrade University. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also maintains the national Orphanet Serbia website<sup>554</sup> in the national language.

#### ***Official information centre for rare diseases***

There is no official information centre for rare diseases in Serbia apart from the services provided by Orphanet Serbia.

#### ***Help line***

There is no rare disease helpline in Serbia

#### ***Other sources of information on rare diseases***

NORBS and patient organisations provide information on rare diseases.

### **Guidelines**

No reported information.

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<sup>551</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-serbia.pdf>

<sup>552</sup> Information extracted from the Orphanet database (January 2014).

<sup>553</sup> <http://www.norbs.rs/>

<sup>554</sup> <http://www.orpha.net/national/RS-SR/index/po%C4%8Detna-strana/>

### **Training and education initiatives**

No reported information.

### **National rare disease events in 2013**

Rare Disease Day events are organised by NORBS at national level.

A Europlan conference, co-organised by the National Organisation for Rare Diseases of Serbia and the Institute for Molecular Genetics and Genetic Engineering of Belgrade University, under the auspices of the Ministry of Health and Eurordis, was held on 6-7 December 2013 in Belgrade bringing together 170 participants from all stakeholder groups. The conference also drew participation from surrounding countries. At the conference the proposal for a national rare disease strategy was presented and priority topics concerning the field of rare diseases were discussed. The conference report is available online for consultation<sup>555</sup>.

### **Hosted rare disease events in 2013**

No activities reported.

### **Research activities and E-Rare partnership**

#### ***National research activities***

There are no funding programmes dedicated to rare disease research in Serbia, but there are some research projects involving rare diseases, which are funded by Ministry of Education, Science and Technological Development.

***Participation in European research projects*** The Institute for Molecular Genetics and Genetic Engineering of Belgrade University coordinates one EU FP7-REGPOT project. A team in Serbia participates in 1 bilateral project related to rare diseases

#### ***E-Rare***

Serbia is not a partner of E-Rare.

#### ***IRDIRC***

Serbia is not a member of the IRDiRC

### **Orphan medicinal products**

#### ***Orphan medicinal product committee***

The National Health Insurance Fond has a committee for medicinal product for treatment of some inborn metabolic errors

#### ***Orphan medicinal product incentives***

There are no specific incentives for orphan medicinal products in Serbia.

#### ***Orphan medicinal product market availability situation***

No reported information.

#### ***Orphan medicinal product pricing policy***

No reported information.

#### ***Orphan medicinal product reimbursement policy***

130 million Dinars (around €1.2 million) were allocated to the use of orphan drugs in Serbia with 280 million Dinars (around €2.6 million) planned for this purpose in 2014. This amount goes towards treatments for only a handful of paediatric patients with metabolic diseases requiring enzyme replacement therapies (ERT). A special fund for rare diseases reimburses this treatment due to the high price of the therapy. Other orphan products are reimbursed from the Republic Health Insurance Fund. The Republic Health Insurance Fund can only reimburse orphan medicinal products that are registered in Serbia. Since Serbia is not an EU Member State there is no centralised market authorisation procedure and the registration procedure can take up to one year.

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<sup>555</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-serbia.pdf>

### **Other initiatives to improve access to orphan medicinal products**

Compassionate and off-label use is not recognised by the health insurance system.

### **Orphan devices**

No reported information.

### **Other therapies for rare diseases**

No reported information.

### **Specialised social services**

Despite recent advances in legislation concerning equality and anti-discrimination for persons with disabilities, mechanisms are lacking to enforce these laws and sometimes rare diseases are not recognised in the categories of possible beneficiaries of this legislation.

There are no specific specialised social services for rare diseases currently in Serbia.

## **RARE DISEASE ACTIVITIES IN 2013 IN SERBIA**

### **National plan/strategies for rare diseases and related actions**

There is currently no national plan for rare diseases in Serbia. A Republic Expert Committee for a Strategy on Rare Diseases has been established and a proposal for a strategy was developed in 2013 envisaging a number of actions over the years leading up to 2020 including: improvement of diagnostics and treatment, improving availability of orphan drugs, registration of rare disease patients, screening for rare diseases, and increasing the participation in patients' associations. The establishment of centres of expertise has been highlighted as a priority topic. The lack of coordination between different parts of public administration is a problem in the field of rare diseases. The Ministry of Health has yet to give their opinion of the proposals. It is hoped that a stakeholder task force will be established to define objectives, activities and next steps for the implementation of key areas of the proposed National Strategy.

Currently there is a policy to provide treatment for limited number of rare diseases and to define centres of expertise for rare diseases.

A Europlan conference, co-organised by the National Organisation for Rare Diseases of Serbia and the Institute for Molecular Genetics and Genetic Engineering of Belgrade University, under the auspices of the Ministry of Health and Eurordis, was held on 6-7 December 2013 in Belgrade bringing together 170 participants from all stakeholder groups. The conference also drew participation from surrounding countries. At the conference the proposal for a national rare disease strategy was presented and priority topics concerning the field of rare diseases were discussed. The conference report is available online for consultation<sup>556</sup>.

### **Centres of expertise**

The proposed strategy recommends that centres of expertise should be formed within existing institutions so that existing resources and expertise can be fully utilised. The Republic Expert Committee for Rare Diseases has already determined that 5 centres should be formed.

### **National alliances of patient organisations and patient representations**

The umbrella organisation the National Organisation of Rare Diseases in Serbia (NORBS<sup>557</sup>) groups 13 rare disease patient organisations in the country. NORBS organises Rare Disease Day events in Serbia and co-organised the 2013 Europlan conference to discuss a proposal for a national strategy for rare diseases.

### **National rare disease events in 2013**

Rare Disease Day events are organised by NORBS at national level.

A Europlan conference, co-organised by the National Organisation for Rare Diseases of Serbia and the Institute for Molecular Genetics and Genetic Engineering of Belgrade University, under the auspices of the Ministry of Health and Eurordis, was held on 6-7 December 2013 in Belgrade bringing together 170 participants

<sup>556</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-serbia.pdf>

<sup>557</sup> <http://www.norbs.rs/>

from all stakeholder groups. The conference also drew participation from surrounding countries. At the conference the proposal for a national rare disease strategy was presented and priority topics concerning the field of rare diseases were discussed. The conference report is available online for consultation<sup>558</sup>.

## 2.5. SWITZERLAND

### Definition of a rare disease

The Therapeutic Products Act (TPA) adopted the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals and this applies for the simplified authorisation of orphan medicinal products. Stakeholders in Switzerland accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

### National plan/strategies for rare diseases and related actions

There is still no national concerted plan or strategy for rare diseases in Switzerland.

With the aim of filling this gap, on 16 December 2010, Ruth Humbel, member of the Health Commission in the Parliament submitted to the National Council a postulate for "*a national strategy for improving the health situation of people with rare diseases*". The National Council followed the recommendation of the Federal Council and accepted the claim in March 2011. The Federal Council has consequently assigned the Federal Office of Public Health the task of submitting a proposal. An alliance<sup>559</sup> encompassing patient organisations, the Swiss Medical Association, university hospitals, the rare disease informational portal Orphanet-Switzerland and representatives from the pharmaceutical industry, then joined forces in August 2011 to promote a national strategy for rare diseases in Switzerland. Chaired by National Councillor Ruth Humbel, this newly-formed community of interest for rare diseases (*IG rare diseases*) is actively engaged in advocating the development of a national action plan for the country's rare disease patients. In September 2012, National Councillor Guy Parmelin requested information concerning the state of advancement of the national strategy for rare diseases. The answer of the Federal Council included the information that a formal meeting between the IG and the Federal Office of Public Health took place on 4 June 2012 to define the expectations and priorities for the development of a national plan. Issues such as financing diagnostic tests and defining the criteria for centres of expertise have been broached. On Rare Disease Day 2013 Pascal Strupler, Director of the Federal Office of Public Health confirmed that the elaboration of a national concept for rare diseases would take place in the second quarter of 2014<sup>560</sup>. In 2013 the Federal Office of Public Health recruited a "Rare diseases project manager" to oversee the assessment of the situation of rare diseases in Switzerland and bring stakeholders together. A number of stakeholder meetings were organised in 2013 to advance with the elaboration of the concept. In addition a working group of the Swiss Academy of Science worked on the definition of rare diseases and proposed a set of criteria when establishing reference centres in Switzerland. The concept focuses on issues such as the difficulties to pose an adequate diagnosis in a timely fashion, the provision of high quality medical care, mechanisms that strengthen the resources available to the patients and their relatives as well as to support research projects at national and international level. The Swiss Conference of the Cantonal Ministers of Public Health (GDK/CDS) also supports the publication of a manual for the employees of the information and counselling centres for prenatal testing and coordinates the offer of highly specialised medicine in Switzerland, including rare disease patients. The only specific project for rare diseases supported by the GDK/CDS is Orphanet Switzerland.

### Centres of expertise

Several specialised care centres have been established as centres of reference by reputation, usually in University Hospitals. In addition to this, the Inter-Cantonal Agreement on Highly Specialised Medical Services (IAHSMS) coordinated by the GDK/CDS came into effect in 2009 the purpose of which is that "*the cantons shall agree, in the interests of a needs-based, high-quality and economical health care system, to ensure coordination in relation to the centralisation of highly specialised medical services. This applies to those medical fields and services that are characterised by their rarity, by their high potential for innovation, by high personnel or*

<sup>558</sup> <http://www.eurordis.org/sites/default/files/flags/finalreport-serbia.pdf>

<sup>559</sup> [http://www.orphanet.ch/PDF/MEDIENMITTEILUNG\\_Gruendung\\_IG\\_Seltene\\_Krankheiten\\_f\\_def.pdf](http://www.orphanet.ch/PDF/MEDIENMITTEILUNG_Gruendung_IG_Seltene_Krankheiten_f_def.pdf)

<sup>560</sup> <http://www.orphanet.ch/PDF/ProRaris25022013cloture.pdf>

technical costs or by complex treatment procedures. For categorisation as a highly specialised medical service, at least three of the aforementioned criteria must be met, whereby rarity must always apply". The appointed centres can be consequently considered as official reference centres of expertise<sup>561</sup>. In 2011, several centres have been officially appointed in the fields of metabolic diseases, retinoblastoma, primary immunodeficiency in children, surgery of the liver and biliary tract in children, rare medullar tumours, surgery of epilepsy and neurosurgery of complex vascular anomalies of the central nervous system. In 2013, new centres have been named in the field of paediatric oncology (haematopoietic stem cells transplants (autologous and allogeneic), treatment of neuroblastoma, treatment of soft tissue sarcomas and other bone tumours and central nervous system tumours), adult oncology (haematopoietic stem cells transplants) and cochlear implants.

### Registries

There are a number of registries for specific rare diseases in Switzerland. Switzerland contributes/contributed to the following European registries: AIR, CAPS, E-IMD, E-HOD, TREAT-NMD, EUROCARE-CF and EUROCAT.

### Neonatal screening policy

A newborn screening programme covering all of Switzerland is in place and includes screening for phenylketonuria, congenital hypothyroidism, galactosaemia, congenital adrenal hypoplasia, biotinidase deficiency, and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. The request to implement the neonatal screening for cystic fibrosis, initiated by the Swiss Cystic Fibrosis Task Force, was approved from the Federal Office of Public Health for a 2-year-pilot project starting in January 2011, and extended with an open end date from 2013.

### Genetic testing

The medical genetics speciality exists for laboratory directors (FAMH) and for medical doctors (FMH) and several specialised care and/or testing centres have been established as centres of reference by reputation, usually in University Hospitals. Genetic testing laboratories require formal authorisation<sup>562</sup> to practice from the government; more than 60 public and private laboratories provide genetic testing, although not all tests are reimbursed. Since 2011, interlaboratory comparisons (EQA or other) must be performed at least once per year for every analysis proposed by genetic testing laboratories. Genetic counselling is formally required and is usually provided by doctors specialised in medical genetics or by referring doctors.

The efforts of genetic health professionals led to the approval on 2 December 2010 by the Federal Department of Home Affairs of the introduction (as of 1 April 2011) of an orphan disease regulation for the reimbursement of genetic laboratory testing of rare genetic diseases by the compulsory health insurance even if this test did *not* appear in previous list of approved tests or if the test is carried out abroad. An individual application for reimbursement is required and has to be submitted to the health insurance medical examiner (HIME) responsible.

Diagnostic tests are registered as available in Switzerland for 396 genes and an estimated 472 diseases in the Orphanet database<sup>563</sup>; this information, however, is not yet complete and does not cover all of Switzerland.

### National alliances of patient organisations

Since 2004, Orphanet Switzerland has identified about one hundred rare disease patient organisations, some of them being related to international networks. Since 2009, the "strategic" position of Orphanet Switzerland with regards to contacts with patient organisations, has actively contributed to the creation of an Alliance of Rare Diseases in Switzerland, facing the challenges of uniting patients from four different linguistic areas. ProRaris, the Swiss Rare Disease Patient Alliance, was founded on 26 June 2010 representing 42 patient organisations.

In 2011, ProRaris<sup>564</sup>, the then newly founded Alliance, put all its efforts into increasing community awareness of rare diseases in Switzerland. In the framework of the third International Rare Disease Day in Switzerland in February 2013, a conference jointly organized by ProRaris and the newly founded Radiz (Rare Disease Initiative Zurich) took place at the University of Zurich. The conference topic was "putting together our know-how to increase the quality of care for rare diseases". Stakeholders of various fields (politics, insurance,

<sup>561</sup> <http://www.gdk-cds.ch/index.php?id=903&L=1>

<sup>562</sup> Federal Act on Human Genetic Testing (HGTA) of 8 October 2004, <http://www.admin.ch/ch/e/rs/8/810.12.en.pdf>

<sup>563</sup> Information extracted from the Orphanet database (January 2014).

administration, medicine etc.) were present and discussed issues related to the formation of a national strategy for rare diseases (see also the announcement of the Director of the Federal Office of Public Health, Mr. Pascal Strupler above). The event received excellent press coverage, including articles in widely read papers in all regions of Switzerland, as well as radio and TV-interviews.

At the end of August 2012 ProRaris submitted a case study on the unequal treatment of the reimbursement of drugs for patients with rare diseases among various insurance companies in different cantons to the director of the Federal Office of Public Health, Mr. Pascal Strupler. In his answer he announced a close monitoring of the interpretation of articles 71 a and b of the ordinance on health insurance (Krankenversicherungsverordnung) on which the decisions of the insurance companies are based until the end of 2013. An evaluation was carried out in 2013<sup>565</sup>.

As a patient representative, ProRaris is part of the “Community of Interest for rare diseases” and is strongly implied in the elaboration of the national concept for rare diseases.

## **Sources of information on rare diseases and national help lines**

### ***Orphanet activity in Switzerland***

Since 2001 there is a dedicated Orphanet team in Switzerland, currently hosted by the Genetics and Laboratory Medicine Department of the University Hospital of Geneva. This team is composed of a country coordinator and, since 2011 of 2 information scientists (1 full time position and 1 part time position). Orphanet Switzerland has a close collaboration with the Health On The Net foundation (HON) for the management of the online forms. The team is in charge of identifying sources of information, collecting and updating data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) at national level for entry into the Orphanet database. In 2011 the team launched the Orphanet Switzerland national website<sup>566</sup> and contributes to the dissemination of information regarding the Orphanet database tool and national initiatives in the field of rare diseases (publications, media coverage, Orphanews, conferences, booth at annual congresses of learned societies, etc.). The website is currently only available in French. Additional resources are necessary to translate the content in German and Italian.

As a collaborating partner of the Orphanet Joint Action, Orphanet Switzerland is not entitled to the EU funding and must ensure its funding at national level. In 2011, the Swiss Conference of the Cantonal Ministers of Public Health (GDK/CDS) guaranteed a global budget for the period 2011-2014 for Orphanet.

### ***Official information centre for rare diseases***

There is no official information centre for rare diseases, however Orphanet is the reference portal for information on rare diseases and orphan medicinal products in Switzerland.

### ***Help line***

There is currently no help line available for rare diseases in Switzerland. However, a joint venture between the University Hospital of Lausanne (CHUV) and the University Hospital of Geneva (HUG) with the support of Orphanet Switzerland was initiated in 2012 in order to create a regional portal on rare diseases and to establish a helpline which was launched in 2013 [www.infomaladiesrares.ch](http://www.infomaladiesrares.ch)). This francophone portal provides access to current information on specialised clinics and allows a greater visibility of local and regional resources, based on existing Orphanet data. This service will be completed by a Helpline in 2014.

### ***Other sources of information on rare diseases***

The GDK/CDS supports the establishment of cantonal information and counselling centres for prenatal testing and the HGTA requires non directive genetic counselling before and after genetic testing. However, the existence of four national languages complicates the organisation of collective national projects. Orphanet Switzerland is currently the only rare disease project supported financially by the GDK/CDS.

The Federal Office of Public health publishes the list of the laboratories with an authorisation to execute genetic tests.<sup>567</sup>

In 2013 the “Romand (French speaking part of Switzerland) portal on rare diseases” [www.info-maladies-rares.ch](http://www.info-maladies-rares.ch) was launched.

<sup>565</sup> Evaluation of the implementation of article 71 a and 71 b KVV, accessible at <http://www.bag.admin.ch/evaluation/01759/02074/13897/index.html?lang=de>

<sup>566</sup> <http://www.orphanet.ch>

<sup>567</sup> <http://www.bag.admin.ch/themen/medizin/00683/02724/03677/index.html?lang=de>



## Guidelines

No specific information reported.

## Training and education initiatives

On 4 -6 July 2013 Radiz (Rare Diseases Initiative Zürich), a clinical research priority program of the University of Zurich, organised its first yearly summer school on rare diseases at the lake of Zurich. The summer school's main goal is to motivate bright young clinicians and scientists to work in the field of rare disease and to make them aware of the many opportunities, but also the challenges. The summer school focuses on a wide variety of subjects in the rare disease arena, from disease mechanisms and animal models, to improving diagnoses and novel therapeutics, with lectures and workshops on drug development, model organisms, how to choose clinical endpoints, clinical trials, regulatory aspects, patient registries, patient initiated research, ethical considerations, as well as what rare diseases may tell us about common diseases. The 2013 summer school was attended by 30 young clinicians and researchers. A 2<sup>nd</sup> Radiz summer school will take place in July 2014.

## National rare disease events in 2013

To mark Rare Disease Day 2013, a number of events were organised and initiatives launched. On 22 February the University of Zurich, University Children's Hospital Zurich and University Hospital Zurich joined forces to launch Radiz with a kick-off meeting followed by a networking dinner with the Gebert-Rüf foundation and a press release entitled "An end to the Odyssey"<sup>568</sup>. The following day (23 February 2013) ProRaris, in partnership with Radiz, organised for the 3<sup>rd</sup> year in a row a conference to discuss the situation for rare disease patients in Switzerland at the University of Zurich which was attended by stakeholders and key political decision makers in Switzerland. The Day was also marked by the launch of the "Romand (French speaking part of Switzerland) portal on rare diseases" [www.info-maladies-rares.ch](http://www.info-maladies-rares.ch).

## Hosted rare disease events in 2013

Amongst the rare disease events hosted in Switzerland in 2013 and announced in *OrphaNews* was Autoinflammation 2013 - 7th International Congress of the International Society of Systemic Auto-Inflammatory Diseases (22- 26 May 2013, Lausanne).

## Research activities and E-Rare partnership

### National research activities

Although there is no specific national budget for rare disease research, the Telethon Suisse raises funds for rare diseases, specifically for neuromuscular disorders. Moreover, many projects on rare diseases are supported by the Swiss National Science Foundation and a few public foundations (i.e. the Gebert Rüf Foundation and the BLACKSWAN Foundation). A new clinical research priority program of the University of Zurich - Radiz - was started in the fall of 2012. Radiz is funding translational research projects and supporting and training young clinicians and researchers with the aim to increase awareness for rare diseases and stimulate interdisciplinary collaborations.

The *Gebert Rüf Foundation*<sup>569</sup>, a Swiss grant programme specifically for rare diseases, announced its fifth call for projects in 2013. The independent foundation is committing CHF2 million (€1.66 million) per year to researchers based at Swiss universities, university hospitals, federal institutes of technology and universities of applied sciences. The Rare Diseases – New Approaches grant programme, which launched in 2009, is established as a five-year area of activity. The initiative aims at developing and implementing innovative technologies or approaches in the diagnosis and treatment of rare diseases. In 2013 5 finalists were chosen from the 73 submissions received. The knowledge gained should lead to a better understanding of the genetic, molecular and biochemical processes underlying these diseases and pave the way towards new forms of treatment or diagnostics. A further aim is to improve the transfer of basic research findings into clinical practice. The focus must be on innovation, feasibility and effectiveness, while attaining high scientific and technological standards.

The *BLACKSWAN Foundation*<sup>6</sup> is active since 2009 and supports advanced research into rare diseases in order to complement the chronic lack of public and private funds in this area. The principal goals are to promote and fund therapeutic application of new scientific protocols in order to find effective treatments and to increase public understanding and awareness of rare diseases.

<sup>568</sup> [www.orphanet.ch/PDF/press\\_release\\_Radiz.pdf](http://www.orphanet.ch/PDF/press_release_Radiz.pdf)

<sup>569</sup> <http://www.grstiftung.ch/en.html> & [http://www.grstiftung.ch/en/portfolio/activity/active\\_areas/rare-diseases.html](http://www.grstiftung.ch/en/portfolio/activity/active_areas/rare-diseases.html)

<sup>6</sup> <http://www.blackswanfoundation.ch/>

### **Participation in European research projects**

Swiss teams participate/have participated in 55 rare disease related FP7 projects and 2 projects were coordinated by a Swiss team.

#### **E-Rare**

Since 2013 Switzerland is a member of the E-Rare project and the BLACKSWAN Foundation is an active collaborator of the network. Switzerland participated in the 5<sup>th</sup> Joint Transnational call in 2013 with Swiss teams participating in 2 out of the 12 consortia selected for funding.

#### **IRDIRC**

Swiss funding agencies have not yet committed funding to the International Rare Diseases Research Consortium (IRDIRC).

### **Orphan medicinal products**

The Swiss Orphan Drug Regulation was introduced in 2006: this regulation stipulates that orphan medicinal product status applies to products treating diseases affecting no more than 1 in 2000 persons. The availability of orphan medicinal products has been improved since 2006 thanks to the simplified authorisation procedures and the recognition of the orphan medicinal product status for any drug for which this status has been granted in a country with a comparable drugs authority.

#### **Orphan medicinal product committee**

No specific activity reported.

#### **Orphan medicinal product incentives**

Companies acquiring orphan medicinal product designation for their products are allowed tax exemption for certain administrative taxes but are not however allowed market exclusivity.

#### **Orphan medicinal product market availability situation**

140 active ingredients for 225 indications subject to the orphan drugs regulation are marketed in Switzerland<sup>8</sup>.

#### **Orphan medicinal product pricing policy**

Compared to European Member States the pricing and reimbursement procedure in Switzerland is considered relatively quick and is speeded up when drugs target unmet medical needs or show high therapeutic benefit<sup>570</sup>.

#### **Orphan medicinal product reimbursement policy**

On 23 November 2010 the Federal Supreme Court decided that a health insurer was not obliged to reimburse the treatment costs (500'000 Swiss Francs per year) of Myozyme<sup>®</sup> for a patient with Pompe Disease, on the grounds that the therapy costs are not proportionate to the expected benefits for this specific patient. Based on this case, the Federal Court of Justice decided to fix limits for reimbursements, and although regretting the risk of unfairness, admits that rationing must be introduced. A limit of 100,000 Swiss Francs (€83'000) per year per patient has been proposed.

As of 2 February 2011 the Federal Council put two new articles of the Federal Ordinance on the Health Insurance into force stipulating that the off label use of drugs and the treatment with drugs not listed on the list of the reimbursed drugs (Spezialitätenliste) is admitted in case of life-threatening diseases if an important therapeutic benefit is expected from the treatment and if there is no reimbursed alternative. The Ordinance gives the insurers the freedom to decide about the maximum amount to be reimbursed.

#### **Other initiatives to improve access to orphan medicinal products**

No specific activity reported.

#### **Other therapies for rare diseases**

No specific activity reported.

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<sup>7</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011) p120

<sup>8</sup> <http://www.swissmedic.ch/daten/00081/index.html?lang=de>

### **Orphan devices**

No specific activity reported.

### **Specialised social services**

No specific activity reported.

## **DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 IN SWITZERLAND**

### **National plan/strategies for rare diseases and related actions**

On Rare Disease Day 2013 Pascal Strupler, Director of the Federal Office of Public Health confirmed that the elaboration of a national concept for rare diseases would take place in the second quarter of 2014<sup>571</sup>. In 2013 the Federal Office of Public Health recruited a “Rare diseases project manager” to oversee the assessment of the situation of rare diseases in Switzerland and bring stakeholders together. A number of stakeholder meetings were organised in 2013 to advance with the elaboration of the concept. In addition a working group of the Swiss Academy of Science worked on the definition of rare diseases and proposed a set of criteria when establishing reference centres in Switzerland. The concept focuses on issues such as the difficulties to pose an adequate diagnosis in a timely fashion, the provision of high quality medical care, mechanisms that strengthen the resources available to the patients and their relatives as well as to support research projects at national and international level.

### **Centres of expertise**

In 2013, new centres have been named in the field of paediatric oncology (haematopoietic stem cells transplants (autologous and allogeneic), treatment of neuroblastoma, treatment of soft tissue sarcomas and other bone tumours and central nervous system tumours), adult oncology (haematopoietic stem cells transplants) and cochlear implants.

### **Neonatal screening policy**

The request to implement the neonatal screening for cystic fibrosis, initiated by the Swiss Cystic Fibrosis Task Force, was approved from the Federal Office of Public Health for a 2-year-pilot project starting in January 2011, and extended with an open end date from 2013.

### **National alliances of patient organisations**

In the framework of the third International Rare Disease Day in Switzerland in February 2013, a conference jointly organized by ProRaris and the newly founded Radiz (Rare Disease Initiative Zurich) took place at the University of Zurich. The conference topic was “putting together our know-how to increase the quality of care for rare diseases”. Stakeholders of various fields (politics, insurance, administration, medicine etc.) were present and discussed issues related to the formation of a national strategy for rare diseases (see also the announcement of the Director of the Federal Office of Public Health, Mr. Pascal Strupler above). The event received excellent press coverage, including articles in widely read papers in all regions of Switzerland, as well as radio and TV-interviews.

At the end of August 2012 ProRaris submitted a case study on the unequal treatment of the reimbursement of drugs for patients with rare diseases among various insurance companies in different cantons to the director of the Federal Office of Public Health, Mr. Pascal Strupler. In his answer he announced a close monitoring of the interpretation of articles 71 a and b of the ordinance on health insurance (Krankenversicherungsverordnung) on which the decisions of the insurance companies are based until the end of 2013. An evaluation was carried out in 2013<sup>572</sup>.

<sup>571</sup> <http://www.orphanet.ch/PDF/ProRaris25022013cloture.pdf>

<sup>572</sup> Evaluation of the implementation of article 71 a and 71 b KVV, accessible at <http://www.bag.admin.ch/evaluation/01759/02074/13897/index.html?lang=de>

## Sources of information on rare diseases and national help lines

### Help line

There is currently no help line available for rare diseases in Switzerland. However, a joint venture between the University Hospital of Lausanne (CHUV) and the University Hospital of Geneva (HUG) with the support of Orphanet Switzerland was initiated in 2012 in order to create a regional portal on rare diseases and to establish a helpline which was launched in 2013 ([www.infomaladiesrares.ch](http://www.infomaladiesrares.ch)). This francophone portal provides access to current information on specialised clinics and allows a greater visibility of local and regional resources, based on existing Orphanet data. This service will be completed by a Helpline in 2014.

### Other sources of information on rare diseases

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### Guidelines

No specific information reported.

### Training and education initiatives

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### National rare disease events in 2013

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### Hosted rare disease events in 2013

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### Research activities and E-Rare partnership

#### National research activities

The *Gebert Rüf Foundation*<sup>575</sup>, a Swiss grant programme specifically for rare diseases, announced its fifth call for projects in 2013. The independent foundation is committing CHF2 million (€1.66 million) per year to researchers based at Swiss universities, university hospitals, federal institutes of technology and universities of

<sup>573</sup> <http://www.bag.admin.ch/themen/medizin/00683/02724/03677/index.html?lang=de>

<sup>574</sup> [www.orphanet.ch/PDF/press\\_release\\_Radiz.pdf](http://www.orphanet.ch/PDF/press_release_Radiz.pdf)

<sup>575</sup> <http://www.grstiftung.ch/en.html> - [http://www.grstiftung.ch/en/portfolio/activity/active\\_areas/rare-diseases.html](http://www.grstiftung.ch/en/portfolio/activity/active_areas/rare-diseases.html)

<sup>6</sup> <http://www.blackswanfoundation.ch/>

applied sciences. The Rare Diseases – New Approaches grant programme, which launched in 2009, is established as a five-year area of activity. The initiative aims at developing and implementing innovative technologies or approaches in the diagnosis and treatment of rare diseases. In 2013 5 finalists were chosen from the 73 submissions received. The knowledge gained should lead to a better understanding of the genetic, molecular and biochemical processes underlying these diseases and pave the way towards new forms of treatment or diagnostics. A further aim is to improve the transfer of basic research findings into clinical practice. The focus must be on innovation, feasibility and effectiveness, while attaining high scientific and technological standards.

### **E-Rare**

Since 2013 Switzerland is a member of the E-Rare project and the BLACKSWAN Foundation is an active collaborator of the network. Switzerland participated in the 5<sup>th</sup> Joint Transnational call in 2013 with Swiss teams participating in 2 out of the 12 consortia selected for funding.

## **2.6. TURKEY**

### **Definition of a rare disease**

According to the National Draft Guideline for Orphan Medicines, the prevalence limit for the definition of a rare disease will be within the EU-defined limit of no more than 5 in 10'000 individuals. The Ministry of Health accepts pricing of human medicinal products to be considered under the 'orphan' approach when such a product is indicated for the treatment of diseases for which the aetiology is not clearly defined and those which affect no more than 1 in 100'000 individuals<sup>576</sup>.

### **National plan/strategies for rare diseases and related actions**

There is currently no national plan or strategy for rare diseases in Turkey: rare diseases are currently funded within the general health system budget<sup>577</sup>.

In 2010, the Turkish Ministry of Health considered collaboration with Orphanet Turkey in specific projects for the establishment of a National Plan for Rare Diseases and a number of meetings have been organised amongst professionals in Turkey in the context of the Europlan project of which Turkey is a collaborating partner. The recognition of a national plan is mandatory for assigning priority actions for rare diseases. Under the "National Health Transformation Programme" the Ministry of Health has suggested developments in medicinal product use, medical and social care, surveillance and other relevant actions<sup>578</sup>.

The 1<sup>st</sup> National Rare Disease Symposium took place on 27 November 2011 in Istanbul. Organised by the Orphanet Turkey team, this event brought together representatives from the Turkish Ministry of Health, Social Security authorities, patient organisations, scientists and industry. The symposium covered 3 main topics: rare disease and orphan medicinal products organisations and databases in EU; International and European Union and legislation on rare diseases and orphan medicinal products, and the current situation in Turkey; and problems and difficulties in the treatment and management of rare diseases in Turkey - how to overcome these obstacles. Participants discussed the current legislation at EU level in the field as well as the current situation in other countries such as Italy, France and Bulgaria. A second symposium was held in November 2013 to discuss the areas to be considered in the scope of a national plan for rare diseases.

### **Centres of expertise**

Though no centres of expertise for rare diseases currently exist, university hospitals and research centres are active in diagnosis and management of rare diseases, including centres at Hacettepe University Ankara) for

<sup>576</sup> Press release regarding the Pricing of Medicinal Products for Human Use

(<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

<sup>577</sup> Notification regarding the Pricing of Medicinal Products for Human Use

(<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawId=225>)

<sup>578</sup> Turkey Health Transformation Program

(<http://www.saglik.gov.tr/EN/BelgeGoster.aspx?17A16AE30572D313AAF6AA849816B2EF1DACD7356F6C2568>)

<http://www.orpha.net/actor/EuropaNews/2009/doc/TurkHealthPolicy.pdf>

metabolic and neuromuscular diseases, Istanbul University for neuromuscular diseases and Gazi University (Ankara) for metabolic diseases with the necessary infrastructure for specialised care (i.e. inpatient beds and outpatients clinics, pathology services, genetic counselling units, genetic testing facilities for post and prenatal diagnosis, biochemistry, physical therapy units, etc). These centres can accept referral patients from other centres/cities and state hospitals and are therefore described as 'reference centres'. For these centres, the Ministry of Health and the social security system covers the invoices of non-private patients.

Turkey is planning to establish national networks for the prevention, surveillance, diagnosis and treatment of rare diseases. Projects to establish national centres of reference for rare diseases are expected. These centres will be part of the overall planning of healthcare in the country. The Ministry of Health and the different regional healthcare authorities will have to coordinate their approach and harmonise regional network activities.

### **Registries**

In order to identify the rare diseases currently prevalent in Turkey, there is a significant need to complete a comprehensive epidemiological survey at national level: this is currently being developed by stakeholders. Within the IT infrastructure of Hacettepe Hospitals a new registry program including clinical and laboratory findings has been established for paediatric rare metabolic diseases. This registry is financed by Hacettepe Hospital and METVAK (Metabolic Diseases Foundation)

Turkey participates in the European registries EIMD, SCNIR, TREAT-NMD and EUROCARE CF.

### **Neonatal screening policy**

The Ministry of Health is responsible for neonatal screening of phenylketonuria and congenital hyperthyroidism since 2007 and bitonidase deficiency since 2009. Data in 2011 shows that over 95% of the population is covered by these screening policies. Neonatal screening is coordinated by the Newborn Screening Coordination Centre based at the Refik Saydam Disease Prevention and Control Centre in Ankara. A free national screening and counselling program for thalassemia is also available through Thalassemia Counselling Centres organised by Turkish Ministry of Health.

### **Genetic testing**

Genetic testing is carried out mainly at University laboratories. There are no national guidelines concerning genetic testing, but two information documents have been prepared by Hacettepe Medical School on ethical principles of genetic testing and counselling through the National Commission for UNESCO Bioethics Committee web site (in Turkish). Tests are reimbursed through the Social Security System and private insurance schemes. Testing abroad is possible.

Diagnostic tests are registered as available in Turkey for 111 genes and an estimated 164 diseases in the Orphanet database<sup>579</sup>.

### **National alliances of patient organisations and patient representations**

The Turkish Rare Diseases Platform<sup>580</sup> is a new Platform bringing together yet a few rare disease patient organisations in Turkey. Established on 28 February 2013, it aims to motivate rare disease patient communities to come together and share their know-how to bring more service to rare diseases patients, family members and caretakers. It aims to be the platform to voice the issues of rare diseases patient associations and rare diseases patients and caretakers. Some private foundations (such as the Foundation for Metabolic Disorders – METVAK) are active in counselling, creating public awareness and networking for patients and families.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activity in Turkey***

There is no official, rare disease specific information centre on rare diseases in Turkey other than Orphanet. Since 2006 there is a dedicated Orphanet team for Turkey currently hosted by the Istanbul University Experimental Medical Research Institute Department of Genetics. This team is in charge of collecting data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. The team also maintains the national Orphanet Turkey website<sup>581</sup> in the Turkish language. The team organised the 6<sup>th</sup> Eastern European

<sup>579</sup> Information extracted from the Orphanet database (January 2014).

<sup>580</sup> <http://www.enderhastaliklar.org/>

<sup>581</sup> <http://www.orpha.net/national/TR-TR/index/orphanet-t%C3%BCrkiye/>

Rare Disease Conference in Istanbul on 24-26 November 2011 and the 1<sup>st</sup> National Rare Disease Symposium in Istanbul on 27 November 2011: a second National Symposium took place in November, 2013.

#### **Official information centre for rare diseases**

There is currently no official information centre for rare diseases in Turkey, although information is provided by the Ministry of Health's Mother and Child Health Directorate in Ankara.

#### **Help line**

There is currently no official help line for rare diseases in Turkey.

#### **Other sources of information on rare diseases**

No specific activity reported.

#### **Guidelines**

Treatment guidelines have been issued by the Ministry of Health for the following rare diseases: Gaucher type I and III; LSD type I, II and VI; Fabry; Niemann Pick; Pompe; and Wolman diseases.

#### **Training and education initiatives**

A bylaw has been accepted for fellowship training program paediatric metabolic diseases.

#### **National rare disease events in 2013**

Some rare diseases have an annual designated day (e.g. phenylketonuria day, 1 June) to raise awareness of these diseases. A second symposium on rare diseases was held in November 2013 to discuss the areas to be considered in the scope of a national plan for rare diseases.

#### **Hosted rare disease events in 2013**

No specific reported activities.

#### **Research activities and E-Rare partnership**

##### **National research activities**

TUBITAK (The Scientific and Technological Research Council of Turkey) has in the past supported research on rare diseases in Turkey.

##### **Participation in European research projects**

Teams from Turkey participate/participated in 16 FP7 rare disease related projects.

##### **E-Rare**

Turkey, represented by TÜBİTAK, has been a member of the E-Rare and E-Rare-2 projects. TÜBİTAK participated in all Joint Transnational Calls (JTC) of the E-Rare-1 and E-Rare-2 projects. In the 1<sup>st</sup> Joint Transnational Call, Turkey was represented in 2 of the 13 consortia/projects selected for funding of €700'000. In the 2<sup>nd</sup> Joint Transnational Call E-Rare, Turkey was represented in 4 of the 16 consortia/projects selected for funding, with a total of around €400,000 funding. In the 3<sup>rd</sup> Joint Transnational Call, TÜBİTAK supported 3 Turkish research teams within 13 selected consortia. Turkey also participated in the 4<sup>th</sup> Joint Transnational Call in 2012, however teams from Turkey are not involved in the selected consortia. The fifth E-Rare joint transnational call (JTC 2013) for funding multilateral research projects on rare diseases have been decided to open on December 7, 2013 by 17 European organisations including TÜBİTAK. The Turkish funding commitment was 0,6 M€ for the fifth call Launched in 2013, however Turkish teams were not amongst those participating in the selected projects.

##### **IRDIRC**

With a Memorandum of Understanding (MoU) documenting, the commitment of the indicated E-Rare group of funders, who agree on making every reasonable effort to fulfil the intents expressed in their participation in IRDiRC, has been signed between each Party including TÜBİTAK. EC responded positively to this demand that the group of E-Rare funders join IRDiRC in 2012.

### **Orphan medicinal products**

At the end of 2011, the Directorate General of Pharmaceuticals and Pharmacy (IEGM), attached to the Turkish Ministry of Health, transformed into the independent national competent authority, The Turkish Medicines and Medical Devices Agency (TİTCK). In Turkey, licencing applications for all human medicinal products are submitted, by accredited licence holders, to TİTCK, in line with the “Regulation on Licensing for Medicinal Products for Human Use”.

In 2010, the Orphan Drug Study Group (ODSG) was formed from officers working at the Directorate-General of Pharmaceuticals and Pharmacy (IEGM), TİTCK from here on. The main purpose of ODSG was to prepare the national Guideline for Orphan Medicines. In the course of activities, ODSG compiled information relating to orphan medicinal products and rare diseases in the European Union (EU), studied Regulations 141/2000/EC and 847/2000/EC, and developed a national approach for orphan medicinal product policies in Turkey. The National Draft Guideline for Orphan Medicines was formed in the first quarter of 2011. The Draft Guideline was open for consultation by the pharmaceutical sector, and responses received by the second half of 2011.

#### **Orphan medicinal product committee**

The Draft Guideline for Orphan Medicines includes the establishment of a “Scientific Commission for Orphan Medicines”.

#### **Orphan medicinal product incentives**

Data exclusivity is applied in terms to original products for which no generic registration application has been submitted in Turkey since 1 January 2005 among the original products which have been registered for the first time in one of the countries within the Customs Union Area after 1 January 2001, and original products which shall be registered for the first time in one of the countries within the Customs Union Area after 1 January 2005. The data exclusivity period consists of 6 years to commence as of the first registration date of these products in the Customs Union Area. With regard to those products which benefit from patent protection in Turkey, the implementation of the data exclusivity period of 6 years is limited to this patent period<sup>582</sup>.

The Orphan Drug Study Group (ODSG), formed in 2010 by the Ministry of Health (MOH) have proposed a draft National Draft Guideline for Orphan Medicines, including incentives for the development and registration of orphan drugs, which has been publicly available since 2011. The Ministry of Health updated the draft guideline in 2013 but did not share information on proposed changes. The updated version is waiting for approval by the head of the regulatory agency TİTCK. Publication of the final National Guideline is not expected before the end of 2014.

Today however, no regulations or guidelines are in place for rare diseases and/or orphan drugs. Only 30% of drugs for rare diseases have marketing authorisation in Turkey, with another 30% imported into Turkey via Turkish Pharmacists’ Association (TEB), subject to approval by the Ministry of Health on a case-by-case basis. The remaining 40% of these drugs are not available in Turkey<sup>583</sup>.

Drugs for the treatment of rare diseases are exempted from the reference pricing policy that is applicable to normal medicinal products. The Ministry of Health accepts pricing of human medicinal products to be considered under the ‘orphan’ approach when such a product is indicated for the treatment of diseases for which the etiology is not clearly defined and diseases which affect no more than 1 in 100’000 individuals. (A recent draft guideline proposes to change this to no more than 1 in 10’000 individuals).

Incentives related to orphan drug status in Turkey (as expected for the near future) are Waivers from MAA.

#### **Orphan medicinal product market availability situation**

At present, the Turkish Ministry of Health (MOH) has not yet developed a national policy with reference to “rare diseases” and “orphan medicinal products”, as commonly defined inside the European Union (EU). Therefore, patients suffering from known rare diseases in Turkey access treatment with nationally licenced or non-licenced human medicinal products that have been granted marketing authorisation by other competent authorities under “orphan designation” and/or indicated for the treatment of specific rare diseases.

<sup>582</sup> Regulation on Licensing of Medicinal Products for Human Use

<http://www.ieg.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawid=226>

<sup>583</sup> Source: Ceren Akdere, AIFD Orphan Drugs Working Group, February 2013



In 2013, 53 (of the 67 designated and centrally authorised medicines under the EU orphan medicinal products legislation) are accessible in Turkey. Of these orphan medicinal products, 21 are licenced in Turkey and 32 are procured by pre-licencing procedures.

Around half of the EU authorised orphan medicinal products accessible in Turkey are oncology-haematology products whereas nearly one quarter is gastroenterology-metabolism products, coming in first and second place, respectively. Oncology-haematology and gastroenterology-metabolism products also dominate the list of EU-authorised orphan medicinal products procured through pre-licencing procedures in Turkey.

#### **Orphan medicinal product pricing policy**

Normally, all drugs in Turkey are subject to a reference pricing policy. However, orphan medicinal products are exempted from this. Orphan products are priced up to the reference price laid down in official documents of the products where these products were imported and manufactured in its country of origin. Price of these products shall be revised making calculation on amounts of sales price every year. The Ministry of Health accepts pricing of human medicinal products to be considered under the 'orphan' approach when such a product is indicated for the treatment of diseases for which the aetiology is not clearly defined and those which affect no more than 1 in 100'000 individuals<sup>584</sup>.

#### **Orphan medicinal product reimbursement policy**

All orphan medicinal products entering the market are 100% reimbursed.

#### **Other initiatives to improve access to orphan medicinal products**

Orphan medicinal products are procured in Turkey by TITCK through 3 means. A medicine may be:

1. Licenced and already on the market for purchase;
2. Currently non-licenced in Turkey, however procured on grounds that it is approved in USA or the EU, or on a case-by-case basis in return for prescription ratification if its efficacy and safety is proven and a clinical trial protocol is running;
3. Approved under the scope of the compassionate use programme, to be clinically administered to patients.

#### **Orphan devices**

No specific activity reported.

#### **Other therapies for rare diseases**

No specific activity reported.

#### **Specialised social services**

Some therapeutic recreational programmes and services aimed at the integration of patients in daily life are provided by patient organisations and private foundations with the aid of private donations. Disability benefits can be obtained from the government towards special education classes.

## **RARE DISEASE ACTIVITIES IN 2013 IN TURKEY**

#### **National plan/strategies for rare diseases and related actions**

A second symposium was held in November 2013 to discuss the areas to be considered in the scope of a national plan for rare diseases.

#### **National alliances of patient organisations and patient representations**

The Turkish Rare Diseases Platform<sup>585</sup> is a new Platform bringing together yet a few rare disease patient organisations in Turkey. Established on 28 February 2013, it aims to motivate rare disease patient communities

<sup>584</sup> Press release regarding the Pricing of Medicinal Products for Human Use

(<http://www.iegm.gov.tr/Default.aspx?sayfa=regulations&lang=en&thelawtype=14&thelawid=225>)

<sup>585</sup> <http://www.enderhastaliklar.org/>

to come together and share their know-how to bring more service to rare diseases patients, family members and caretakers. It aims to be the platform to voice the issues of rare diseases patient associations and rare diseases patients and caretakers.

#### **National rare disease events in 2013**

Some rare diseases have an annual designated day (e.g. phenylketonuria day, 1 June) to raise awareness of these diseases. A second symposium on rare diseases was held in November 2013 is to discuss the areas to be considered in the scope of a national plan for rare diseases.

#### **Research activities and E-Rare partnership**

##### ***E-Rare***

Turkey, represented by TÜBİTAK, has been a member of the E-Rare and E-Rare-2 projects. The Turkish funding commitment was 0,6 M€ for the fifth call Launched in 2013, however Turkish teams were not amongst those participating in the selected projects.

#### **Orphan medicinal products**

##### ***Orphan medicinal product incentives***

The Orphan Drug Study Group (ODSG), formed in 2010 by the Ministry of Health (MOH) have proposed a draft National Draft Guideline for Orphan Medicines, including incentives for the development and registration of orphan drugs, which has been publicly available since 2011. The Ministry of Health updated the draft guideline in 2013 but did not share information on proposed changes. The updated version is waiting for approval by the head of the regulatory agency TITCK. Publication of the final National Guideline is not expected before the end of 2014.

## CONTRIBUTIONS AND SOURCES<sup>586</sup>

A full list of the over one hundred contributors to the State of the Art report and its sources can be found here: [http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivities\\_ContributionsSources.pdf](http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivities_ContributionsSources.pdf)

This report was compiled by Charlotte Rodwell

(Scientific Secretariat of the European Union Committee of Experts on Rare Diseases, INSERM US14, France)

## METHODOLOGY AND STRUCTURE

### 1. SOURCES

The main sources of data for the update of the present report were those collected through the systematic surveillance of international literature and the systematic query of key stakeholders carried out in order to produce the OrphaNews Europe newsletter, various reports published by the European Commission (including past reports of the workshops of the EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan medicinal products. The principal information sources and the collection of data are described in detail here below.

- **European Commission websites and documents**

Information and documentation from the European Commission was used in order to establish this report, principally accessed through the rare disease information web pages of the Directorate General Public Health<sup>587</sup> and Directorate General Research CORDIS website<sup>588</sup> as well as the site of the European Medicines Agency<sup>589</sup>, in particular the pages of the COMP<sup>590</sup> (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**

Data from the OrphaNews Europe<sup>591</sup> newsletter for the 2013 period was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France<sup>592</sup> (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

- **EUCERD Publications**

Parts III, IV and V of this report present an update of the information previously published in the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*<sup>593</sup> (July 2010), 2011

<sup>586</sup> The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

<sup>587</sup> [http://ec.europa.eu/health/rare\\_diseases/policy/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/policy/index_en.htm)

<sup>588</sup> [http://cordis.europa.eu/home\\_fr.html](http://cordis.europa.eu/home_fr.html)

<sup>589</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

<sup>590</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000263.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac0580028e30](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30)

<sup>591</sup> <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

<sup>592</sup> <http://www.orpha.net/actor/cgi-bin/OAhome.php>

<sup>593</sup> <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD<sup>594</sup>, 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD<sup>595</sup>, and the 2013 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD<sup>596</sup>. The methodology for the production of these previous reports is outlined in their respective introductions. In addition, reports from previous workshops of the EUCERD, including the EUCERD Joint Action have been used.

- **Reports of the EUCERD meetings**

The reports of 2013 meetings of the EUCERD were used in order to identify upcoming initiatives and incentives in the field of rare diseases, and to report on the events held to mark Rare Disease Day 2013.

- **Reports on orphan medicinal products**

The information provided for each Member State concerning the state of affairs in the field of orphan medicinal products has been elaborated, when referenced, from the basis of the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*<sup>597</sup> published in 2006 by the European Commission and produced using data collected by the EMA and Orphanet. This information has been updated when information is available and quoted when still applicable. Another valuable source of information on Orphan Drug policy, at EU and Member State levels was the 2009 KCE 112B report published by the KCE-Belgian Federal Centre of Healthcare Expertise (*Federaal Kenniscentrum voor de Gezondheidszorg/Centre federal d'expertise des soins de santé*) entitled "*Orphan Disease and Orphan Drug Policies*" (*Politiques relatives aux maladies orphelines et aux médicaments orphelins*)<sup>598</sup>. This report notably provided information for the Member State sections on Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The Office of Health Economics Briefing Document "*Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries (No. 52 October 2009)*" also provided information on orphan medicinal product availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V was added during the revision of the 2012 edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*<sup>599</sup> by Donald Macarthur: this report is referenced in footnotes when used.

- **EURORDIS website and websites of national alliances of patient organisation**

The site of EURORDIS, the European Organisation for Rare Diseases<sup>600</sup> was used to provide information on EURORDIS activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national patient alliances were also consulted for information. In addition to this the Rare Disease Day site<sup>601</sup>, maintained by EURORDIS, also provided information on events at Member State level<sup>602</sup> concerning Rare Disease Day.

- **Orphanet**

The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials, patient organisations and rare disease/orphan

<sup>594</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf> ;  
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf> ; and  
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

<sup>595</sup> <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf> ;  
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesII.pdf> ; and  
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf>

<sup>596</sup> <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf>

<sup>597</sup> [http://ec.europa.eu/health/files/orphanmp/doc/inventory\\_2006\\_08\\_en.pdf](http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf)

<sup>598</sup> *Politiques relatives aux maladies orphelines et aux médicaments orphelins*

[https://kce.fgov.be/sites/default/files/page\\_documents/d20091027332.pdf](https://kce.fgov.be/sites/default/files/page_documents/d20091027332.pdf)

<sup>599</sup> <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

<sup>600</sup> <http://www.EURORDIS.org/secteur.php3>

<sup>601</sup> <http://www.rarediseaseday.org/>

<sup>602</sup> <http://www.rarediseaseday.org/country/finder>

medicinal product policies outside of Europe for Part I. Orphanet also provides links<sup>603</sup> to other web-based information services and help-lines which were used to collect information at country-level. The Orphanet Country Coordinators also provided valuable input into the elaboration of information at country level, notably via contributions to OrphaNetWork News. The national Orphanet websites were also consulted to gather national events and initiatives.

**A selected bibliography and contributions are provided at the end of each volume of the report.**

## 2. METHODOLOGY

The present report provides an updated compilation of information from the previous reports of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the European Union Committee of Experts on Rare Diseases, 2011 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases, 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases and 2013 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Disease* ) which have covered activities up to the end of 2012. The present edition takes into account advances and activities in the field of rare diseases and orphan medicinal products at EU and MS level in 2013.

Once this information from the previous report was updated using the sources cited above, a draft of each country section (Part V) was sent in March 2014 to EC Expert Group on Rare Diseases Member States representatives with a guidance document providing an explanation of the type of information to include if available for each category. The Member State representatives were asked to contact a range of identified key stakeholders in their country for input. The stakeholders identified for each country included: the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, partners of the E-Rare consortium, Member State representatives on the COMP, representatives of national competent authorities, coordinators of national plans for rare diseases and other rare diseases experts identified at national level. The Member State representatives integrated the stakeholder feedback into their report before returning it to the Scientific Secretariat for homogenisation and extraction of developments in 2013 to be included in Part II. Final drafts of Parts II, V, VI concerning their country were sent to the EC Expert Group on Rare Diseases Member State representatives for final validation, to the best of their knowledge, in May 2014.

Part III and IV of the report on activities at European Union level was for input, to the best of their ability, to colleagues at the European Commission and the European Medicines Agency (EMA) respectively: this process was carried out in April 2014 by the Scientific Secretariat of the EUCERD Joint Action. The European Commission and its agencies are not responsible, however, for the completeness and the accuracy of the information presented in this report. The new activities in 2013 were extracted and added to Part II.

Part I was the final volume of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe is the result of an analysis of the information collected for Parts II, III, IV and V. Part I was drafted by the Scientific Secretariat of the EUCERD Joint Action and then sent to all EC Expert Group on Rare Diseases Member State representatives for their input concerning their country's activities before publication in June 2014.

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<sup>603</sup> [http://www.orpha.net/consor/cgi-bin/Directory\\_Contact.php?lng=EN](http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN)

### 3. REPORT STRUCTURE

The report is structured into three main parts: Part I consists of an overview of the activities in the field of rare diseases in Europe at EU and MS level; Part II is an extraction of the developments at EU and MS level in 2013 based on Parts III, IV and V; Part III concerns activities of the European Commission; Part IV concerns European Medicines Agency activities and other European activities/events at European level apart from the activities of the European Commission; Part V concerns activities at EU MS level, as well as five other non-EU European countries where information was available; Part V provides the content of Parts II and V in individual country-specific reports.

Each part is followed by a link to a selected bibliography outlining the sources used to produce that part of the report, which includes a list of the European Commission documents referred to in the report and a list of web addresses by country listing national sources of information on rare diseases and links to documents concerning national plans or strategies for rare diseases when in place. Each part is also followed by a link to the list of contributors to the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous edition of the report. A list of frequently used acronyms has also been included in each part to ease reading.

**Part I** provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts III, IV and V, which serve to provide more detailed background information at EU and MS level. The overview is structured into a number of topics: political framework, expert services in Europe, research and development, orphan medicinal products and therapies for rare diseases, patient organisations and information services.

**Part II** is a new section of the report, providing information extracted from Parts III, IV and V, relative only to the new activities and initiatives reported for the year 2013.

**Part III** of the report focuses on activities in the field of rare diseases at EC level is split into four sub-sections:

1. EC activities related to rare diseases in the field of public health;
2. EC activities related to rare diseases in the field of research;
3. EC activities in the field of orphan medicinal products and therapies for rare diseases.

The sub-section concerning the EC activities actions in the area of Public Health is divided into three parts: an overview of DG Health and Consumers' activities in the field of public health, activities in the field of rare diseases funded by DG Health and Consumers, and activities of DG Health and Consumers indirectly related to rare diseases. The sub-section concerning the EC activities in the field related to research in the field of rare diseases presents information concerning DG Research and Innovation's 5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> framework programmes for research, technological development and demonstration activities and Horizon 2020 related to rare diseases, as well as information concerning the International Rare Disease Research Consortium (IRDiRC).

**Part IV** of the report contains information on the activities in the field of rare diseases of the EMA and other rare disease activities at the European level, including selected transversal EU activities and conferences at European level:

- European Medicine Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases, EMA Committee for Orphan Medicinal Products' activities, EMA Committee on Human Medicinal Products' activities, European legislation and activities in the field of clinical trials, European legislation and activities in the field of advanced therapies, European legislation and activities in the field of medicinal products for paediatric use, other EMA activities and initiatives relevant to rare diseases and orphan medicinal products, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan medicinal products.
- The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-

Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2013.

**Part V** concerns the rare disease activities in the field of rare diseases in each of the 28 Member States plus Iceland, Norway, and Switzerland in addition to Serbia and Turkey as candidates for EU membership, as well as Israel. These sections are organised in alphabetical order by country.

The information on each country is clearly divided into a number of categories:

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise<sup>604</sup>
- Registries
- Neonatal screening policy
- Genetic testing<sup>605</sup>
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Guidelines
- Training and education initiatives
- National rare disease events in 2013<sup>606</sup>
- Hosted rare disease events in 2013<sup>607</sup>
- Research activities (National research activities, Participation in European research projects<sup>608</sup>, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability<sup>609</sup>, Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products), Other therapies for rare diseases
- Orphan devices
- Specialised social services

The categories for which information is provided depend wholly on the information available following data collection from the described sources and contact with stakeholders. If no detail has been given for a topic, the mention “no specific activity/information reported” has been added.

**Part VI** concerns the rare disease activities in the field of rare diseases in each of the 28 Member States plus Iceland, Norway and Switzerland in addition to Serbia and Turkey as candidates for EU membership, as well as Israel. This section is the same as Parts II and V, except that the information is presented as a separate document for each country to facilitate dissemination at country level.

Each section has two parts: firstly the state of the art up until the end of 2013, and secondly the state of the art of activities in 2013 only so as to easily identify new actions and activities.

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<sup>604</sup> The term “official centre of expertise” used in this report means officially designated via a (ministerial) procedure.

<sup>605</sup> This section contains data extracted in January 2014 from [www.orpha.net](http://www.orpha.net) of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term ‘estimated’ is used as the concept of a single disease is a variable one).

<sup>606</sup> As announced in OrphaNews Europe.

<sup>607</sup> As announced in OrphaNews Europe.

<sup>608</sup> Number of projects (Framework Programme 7 funded, including E-Rare) in which research teams from the country are participating as extracted from [www.orpha.net](http://www.orpha.net) in March 2014.

<sup>609</sup> Contacts were asked to provide information on availability of orphan medicinal products (i.e. which drugs are launched on the market/sold at national level). As this information is often hard to identify, some countries instead provided information on which drugs are accessible (i.e. reimbursed, on a positive drug list etc.). It is explicitly explained in each case which of these concepts is being referred to.

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