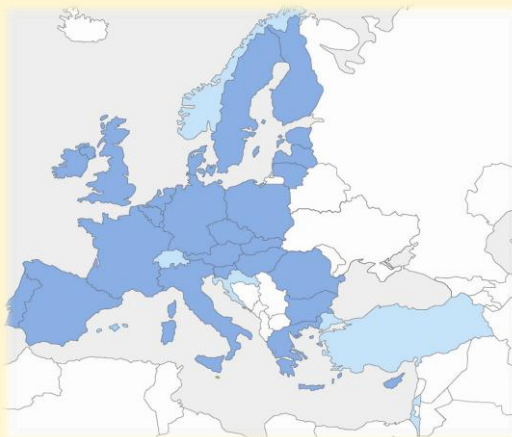


**2012 REPORT ON THE STATE OF THE ART  
OF RARE DISEASE ACTIVITIES IN EUROPE  
OF THE  
EUROPEAN UNION COMMITTEE OF EXPERTS  
ON RARE DISEASES**



**PART I: OVERVIEW OF RARE DISEASE  
ACTIVITIES IN EUROPE**

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This document has been produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD, formerly the European Commission's Rare Diseases Task Force) through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01, Coordinator: Kate Bushby, University of Newcastle, United Kingdom), within the European Union's Second Programme of Community Action in the Field of Health.

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

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## ACRONYMS

### General

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  
ECRD - 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

### Pilot European Reference Networks

Dyscerne - European network of centres of expertise for dysmorphology  
ECORN-CF - European centres of reference network for cystic fibrosis  
Paediatric Hodgkin Lymphoma Network - Europe-wide organisation of quality controlled treatment  
NEUROPED - European network of reference for rare paediatric neurological diseases  
EUROHISTIONET - A reference network for Langerhans cell histiocytosis and associated syndrome in EU  
TAG - Together Against Genodermatoses – improving healthcare and social support for patients and families affected by severe genodermatoses  
PAAIR - Patients' Association and Alpha-1 International Registry Network  
EPNET - European Porphyria Network - providing better healthcare for patients and their families  
EN-RBD -European Network of Rare Bleeding Disorders  
CARE-NMD -Dissemination and Implementation of the Standards of Care for Duchenne Muscular Dystrophy in Europe project  
ENERCA - European network for rare and congenital anaemia – Stage 3

## GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 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 2011. 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 European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of either the European Commission, its Agencies or national health authorities.

The report is split into five parts:

Part I: Overview of rare disease activities in Europe<sup>1</sup>

Part II: Key developments in the field of rare diseases in 2011<sup>2</sup>

Part III: European Commission activities in the field of rare diseases<sup>3</sup>

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases<sup>4</sup>

Part V: Activities in EU Member States and other European countries in the field of rare diseases<sup>5</sup>

Each part contains the following description of the methodology, sources and validation process of the entire report, and concludes with a selected bibliography and list of persons having contributed to the report.

### 1. METHODOLOGY AND 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 Rare Diseases Task Force and EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan medicinal products, including the reports of the national conferences organised in the context of the EUROPLAN project. 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>6</sup> and Directorate General Research CORDIS website<sup>7</sup> as well as the site of the European Medicines Agency<sup>8</sup>, in particular the pages of the COMP<sup>9</sup> (Committee of Orphan Medicinal Products).

<sup>1</sup> <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArRDActivities.pdf>

<sup>2</sup> <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArRDActivitiesII.pdf>

<sup>3</sup> <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArRDActivitiesIII.pdf>

<sup>4</sup> <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArRDActivitiesIV.pdf>

<sup>5</sup> <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArRDActivitiesV.pdf>

<sup>6</sup> [http://ec.europa.eu/health/rare\\_diseases/policy/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/policy/index_en.htm)

<sup>7</sup> [http://cordis.europa.eu/home\\_fr.html](http://cordis.europa.eu/home_fr.html)

<sup>8</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

<sup>9</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)

- **OrphaNews Europe**

Data from the OrphaNews Europe<sup>10</sup> newsletter for the period 2007-2011 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>11</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>12</sup> (July 2010) and the 2011 EUCERD Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases<sup>13</sup>. The methodology for the production of these previous reports is outlined in their respective introductions.

- **Reports of the EUCERD meetings**

The reports of 2011 meetings of the EUCERD (22-23 March 2011 and 24-25 October 2011) 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 2011.

- **Rare Diseases Task Force publications**

Various reports of the RDTF have been used as sources of data to collect information on the state of affairs at both EU and Member State levels pre-2010, notably the reports of the RDTF WG on Standards of Care (concerning European Centres of Reference) produced between 2005-2008, including the RDTF Final Report – Overview of Current Centres of Reference on rare diseases in the EU – September 2005<sup>14</sup> and the RDTF Meeting Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – September 2006<sup>15</sup>, as well as the RDTF Final Report – State of the Art and Future Directions – March 2008<sup>16</sup>.

- **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>17</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>18</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

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<sup>10</sup> <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

<sup>11</sup> <http://www.orpha.net/actor/cgi-bin/OAhome.php>

<sup>12</sup> <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

<sup>13</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>14</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>

<sup>15</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

<sup>16</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

<sup>17</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>18</sup> *Politiques relatives aux maladies orphelines et aux médicaments orphelins*

[http://www.kce.fgov.be/index\\_fr.aspx?SGREF=3460&CREF=13646](http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646)

reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V has been provided for this year's edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*<sup>19</sup> by Donald Macarthur: this report is referenced in footnotes when used. Information for the overview was also provided by the *Nature Reviews: Drug Discovery* article produced by the COMP/EMA Scientific Secretariat, *European regulation on orphan medicinal products: 10 years of experience and future perspectives*<sup>20</sup>.

- **EURORDIS website and websites of national alliances of patient organisation**

The site of EURORDIS, the European Organisation for Rare Diseases<sup>21</sup>, and the book *The Voice of 12,000 Patients: Experiences & Expectations of Rare Disease Patients on Diagnosis & Care in Europe* (produced using the results of the EURORDISCare<sup>22</sup> surveys), were 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 2011 site<sup>23</sup>, maintained by EURORDIS, also provided information on events at Member State level<sup>24</sup> concerning Rare Disease Day.

- **EUROPLAN national conferences final reports**

In the context of the EUROPLAN project (2008-2011), 15 national conferences were organised in collaboration with EURORDIS and national rare disease patient alliances in 2010-2011 in order to present the Council Recommendation on an action in the field of rare diseases, as well as discuss the Europlan recommendations/guidance document for the development of national plans and strategies in the field of rare diseases<sup>25</sup> and its application at national level. These conferences were attended by a range of stakeholder groups at national level and the final reports<sup>26</sup> of these conferences were presented in a common format for ease of comparison. Information provided in these reports has helped update the information provided in this document. Readers of this report are encouraged to refer to these reports in addition to the present report as they provide further detail of the discussions of national approaches to rare disease policy.

- **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 medicinal product policies outside of Europe for Part I. Orphanet also provides links<sup>27</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 report produced by the RDPlatform project<sup>28</sup>, in particular the report *Rare diseases research, its determinants in Europe and the way forward*<sup>29</sup> was also used as a source for Part I.

- **OrphaNetWork News**

OrphaNetWork News is the internal newsletter of Orphanet, which communicates information to partners on Orphanet activities in each partner country. The data for this newsletter is collected through a systematic query of Orphanet Country Coordinators and Information Scientists in order to collect information concerning Orphanet country teams' involvement in rare disease meetings and

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<sup>19</sup> <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

<sup>20</sup> <http://www.ncbi.nlm.nih.gov/pubmed/21532564>

<sup>21</sup> <http://www.EURORDIS.org/secteur.php3>

<sup>22</sup> [http://www.EURORDIS.org/article.php3?id\\_article=1960](http://www.EURORDIS.org/article.php3?id_article=1960)

<sup>23</sup> <http://www.rarediseaseday.org/>

<sup>24</sup> <http://www.rarediseaseday.org/country/finder>

<sup>25</sup> [http://www.europlanproject.eu/public/contenuti/files/Guidance\\_Doc\\_EUROPLAN\\_20100601\\_final.pdf](http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf)

<sup>26</sup> <http://www.EURORDIS.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN%20%20National%20Conference%20Final%20Reports>

<sup>27</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)

<sup>28</sup> <http://www.rdplatform.org/>

<sup>29</sup> [http://asso.orpha.net/RDPlatform/upload/file/RDPlatform\\_final\\_report.pdf](http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf)

conferences, as well as participation in Rare Disease Day events and partnerships. The review at national level yielded information for the events section for each Member State report.

**A selected bibliography and contributions are provided at the end of each volume of the report.**

## 2. REPORT PREPARATION, REVISION AND VALIDATION

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* and *2011 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases*) which have covered activities up to the end of 2010. 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 2011.

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 February 2012 to EUCERD 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: representatives at the EUCERD in the respective countries and their alternates, 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 2011 to be included in Part II. Final validation of Parts II and V were sent to the EUCERD Member State representatives for final validation, to the best of their knowledge, in May 2012.

Part III and IV of the report on activities at European Union level was sent for validation, to the best of their ability, by the representatives at the EUCERD of the European Commission Directorate Generals for Health and Consumers, Research and Innovation, Enterprise and Industry, and the European Medicines Agency (EMA) respectively: this process was carried out in March/April 2012 by the Scientific Secretariat of the EUCERD. 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 2011 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 and then sent to all EUCERD members and their alternates for their input before publication.

## 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 2011 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.

Each part is followed by 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 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 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 2011.

**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 related to rare diseases, as well as information concerning the International Rare Disease Research Consortium (IRDiRC) and Open Access Infrastructure for Research in Europe (OpenAire) initiatives.

**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 2011.

**Part V** concerns the rare disease activities in the field of rare diseases in each of the 27 Member States plus Norway and Switzerland as EFTA countries, Croatia and Turkey as candidates for EU membership, and Israel: Iceland has chosen to not contribute a country report this year. 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>30</sup>

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<sup>30</sup> The term "official centre of expertise" used in this report means officially designated via a (ministerial) procedure.

- Pilot European Reference Networks
- Registries
- Neonatal screening policy
- Genetic testing<sup>31</sup>
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Good practice guidelines
- Training and education initiatives
- National rare disease events in 2011<sup>32</sup>
- Hosted rare disease events in 2011<sup>33</sup>
- Research activities (National research activities, Participation in European research projects<sup>34</sup>, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability<sup>35</sup>, Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products)
- 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.

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<sup>31</sup> This section contains data extracted in September 2011 from the Orphanet database 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>32</sup> As announced in OrphaNews Europe.

<sup>33</sup> As announced in OrphaNews Europe.

<sup>34</sup> Past and ongoing participation in DG Research and Innovation financed projects. Some countries have added information on additional European projects.

<sup>35</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.

## INTRODUCTION: OVERVIEW OF RARE DISEASE ACTIVITIES IN EUROPE

Rare diseases are diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect not more than 5 per 10 000 persons in the European Union. It is estimated that between 5 000 and 8 000 distinct rare diseases exist, affecting between 6% and 8% of the population in the course of their lives. In other words, although rare diseases are characterised by low prevalence<sup>36</sup> for each of them, the total number of people affected by rare diseases in the EU is between 27 and 36 million. Most of them suffer from less frequently occurring diseases affecting one in 100 000 people or less. These patients are particularly isolated and vulnerable. The definition of a rare disease as having a prevalence of not more than 5 in 10 000 first appeared in EU legislation in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products<sup>37</sup>. The Community action programme on rare diseases including genetic diseases for the period 1 January 1999 to 31 December 2003 then applied this definition to the field of public health.

Most rare diseases are genetic diseases, the others being rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases among other categories. Research on rare diseases has proved to be very useful to better understand the mechanism of common conditions such as obesity and diabetes, as they often represent a model of dysfunction of a single biological pathway. However, research on rare diseases is not only scarce, but also scattered in different laboratories throughout the EU. The lack of specific health policies for rare diseases and the scarcity of expertise, translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, inadequate or even harmful treatments and loss of confidence in the health care system, despite the fact that some rare diseases are compatible with a normal life if diagnosed on time and properly managed. Misdiagnosis and non-diagnosis are the main hurdles to improving quality of life for thousands of rare disease patients.

The specificities of rare diseases, including a limited number of patients and scarcity of relevant knowledge and expertise, single them out as a distinctive domain of very high European added-value. European cooperation can help to ensure that scarce knowledge can be shared and resources combined as efficiently as possible, in order to tackle rare diseases effectively across the EU as a whole. The European Commission has already taken specific steps in many areas to address the issues of rare diseases. Building on those achievements, the Commission Communication on Europe's Challenges in the field of Rare Diseases (11.11.2008)<sup>38</sup> and the Council Recommendation on an action in the field of rare diseases (08.06.2009) aim to give a clear direction to present and future Community activities in the field of rare diseases in order to further improve the access to and equity of prevention, diagnosis and treatment for patients suffering from a rare disease throughout the European Union.

All information given in this summary concerning the state of activities at Member State level concerns the state of activities at the end of the year 2011 unless otherwise stated.

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<sup>36</sup> For a list of rare diseases and their prevalence, please consult the Orphanet Reports Series "Prevalence of rare diseases: Bibliographic data", Orphanet Report Series, Rare Diseases collection, Number 1 : Listed in alphabetical order of diseases,

[http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence\\_of\\_rare\\_diseases\\_by\\_alphabetical\\_list.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf)

<sup>37</sup> [http://ec.europa.eu/health/files/eudralex/vol-1/reg\\_2000\\_141/reg\\_2000\\_141\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf)

<sup>38</sup> [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/rare\\_com\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf)

## 1. Political framework

Since the 1990s at both European Union (EU) and Member State (MS) level political concepts and initiatives concerning rare diseases have emerged (Figure 1). Indeed, a number of countries led the way in the decade leading up to the first European legislative text concerning rare diseases, the Orphan Medicinal Product Regulation of 16 December 1999<sup>39</sup>, and the ensuing Commission Communication (2008) and Council Recommendation (2009). Sweden, for example established the first centres of expertise for rare diseases in 1990 and a rare disease database and information centre in 1999; Denmark established an information centre in 1990 and then centres of expertise for rare diseases in 2001; in Italy, a decree on rare diseases came into force in 2001; and in France, Orphanet was established in 1997 with the support of the French Ministry of Health as the portal for information on rare diseases and orphan medicinal products, followed by the first national plan/strategy for rare diseases in Europe (2004). A number of other countries (Bulgaria, Greece, Portugal, and Spain) elaborated a national plan/strategy for rare diseases at the very same time as EU policy in the field was defined through the Commission Communication and Council Recommendation. In 2011, it can be observed that policy at Member State level is gathering momentum in the wake of EU policy, in particular the elaboration of national plans or strategies for rare diseases, in response to the recommendation of the Council to “elaborate and adopt a plan or strategy as soon as possible, preferably by the end of 2013 at the latest, aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems<sup>40</sup>”.

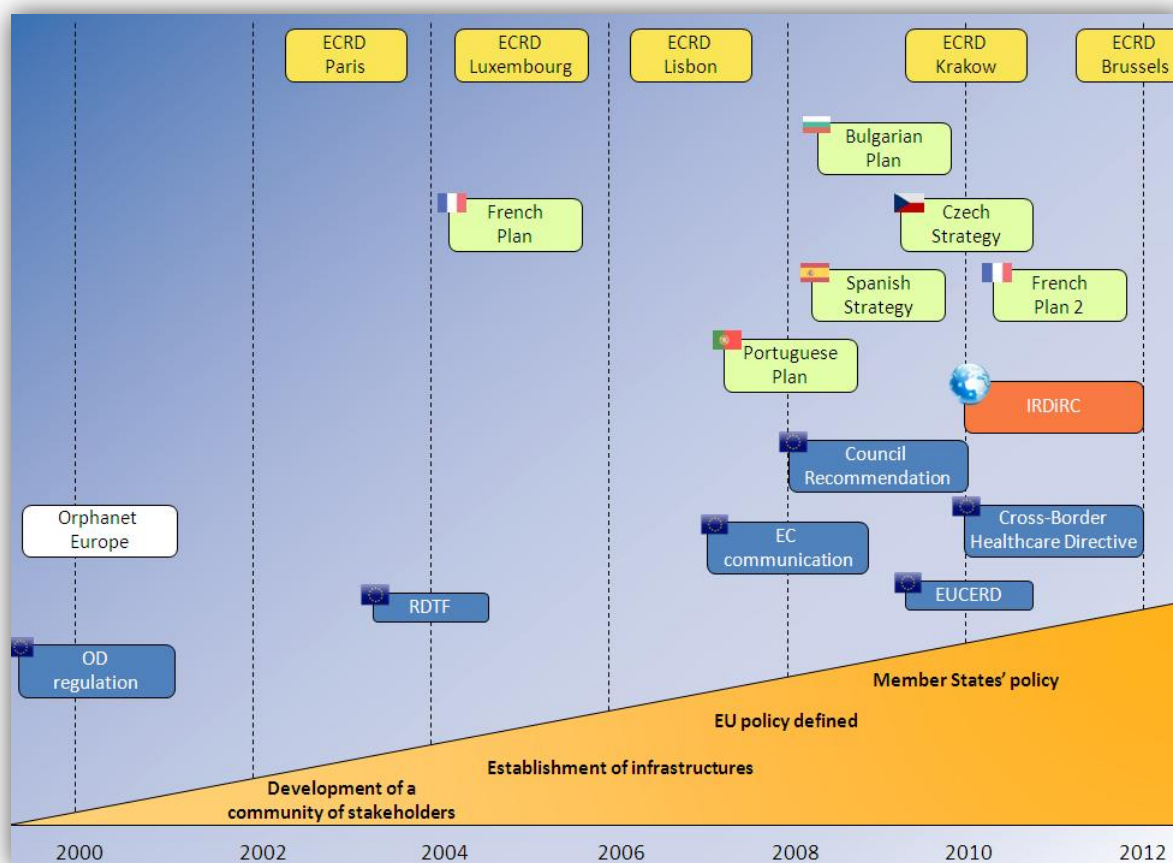


Figure 1: Emergence of concepts and initiatives surrounding rare diseases in Europe<sup>41&42</sup>

<sup>39</sup> [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/rare\\_com\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf)

<sup>40</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

<sup>41</sup> ECRD – European Conference on Rare Diseases

<sup>42</sup> Graphic courtesy of the EUCERD Scientific Secretariat.

## 1.1. Political framework at European level

### 1.1.1. Key policy documents

At European level, there are currently three key policy documents establishing a political framework for action in the field of rare diseases and orphan medicinal products at European level:

- a) **The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products)**<sup>43</sup> was proposed to set up the criteria for orphan designation in the EU and describes the incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) to encourage the research, development and marketing of medicines to treat, prevent or diagnose rare diseases. The Regulation provides that a medicinal product can be designated as an ‘orphan medicinal product’ when intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 000 persons in the Community when the application is made, and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition. This EU policy for orphan medicinal products has been heralded as a success (see section 4.1). Despite the efforts of Member States to ensure access to orphan medicinal products, not all Member States currently ensure full access to each authorised orphan medicinal product approved.
- b) **The Commission Communication on Rare Diseases: Europe’s challenge**<sup>44</sup>, adopted on 11 November 2008, set out an overall Community strategy to support Member States in diagnosing, treating and caring for the 36 million EU citizens with rare diseases. The Communication was drafted by the European Commission in close collaboration with the EC Rare Diseases Task Force between June and October 2007. This Communication focuses on three main areas: 1) improving recognition and visibility of rare diseases, 2) supporting policies on rare diseases in MS for a coherent overall strategy, and 3) developing cooperation, coordination and regulation for rare diseases at EU level. The Communication recognised the potential for maximising the scope for cooperation and mutual support in this challenging area across Europe as a whole, and the Commission voiced its intention to support Member States in putting in place their own national and regional strategies for rare diseases. Through the overall Community strategy laid out in this document, it is hoped that the patients and families affected by rare diseases will be provided with a tangible benefit from European integration in their daily lives. The Commission Communication also served to pave the way for the Council Recommendation on an action in the field of rare diseases.
- c) **The Council Recommendation on an action in the field of rare diseases**<sup>45</sup> was adopted on 8 June 2009. The Recommendation engages the responsibility of Member States and concentrates on supporting and strengthening the adoption before the end of 2013 of national plans and strategies for responding to rare diseases, on improving recognition and visibility of rare diseases, on encouraging more research into rare diseases and forging links between centres of expertise and professionals in different countries through the creation of European reference networks in order to share knowledge and expertise and, where necessary, to identify where patients should go when such expertise cannot be made available to them. The role of patients’ organisations is also highlighted as particularly important.

<sup>43</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

<sup>44</sup> [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/rare\\_com\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf)

<sup>45</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

The seven key themes of the Council Recommendation are:

- *I. Plans and strategies in the field of rare diseases* – calls on the MS to elaborate and adopt a plan or strategy by the end of 2013.
- *II. Adequate definition, codification and inventorying of rare diseases* – evokes the common definition of a rare disease as a condition affecting no more than 5 per 10 000 persons; aims to ensure that rare diseases are adequately coded and traceable in all health information systems based on the ICD and in respect of national procedures; and encourages MS to contribute actively to the inventory of rare diseases based on the Orphanet network.
- *III. Research on rare diseases* – calls for the identification and fostering of rare disease research at all levels.
- *IV. Centres of expertise and European reference networks for rare diseases* – asks the MS to identify and facilitate networks of expertise based on a multidisciplinary approach to care, and foster the diffusion and mobility of expertise and knowledge.
- *V. Gathering the expertise on rare diseases at European level* – calls on MS to share best practices, develop medical training relevant to the diagnosis and management of rare diseases, coordinate European guidelines, and, to minimise the delay in access to orphan drugs, as well as to share clinical/therapeutic added-value assessment reports at the Community level.
- *VI. Empowerment of patient organisations* – calls on MS to consult patient representatives on policy development; facilitate patient access to updated information on rare diseases; promote patient organisation activities.
- *VII. Sustainability* – highlights that long-term sustainability in the field of information, research and healthcare of infrastructures must be ensured.

The European Commission shall produce, in order to allow proposals in any possible future programme of Community action in the field of health, by the end of 2013 an implementation report on both the Council Recommendation and Commission Communication, addressed to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions and based on the information provided by the Member States, which should consider the extent to which the proposed measures are working effectively and the need for further action to improve the lives of patients affected by rare diseases and those of their families.

To aid the European Commission with the preparation and implementation of Community activities in the field of rare diseases, **The European Union Committee of Experts on Rare Diseases (EUCERD)**<sup>46</sup> was formally established via the **European Commission Decision of 30 November 2009 (2009/872/EC)**<sup>47</sup> (see Section 1.1.1.1.).

The European Commission also funded the European Project for Rare Diseases National Plans Development (EUROPLAN<sup>48</sup>) between 2008-2011. The main goal of the project was to provide National Health Authorities with supporting tools for the development and implementation of National Plans and Strategies for rare diseases as recommended by the Council. The supporting tools included a Guidance document on recommendations for the definition and implementation of National Plans and Strategies for rare diseases<sup>49</sup>; a joint report with the RDTF on initiatives and incentives in the field of rare diseases in Europe<sup>50</sup>; and a document on the recommended set of indicators for monitoring and evaluating the implementation of national initiatives<sup>51</sup>. In the context of the EUROPLAN project, national conferences and workshops on the subject of national plans and strategies, took place throughout 2010 in 15 EU MS: these national conferences were organised by National Alliances of rare disease patient organisations under the supervision of EURORDIS. The conferences aimed both to

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<sup>46</sup> The EUCERD [www.eucerd.eu](http://www.eucerd.eu) replaces the European Commission's Rare Diseases Task Force [www.rdtf.org](http://www.rdtf.org) (2004-2009).

<sup>47</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:315:0018:0021:EN:PDF>

<sup>48</sup> <http://www.europlanproject.eu/>

<sup>49</sup> [http://www.europlanproject.eu/public/contenuti/files/Guidance\\_Doc\\_EUROPLAN\\_20100601\\_final.pdf](http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf)

<sup>50</sup> <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

<sup>51</sup> <http://www.europlanproject.eu/public/contenuti/files/EP-D6-Indicators.pdf>

raise awareness of the Council Recommendation and to move forward the process of developing a national strategy for rare diseases in each particular country. The support activities of Europlan will continue in the context of the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01 from March 2012 for a 3 year period.

- d) **Directive 2011/24/EU on the application of patients' rights in cross-border healthcare**<sup>52</sup>, was approved in early 2011 to coincide with Rare Disease Day (28 February 2011). Highly relevant to rare disease patients suffering from scarce and scattered resources for care and diagnostics, the Directive seeks to facilitate access to health care for EU citizens and encourage cooperation between EU Member States in the field of health. Member States will have 30 months to put the provisions of the Directive into national legislation following the publication in the Official Journal of the European Union. The Directive will have no impact on the rights of each Member State to determine which health benefits they will provide. Thus, if a particular treatment is not reimbursed in a patient's home country, it will not be reimbursed if accessed in another Member State. Member States would be able to require prior authorisation for "hospital care" and reimbursement would match the amount that patients would receive in their home country. However, Article 13 of the Directive specifically addresses the commitment of the Commission on behalf of rare disease patients: *"The Commission shall support Member States in cooperating in the development of diagnosis and treatment capacity in particular by aiming to:*

*(a) make health professionals aware of the tools available to them at Union level to assist them in the correct diagnosis of rare diseases, in particular the Orphanet database, and the European reference networks;*

*(b) make patients, health professionals and those bodies responsible for the funding of healthcare aware of the possibilities offered by Regulation (EC) No 883/2004 for referral of patients with rare diseases to other Member States even for diagnosis and treatments which are not available in the Member State of affiliation."*

The focus from 2012 will be the implementation of the Directive, led by the Committee on Cross-Border Healthcare, a legal forum where all 27 Member States will meet to vote on implementing acts and discuss general issues concerning the transposition of the directive. Delegated and implementing acts will, by defining the criteria as provided in the Directive, establish the methodology of the whole process of deciding which European Reference Networks to support, including the process of selection and designation of the healthcare providers to be considered members of the European Reference Networks and several categories of criteria for the adequate management, monitoring and evaluation of the networks.

#### **1.1.1.1. The European Union Committee of Experts on Rare Diseases (EUCERD)**

The European Union Committee of Experts on Rare Diseases (EUCERD) is charged with aiding the European Commission in cooperation and consultation with the specialised bodies in Member States, the relevant European authorities in the fields of research and public health action and other relevant stakeholders acting in the field. The EUCERD will foster exchanges of relevant experience, policies and practices between these parties. The EUCERD is specifically charged with the following responsibilities:

- assisting the Commission in the monitoring, evaluating and disseminating the results of measures taken at Community and national level in the field of rare diseases;
- contributing to the implementation of Community actions in the field, in particular by analysing the results and suggesting improvements to the measures taken;
- contributing to the preparation of Commission reports on the implementation of the Commission Communication and the Council Recommendation;
- delivering opinions, recommendations or reports to the Commission either at the latter's request or on its own initiative;
- assisting the Commission in international cooperation on matters relating to rare diseases;
- assisting the Commission in drawing up guidelines, recommendations and any other action defined in the Commission Communication and in the Council Recommendation;
- providing an annual report of its activities to the Commission.

<sup>52</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF>

The activities of the EUCERD were supported by Joint Action N° 2008 22 91 (Support to the Scientific Secretariat of the RDTF/EUCERD) and will be supported by the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01 as of March 2012.

The EUCERD held two plenary meetings in 2011 (22-23 March 2011<sup>53</sup> and 24-25 October 2011<sup>54</sup>) and held a number of workshops: EUCERD Workshop on centres of expertise for rare diseases and European collaboration between centres of expertise<sup>55</sup> (21-23 March 2011), EUCERD/EMA Workshop: Towards a public-private partnership for registries in the field of rare diseases<sup>56</sup> (4 October 2011), EUCERD/Eurobiomed Event: Rare 2011 European Day<sup>57</sup> (4 November 2011) and EUCERD/WHO Technical Workshop on the Classification of Genetic Diseases (1 December 2011).

The EUCERD issued two reports in 2011: *Preliminary Analysis of the Outcomes and Experiences of Pilot European Reference Networks for Rare Diseases (May 2011)*<sup>58</sup> and the annual *EUCERD Report on the State of the Art of Rare Disease Activities in Europe (July 2011)*<sup>59</sup>. In October 2011 the EUCERD adopted their first set of recommendations on *Quality Criteria for Centres of Expertise for Rare Diseases in Member States*<sup>60</sup>.

The EUCERD also started work in 2011 on a number of priority topics in the Council Recommendation: this work includes the elaboration of recommendations for European Reference Networks on rare diseases, recommendations on improving informed decisions based on the Clinical Added Value of Orphan Medicinal Products information flow, discussion on public-private partnerships for registries in the field of rare diseases, support to Member States in their efforts the elaboration of national plans or strategies for rare diseases, and support to the Topic Advisory Group on Rare Diseases in their efforts to ensure that all rare diseases are present in the revised version of the WHO International Classification of Diseases.

### 1.1.2. Work programmes at European level

**A Community action programme on Rare Diseases**, including genetic diseases, was adopted for the period of 1 January 1999 to 31 December 2003 with the aim of ensuring a high level of health protection in relation to rare diseases. As the first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases. As a consequence rare diseases are now one of the priorities in the **Second Programme of Community Action in the Field of Health 2008-2013**<sup>61</sup>. The DG Health and Consumers work plans for the implementation of the Public Health Programme include main lines of action and priorities in the field of rare diseases every year.

At European level, research on rare diseases is being addressed as one of the priority areas in the health field under the **EU Framework Programmes for Research and Technological Development (FP)** since the early 1990s. In the current Framework Programme (FP7 2007-2013<sup>62</sup>) the Health Theme of the "Cooperation" Specific Programme, is designed to support multinational collaborative research in different forms. The main focus of the Health theme in the rare diseases area are Europe-wide studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions. More information on the Framework Programmes is provided in section 3.1.2.

<sup>53</sup> <http://www.eucerd.eu/upload/file/Meeting/EUCERD/EUCERDPublicSummaryReport230311.pdf>

<sup>54</sup> <http://www.eucerd.eu/upload/file/EUCERD3Abstract.pdf>

<sup>55</sup> <http://www.eucerd.eu/upload/file/EUCERDReport220311.pdf>

<sup>56</sup> <http://www.eucerd.eu/upload/file/EUCERDWorkshopRegistries2011.pdf>

<sup>57</sup> <http://www.eucerd.eu/upload/file/Rare2011.pdf>

<sup>58</sup> <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

<sup>59</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf>

<sup>60</sup> <http://www.eucerd.eu/upload/file/EUCERDRecommendationCE.pdf>

<sup>61</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>

<sup>62</sup> [http://cordis.europa.eu/fp7/home\\_en.html](http://cordis.europa.eu/fp7/home_en.html)



## 1.2. Political framework at Member State level

At Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. The Council Recommendation on an action in the field of rare diseases (8 June 2009) recommends that MS elaborate and adopt, by the end of 2013, a national plan or strategy for rare diseases.

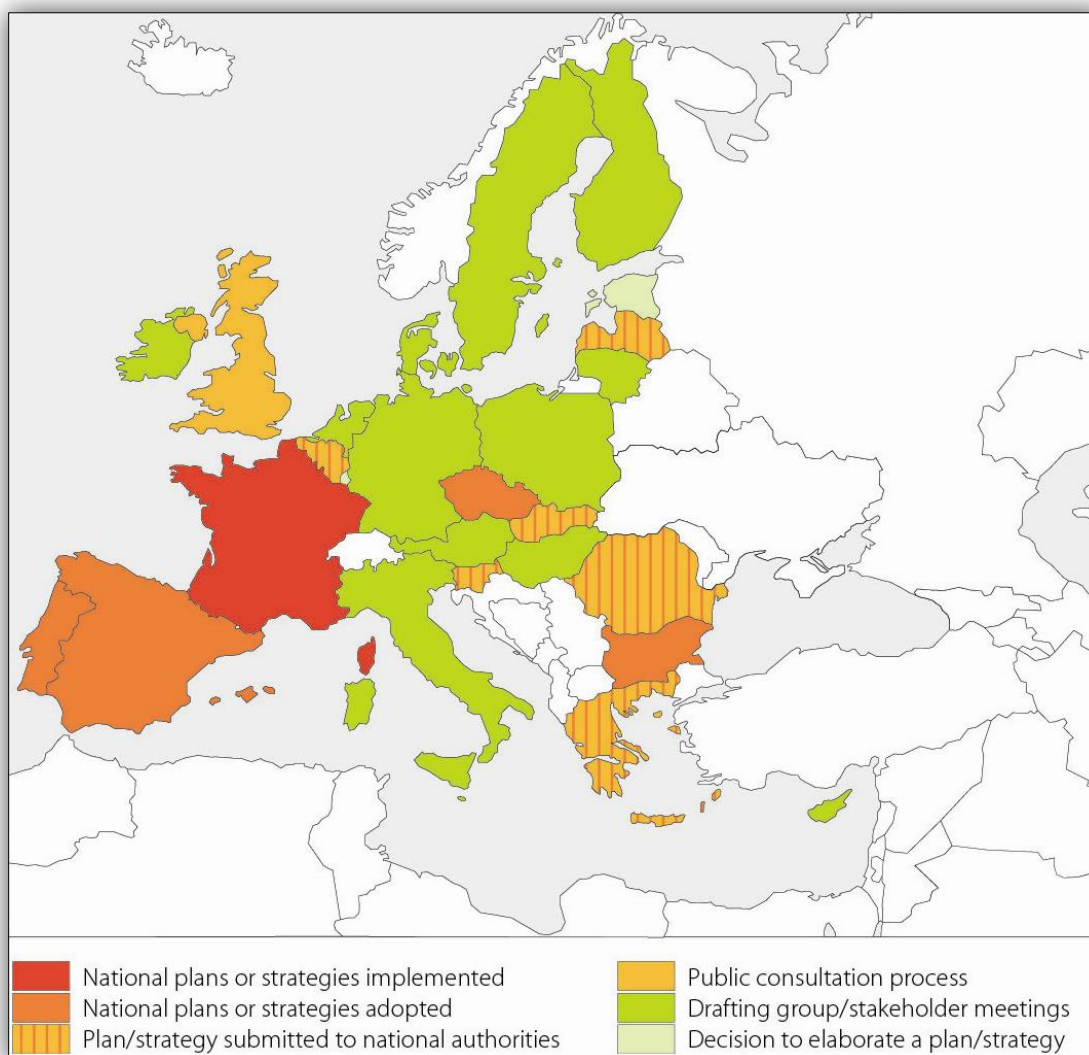


Figure 2a: Current stages of development of national plans or strategies for rare diseases in EU MS (in December 2011)<sup>63</sup>

<sup>63</sup> Graphic courtesy of the EUCERD Scientific Secretariat.



Figure 2b: Current stages of development of national plans or strategies for rare diseases in EU MS (in December 2011)<sup>64</sup>

Five Member States had, by the end of 2011, officially adopted a national plan/strategy for rare diseases (France, Portugal, Bulgaria, Spain and the Czech Republic).

These plans/strategies vary in their scope and also their financing, which will ultimately influence the extent of their impact at national level. The Czech Republic and Portugal<sup>65</sup> have not yet implemented their national plans/strategies. Bulgaria and Spain have partially implemented their plans/strategies. Only France has fully implemented their national plan for rare diseases.

#### a) France

France was the first EU country to adopt, at the end of 2004, a comprehensive rare disease plan<sup>66</sup> with allocated funding. This first plan (2005-2008) 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 rare diseases and develop support for patient organisations;
- Promote research and innovation on rare diseases, in particular on treatments;
- Develop national and European partnerships in the domain of rare diseases.

The second French National Plan for Rare Diseases<sup>67</sup> was elaborated by the Ministry of Health during 2009-2010 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,

<sup>64</sup> Graphic courtesy of the EUCERD Scientific Secretariat.

<sup>65</sup> Although some of the aspects of planned measures are underway (see Part V of this report for further detail).

<sup>66</sup> [http://www.orpha.net/actor/EuropaNews/2006/doc/French\\_National\\_Plan.pdf](http://www.orpha.net/actor/EuropaNews/2006/doc/French_National_Plan.pdf)

<sup>67</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)

researchers, patient 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.

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 French Reference Centres;
- Improvement of access to biological and 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 to 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 (called the “*Fondation Maladies Rares*”<sup>68</sup>);
- Creation of a National Rare Disease Database (called “*Banque Nationale de Données Maladies Rares*” or BNDMR) to allow mapping of patients’ needs and healthcare delivered, and facilitate their recruitment for clinical trials;
- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature;
- Organisation of 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 molecular diagnosis for a large set of rare diseases. Various levels of NGS will be developed during the plan for maximal diagnosis coverage;
- Restructuring of rare disease Reference and Competence Centres into a limited number (around twenty) of coherent “clinical networks” (called “*filières maladies rares*”), gathering all rare disease relevant stakeholders and centered on a homogeneous group of diseases. These networks aim to allow a better and easier orientation of patients towards appropriate diagnosis, treatment, social care and follow-up. These future French clinical networks should be connected to the future European networks for rare diseases.

The additional actions foreseen in the plan to improve the quality of care are:

- Setting up of a permanent working group for the monitoring of rare disease Reference Centres and future reference networks;
- Measures to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed out of their marketing authorisation;
- Enhancement of clinical practice guideline development;
- Training of medical doctors and paramedical professionals;
- Coordination of health care and social care.

The implementation of the second plan is the mission of a dedicated Steering Committee (called the “*Comité de suivi et de prospective*”) which held its first meeting on 19 May 2011. Five thematic working groups reporting to the Steering Committee were established to help implementing the plan. These include a permanent group dedicated to the monitoring of Reference Centres and their future networks. The Steering Committee is in charge of the follow up of the plan and making sure that the implementation of the plan is on schedule, of the effective involvement of relevant bodies and institutes in the implementation, and of surveying new methods of diagnosis, prevention, treatment and care for patients with rare diseases.

In addition to this, the evaluation of this second plan will soon be considered, and before the end of 2013 a third plan will be discussed to extend this work.

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<sup>68</sup> The “Fondation Maladies Rares” was created in February 2012: <http://fondation-maladiesrares.org>

## b) Portugal

On 12 November, 2008, the Portuguese Minister of Health approved a national plan for rare diseases for Portugal, the “*Programa Nacional de Doenças Raras*”<sup>69</sup>.

The two main objectives of the National Plan are:

- 1) to create and improve the national measures in order to satisfy the needs of people with rare diseases and their families in regards to medical services and care;
- 2) to improve the quality and the equity of the health care measures provided to people with RD.

These objectives will be achieved by:

- The creation of reference centres for rare diseases;
- Improving the access of people with rare diseases to adequate care;
- Improving the knowledge on rare diseases;
- Promoting innovations in the treatment of rare diseases and accessibility of orphan medicinal products;
- Assuring cooperation at national and international level, including the countries in the EU and the community of countries with Portuguese as their official language.

The specifics of the plan include in total 30 intervention strategies, 9 education and training strategies, and 8 strategies for data collection and information analysis. The plan also details 15 actions for evaluation. The Minister has chosen a coordinator and a national commission to oversee and put into action the various elements of the plan. The Directorate General of Health, together with the Office of the High Commissioner for Health, have co-funded, a total amount of €1.9 million, during the years of 2008 to 2011, a few projects on rare diseases, which are currently being developed by several patient associations, which enabled the implementation of a number of strategies mentioned in the National Plan.

## c) Bulgaria

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)<sup>70</sup>. The Bulgarian National Plan for Rare Diseases started on 1 January 2009 and will last for 5 years. Bulgaria’s National Plan for Rare Diseases is currently active and 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 has been established by the Ministry of Health, and meets once a month to supervise the progress and implementation of the plan: the Council includes medical professionals, Ministry representatives and a representative of the National Alliance of People with Rare Diseases. Although the estimated budget of the Plan is €11.3 million, the assigned funds are much less and are disproportionally distributed (i.e. directed towards genetic testing activities). The estimated budget does not take into account the costs for the provision of clinical services for rare disease patients.

<sup>69</sup> [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/portugal.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/portugal.pdf)

<sup>70</sup> <http://www.raredis.org/pub/events/NPRD.pdf> (Unofficial translation)

#### d) Spain

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>71</sup>. It is set within the framework of the Quality Plan of the Spanish National Health System (NHS) which includes, amongst its other objectives, improving care for people with rare diseases and their families. 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 was elaborated by the consensus of the regional health authorities, scientific societies and patient organisations.

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. In addition it covers their historical development and epidemiological situation. Finally, it sets out the strategy development methodology. The second part, 'Development of strategic lines', sets out the objectives and recommendations.

The Spanish Strategy for Rare Diseases of NHS includes the following strategic lines:

1. Information on RD (specific information on the disease and on the available care resources);
2. Prevention and early detection of RD;
3. Health care (coordination among health care different levels);
4. Therapies: orphan medicinal products, adjuvant drugs and medical devices, advanced therapies and rehabilitation;
5. Social and health care;
6. Research;
7. Education and training.

Given the decentralised health administration of Spain in Autonomous Communities, 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. 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 Ministry of Health, Social Services and Equality uses the *Funds for the Implementation of Health Strategies* in particular: these funds are used by the Autonomous Communities to implement the Rare Diseases Strategy of the Spanish National Health System. The Strategy was evaluated in 2011 and the results are now to be analysed. This assessment will focus mainly on the implementation of the Strategy over the first two years, although it is too soon to measure quality of life this process could help to update recommendations and objectives.

#### e) Czech Republic

In October 2010, the Czech Republic released for the first time a ten-year strategy<sup>72</sup> (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 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 has created dedicated working parties with the aim to establish the basis for the National Action Plan by 2013.

<sup>71</sup> <http://www.msc.es/organizacion/sns/planCalidadSNS/docs/enfermedadesRaras.pdf> and <http://www.msc.es/organizacion/sns/planCalidadSNS/docs/RareDiseases.pdf>

<sup>72</sup> [http://nestor.orpha.net/EUCERD/upload/file/Docs/CZPlan\\_en.pdf](http://nestor.orpha.net/EUCERD/upload/file/Docs/CZPlan_en.pdf)

The stage of the elaboration of national plans/strategies for rare diseases in the other Member States was varied at the end of 2011, however all Member States have declared their intention to elaborate such a policy<sup>73</sup>.

In the following countries a decision has been taken to elaborate national plan/strategy, often as a result of an active request by stakeholders for the establishment of a plan: Estonia and Luxembourg.

Drafting group meetings/stakeholder meetings to discuss the elaboration of a national plan/strategy have taken place/are taking place in: Austria, Cyprus, Denmark, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Malta, the Netherlands, Poland and Sweden.

A public consultation process is underway in the United Kingdom.

A plan/strategy has been submitted to national authorities in: Belgium, Greece, Latvia, Romania, Slovenia, and Slovakia.

### 1.3. Political framework in other world regions

Outside of the European region, a number of countries have developed political frameworks in the field of rare diseases. Mostly, these initiatives concern the regulation of orphan medicinal products<sup>74</sup>. Policies for orphan medicinal products started as early as 1983 in the United States with the adoption of the Orphan Drug Act, then in Japan and in Australia in 1993 and 1997. Europe followed in 1999 by implementing a common EU policy on orphan medicinal products. In addition, the European Council Recommendation on an action in the field of rare diseases and the successful completion of the first French National Plan for Rare Diseases – considered a model by other countries – is inspiring other countries around the world to reflect on the elaboration of national plans/strategies for rare diseases. Below, a few examples of existing political frameworks in the field of rare diseases are presented in other world regions outside of Europe.

#### a) North America

##### i. USA

The Office of Rare Diseases<sup>75</sup> (ORD) was established in 1993 within the Office of the Director of the National Institutes of Health (NIH). On November 6, 2002, the President established the Office in statute (Public Law 107-280, the Rare Diseases Act of 2002). The Rare Diseases Act<sup>76</sup> defines a rare disease as having a prevalence of fewer than 200 000 affected individuals in the United States. It also establishes the mandate of the ORD, which includes the promotion of cooperation between the National Institutes of Health to advance research in the field of rare diseases as well as to support cooperation with the regional centres of excellence for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases.

The Rare Diseases Act also takes note of the success of the 1983 US “Orphan Drug Act<sup>77</sup>”: this law defines the 'orphan drug' with regard to prevalence (frequency) of the disease for which it is indicated in the American population. In the US, the concept of 'orphan drug' does not simply cover pharmaceutical or biological products. It also covers medical devices and dietary or diet products. The OOPD<sup>78</sup> (Office of Orphan Products Development) within the FDA (Food and Drug Administration) is in charge of promoting the availability of safe and efficacious products for the treatment of rare diseases in the US. The 'orphan' status allows the drug sponsor to benefit from incentives for the development of these products until the marketing approval. The measures apply to all stages of the drug development and include:

<sup>73</sup> See Part V of this report for detailed information.

<sup>74</sup> Information provided by Orphanet [http://www.orpha.net/consor/cgi-bin/Education\\_AboutOrphanDrugs.php?lng=EN](http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN)

<sup>75</sup> <http://rarediseases.info.nih.gov/>

<sup>76</sup> <http://history.nih.gov/research/downloads/PL107-280.pdf>

<sup>77</sup> <http://history.nih.gov/research/downloads/PL97-414.pdf>

<sup>78</sup> <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

- Tax credits on clinical research;
- Technical assistance during the elaboration of the application file necessary for marketing approval as well as simplification of administrative procedures (reduction of the waiting period and reduction of the amount of registration fees);
- Marketing exclusivity of 7 years after the marketing approval is granted.

In 2011 two new acts were introduced on behalf of rare disease patients in the USA. On 27 July 2011, the H.R.2671: CAL Undiagnosed Diseases Research and Collaboration Network Act of 2011<sup>79</sup> was introduced in the House of Representatives to amend the existing Public Health Service Act in order to provide for the establishment and maintenance of an undiagnosed diseases network, and for other purposes. The bill has been referred to the House Committee on Energy and Commerce. Also on 27 July 2011 the H.R. 2672: Preserving Access to Orphan Drugs Act of 2011<sup>80</sup> was also introduced in the US House of Representatives. Seeking to “clarify the orphan drug exception to the annual fee on branded prescription pharmaceutical manufacturers and importers,” this motion has been referred to the House Energy and Commerce and the House Ways and Means Committees for consideration.

In addition, a proposed legislative measure is gathering force in the USA seeks to promote low prevalence rare diseases, which the bill promoters assert garner less attention from potential drug developers. The Ultra-orphan Life Saving Treatment Act of 2012 (ULTRA Act) would cover 83% of all rare diseases, according to a fact sheet<sup>81</sup>. Citing a disease prevalence of 6000 or less (in the USA) the ULTRA Act would tweak the regulatory system, facilitating an accelerated approval system from the FDA for very low prevalence diseases. According to the fact sheet, the ULTRA Act would provide the FDA “...with the tools necessary to allow for alternative qualification criteria for the rarest diseases that could never have prior clinical data”.

## ii. Canada

In October 2011, the Health Minister of Quebec announced that rare diseases would indeed be “adopted” by Quebec’s health system. A specific committee dedicated to rare diseases will be created at Quebec’s Institut National d’Excellence en Santé et Services Sociaux. This Institution published in Summer 2011 a French language report<sup>82</sup> on the experiences of countries having developed policies for rare diseases.

As of 19 January 2011, the province of Ontario will expand its compassionate review policy to allow more patients with “rare clinical circumstances” to benefit. The Ontario Public Drug Programs “...will consider covering drugs that have been reviewed by the Committee to Evaluate Drugs (CED) and where Ontario is in funding negotiations with the manufacturer. Previously, applicants could not be approved for coverage in cases where the CED had made a recommendation, but the ministry was still in negotiations with the manufacturer”. The expanded policy covers “requests to cover drugs in cases where an individual has been urgently hospitalized due to an immediate life, limb or organ-threatening condition and the requested drug therapy is directly related to the condition that resulted in the hospitalization”.

## b) South America

### i. Argentina

Both the Senate and the House representatives of the Argentinean Parliament endorsed the first national law<sup>83</sup> concerning rare diseases on 29 June 2011. Based on proposals elaborated by representatives, the main topics of the act include the definition of a rare disease (Argentina is adopting the same prevalence of no more than 1 person in 2 000 that is used in the European Union). Furthermore, the health system must now provide specific assistance to patients and their care-givers. In addition, public and private social security schemes are obliged to provide specific support. A central multidisciplinary committee is to be created in order to coordinate these actions and will include patient organisations. A national registry of patients will be elaborated, a neonatal screening programme will be considered, along with educational, social and support activities that

<sup>79</sup> <http://thomas.loc.gov/cgi-bin/query/z?c112:H.R.2671>:

<sup>80</sup> <http://www.govtrack.us/congress/billtext.xpd?bill=h112-2672>

<sup>81</sup> <http://www.kakkis.org/blogs/post/2011/11/29/Ultra-orphan-Life-saving-Treatments-Act-of-2012.aspx>

<sup>82</sup> [http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/OrganisationsSoins/ETMIS2011\\_Vol7\\_No6.pdf](http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/OrganisationsSoins/ETMIS2011_Vol7_No6.pdf)

<sup>83</sup> <http://www.orpha.net/actor/EuropaNews/2011/doc/ArgentinaLaw.pdf>

are all mentioned in the law. All of these activities need governance and different levels of government must be coordinated before the effects of this dramatic development can be felt, but stakeholders believe that a significant first step has been taken.

The Geiser Foundation (Grupo de Enlace, Investigación y Soporte - Enfermedades Raras), a regional initiative created in 2001 to pool rare disease resources, started campaigning in 2002 for specific measures compelling care and protection for rare disease patients and their families, as well as resources for professionals. Geiser also promotes and encourages other countries to take action, such as Chile, Uruguay, Brazil, Panama and Mexico, where rare diseases laws are also being elaborated.

## ii. Peru

Peru established its first national law concerning patients with rare diseases in Summer 2011. Law 29698<sup>84</sup> promotes treatments for rare conditions and includes a national strategy encompassing diagnostics, surveillance, prevention, care, and rehabilitation. While Peru has not developed a precise definition based on prevalence, this legislation, a result of efforts from Geiser, Peruvian rare disease patient groups, and policymaker Michael Urtecho, is also considered a big step forward for rare disease patients in Peru.

## iii. Columbia

An Orphan Disease Law was ratified in July 2010. On 3 March 2011, the Second National Forum of Orphan Diseases in the Health System of Colombia was held.

## c) Asia

### i. Japan

Japan bears the distinction of having the oldest programme for rare disease research and care in the world. Established in 1972, the Medical Care Program for Specific Diseases encompasses “Nanbyo” (Intractable Diseases) and the closely-related “Tokutei Shikkan” (Specified Rare and Intractable Diseases)<sup>85</sup>. Japan’s Nanbyo programme includes any troubling, untreated disorder, though the vast majority of conditions it accepts – determined by a consultative committee - are rare. While historically infectious diseases such as cholera or tuberculosis were considered Nanbyo, today the intractable diseases are defined as those “...that have resulted from an unidentifiable cause and, without a clearly established treatment, have a considerably high risk of disability” and “...that chronically develop and require a significant amount of labor for the patient’s care, causing a heavy burden on other family members of the patient, both financially and mentally”. Requests for inclusion can come from medical professionals as well as the patient organisations. Diseases taken up under the programme receive funding for research and allow patients full health coverage. Currently, of the 130 disease groups covered under the Nanbyo programme for clinical research, 56 diseases in the Tokutei Shikkan programme receive specific subsidies from public funding. Some 650 000 patients benefit from medical expense support in Japan.

On 1 October 1993, the Japanese government revised the pharmaceutical law by introducing special provisions relative to research and development of orphan drugs. According to these new provisions, orphan drug status can be granted to a drug, provided it fulfils the following two criteria:

- The disease for which use of the drug is claimed must be incurable. There must be no possible alternative treatment; or the efficacy and expected safety of the drug must be excellent in comparison with other available drugs.
- The number of patients affected by this disease in Japan must be less than 50 000 on the Japanese territory, which corresponds to a maximal incidence of four per ten thousand.

Since 1 July 2011 there is a pharmaceuticals affairs consultation on R&D strategy for products originating from Japan.

### ii. Singapore

In Singapore, the Orphan Drugs Policy is based upon a Medicine Order ('Orphan drugs Exemption'). The legislation, which came into force at the end of 1991, gave a definition of orphan

<sup>84</sup> <http://www.orpha.net/actor/EuropaNews/2011/doc/PeruLaw.pdf>

<sup>85</sup> <http://www.nanbyou.or.jp/english/index.htm>



drugs and of the legal framework for imports into Singapore. A rare disease is defined in Singapore as a life threatening and severely debilitating illness. An orphan drug is a medicinal product which has been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute for the treatment of a rare disease. The product should not hold a previous product licence under the Medicine Act and should be approved by the competent Health Authorities either from the country of origin or from any other country where the orphan drug has been used. Orphan drugs importers must maintain proper records, including:

- The quantity imported or supplied;
- The date of reception or supply;
- The name and address of the person for whom the orphan drug is provided.

In addition, any other drug imported shall be kept in a hospital and be under the charge and control of a 'custodian' who must be a physician, dentist or pharmacist appointed by the hospital. Any doctor or dentist who requires an orphan drug for the treatment of their patient suffering from a rare disease may request the custodian to provide them with the drug. So far, there have been no other incentives, such as marketing exclusivity or subsidies in the orphan drug policy.

### iii. Taiwan<sup>86</sup>

In Taiwan the Rare Diseases and Orphan Drugs Act was adopted in 2000<sup>87</sup>. This act comprised 36 articles, detailing resources from the prevention to the treatment of rare diseases. The articles covered: the acquisition of orphan drugs, R&D, manufacturing orphan drugs, diagnosis and treatment of rare diseases, prevention acknowledgement of rare diseases, cooperation with international rare disease organisations, and the subsidised supply of specific pharmaceuticals and special nutrients. Rare diseases are defined in Taiwan as having a prevalence of less than 1 person in 10 000, being difficultly treatable and genetic in origin.

In Taiwan, to be recognised officially as having a rare disease, patients can apply through their doctors or medical institutions by presenting a rare disorders report sheet (including suspected cases), abstract of the disease and related medical essays to the Bureau of Health Promotion, Department of Health, Executive Yuan to proceed with the application. Patients that have been acknowledged officially as having rare diseases can apply for reimbursement for the medical expenses occurred in local medical centre, or regional teaching hospitals. Expenses include diagnosis, treatment, drugs, and special nutritional supplements. The reimbursement cap is 70% of actual expenses but families that qualify for low-income status can receive reimbursements up to 100% for drugs and nutritional supplements for the patient.

### iv. Korea<sup>88</sup>

Although there is currently no rare disease/orphan medicinal product legislation in place in Korea, nor a national plan or strategy for rare diseases, a number of actions have been initiated by the Ministry of Health and Welfare. This includes the establishment of a non-profit organisation Orphan Drug Centre in 1999, supported by the Korean Food and Drug Administration (KFDA), which supplies medications for rare diseases. The KFDA has also defined, in an official notice, rare diseases as diseases affecting less than 20 000 persons in Korea without appropriate treatment and substitution treatment modalities. The Ministry of Health has also established a Genetic and Rare Disease Centre in 2004 which deals with the subsidies for medical expenses related to rare diseases, organises national reference centres (established in 2006) and research in the field of genetic and rare diseases. The Rare Disease Centre also acts as an information centre, and from 2006 provides a help line<sup>89</sup> service for patients: the centre has produced information on 818 diseases which is regularly updated. In 2008, a research grant for rare diseases was launched by the Ministry of Health for the period 1 April 2008 to 31 March 2012, to fund basic research and a

<sup>86</sup> Information from:

[http://www.tfrd.org.tw/english/laws/cont.php?kind\\_id=25&top1=What%20we%20do&top2=Public%20Policy%20Issues&top3=Rare%20Disease%20and%20Orphan%20Drug%20Act](http://www.tfrd.org.tw/english/laws/cont.php?kind_id=25&top1=What%20we%20do&top2=Public%20Policy%20Issues&top3=Rare%20Disease%20and%20Orphan%20Drug%20Act) (accessed 21 June 2011)

<sup>87</sup> [http://www.tfrd.org.tw/english/laws/upload/20080328098114\\_01.html](http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html)

<sup>88</sup> Source: 2009 ICORD conference, Soo Kyung Koo of the Genetic and Rare Diseases Centre of the Korea National Institute of Health: [http://www.google.com/url?sa=t&source=web&cd=3&ved=0CCOQfjAC&url=http%3A%2F%2Fficord.se%2Fdocuments%2Fficord\\_2009%2Fpresentations%2FKoo.ppt&rct=i&q=korea%20rare%20diseases%20center&ei=8m8ATngNla2hAefp4S8DQ&usg=AFQjCNEQ6r3z5e0UuYx3KBHv839W3MSgpw&sig2=LRZURh40JbNM8yLdaQT\\_Ig&cad=rja](http://www.google.com/url?sa=t&source=web&cd=3&ved=0CCOQfjAC&url=http%3A%2F%2Fficord.se%2Fdocuments%2Fficord_2009%2Fpresentations%2FKoo.ppt&rct=i&q=korea%20rare%20diseases%20center&ei=8m8ATngNla2hAefp4S8DQ&usg=AFQjCNEQ6r3z5e0UuYx3KBHv839W3MSgpw&sig2=LRZURh40JbNM8yLdaQT_Ig&cad=rja)

<sup>89</sup> <http://helpline.cdc.go.kr/cdchelp/index.gst>

clinical research network with around 5.5 million USD. There is also a Korean Mutation Database in place with data from 4 major laboratories, and a database of clinical trials in general.

**v. China**

In China, a definition of rare diseases was proposed by a group of medical experts on 17 May 2010. This definition is of 1 person in 10 000 covering genetic diseases in infants. An initial list of 23 rare diseases has been proposed.

**d) Australasia**

**i. Australia**

An Australian orphan drugs policy was established in 1997. This orphan drugs programme aims to ensure the availability of a greater range of treatments for rare diseases and allows the Australian Therapeutic Goods Administration (TGA) to use information from the US Food and Drug Administration (FDA) Orphan Drugs Program as part of the Australian evaluation process. The Australian Orphan Drugs Program helps manufacturers to overcome the high cost of marketing drugs which have proved to be commercially not viable because of small patient population. Orphan designation is intended for drugs which aim to treat diseases with a prevalence of 2000 patients/subjects or less in the Australian population (around 18 million inhabitants). Another alternative criterion which leads to orphan designation consists in combining the fact that the drug is not commercially viable, when used in the patient population it is indicated for, and an acceptable rationale for the drug and its indication.

The main characteristics of the orphan drug policy in Australia are:

- A legal framework for orphan drug designation ;
- Waiver of application and evaluation and no annual registration fees ;
- A five-year exclusivity period (under consideration by the Australian jurisdiction).

Australia is also taking the first steps towards a national strategy for rare diseases. In 2010, a draft of a proposal for a national strategy was opened for consultation on the website of the Australian Paediatric Surveillance Unit. The proposal serves as a platform and a framework from which to develop strategies for implementing elements identified by a National Rare Diseases Working Group that are gathered into eight central principles:

- Raise awareness of the burden of rare diseases on patients, families, health professionals and the community;
- Provide educational resources and networking opportunities for health professionals to allow them to better identify and manage rare diseases;
- Improve health care for people with rare diseases through access to diagnostic tests, new drugs and other treatments, improved primary care and specialised services;
- Promote research on rare diseases through advocacy for targeted research funds and development of national and international multidisciplinary research partnerships;
- Increase knowledge of the epidemiology and impact of rare diseases in Australia through research;
- Develop and disseminate information to educate patients, parents, carers and the general public, about rare diseases that is relevant in the Australian context;
- Develop an umbrella organisation to support people affected by any rare disease by linking existing organisations to facilitate the co-ordinated development of integrated peer support networks, contact among families and contact among rare diseases interest groups;
- Advocate to government in partnership with families, for people affected by rare diseases.

A rare disease symposium, entitled *Awakening Australia to Rare Diseases: Global perspectives*, was hosted by Western Australia on 18-20 April 2011. Building on the work initiated by the Australian Paediatric Surveillance Unit and the National Rare Disease Taskforce, the symposium was an important step in the process of developing a rare disease strategy in Australia. Decisions taken included an endorsement to develop a National Plan, an agreement to form a single overarching advocacy group for rare diseases in Australia, an agreement on the need for national rare disease registries, and an agreement on the need to explore how service delivery could be improved.

## 2. Expert services in Europe

### 2.1. Centres of expertise in Member States

DG Health and Consumers established the High Level Group (HLG) on Health Services and Medical Care as a means of taking forward the recommendations made in the reflection process on patient mobility. One of the working groups of this High Level Group, in collaboration with the EC Rare Diseases Task Force (RDTF), focused on reference networks of centres of expertise for rare diseases. In the context of this working group, a number of criteria for national centres of expertise for rare diseases were defined in 2006<sup>90</sup> based on the experience of countries with designation processes already in place.

Based on this work, the EUCERD elaborated a set of recommendations which were adopted on 24 October 2011 as the first EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States<sup>91</sup>. The homogeneity of quality criteria for centres of expertise in Member States will be a key concept and concern in the context of the future implementation of the EU Cross-Border Healthcare Directive<sup>92</sup>, in which rare diseases are specifically mentioned.

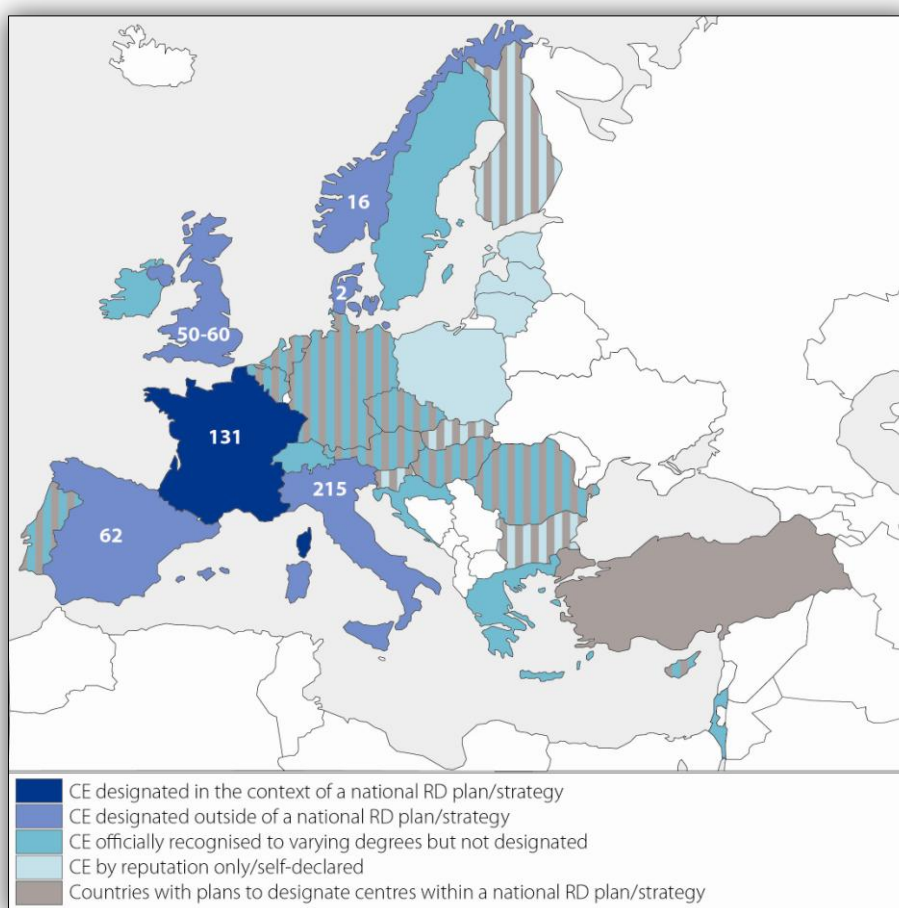


Figure 3: State of the art of centres of expertise at national level in Europe and number of designated centres where they exist (December 2011)

<sup>90</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

<sup>91</sup> <http://www.eucerd.eu/upload/file/EUCERDRecommendationCE.pdf>

<sup>92</sup> <http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf>

Only France has designated centres of expertise for rare diseases in the context of a national plan/strategy for rare diseases.

A few countries currently have officially designated centres of expertise for rare diseases (i.e. selected and financed by health authorities) outside of a national plan/strategy for rare diseases: Denmark, Norway, Spain and the United Kingdom<sup>93</sup>. Italy has regionally designated centres of expertise for rare diseases. It should be highlighted that the designation criteria vary from country to country, even if these criteria are often in line with the recommendations of the EUCERD.

A number of countries have non-designated centres of expertise for rare diseases which are acknowledged by authorities to varying degrees: Austria, Belgium, Croatia, Czech Republic, Cyprus, Germany, Greece, Hungary, Ireland, Israel, the Netherlands, Portugal, Romania, Sweden and Switzerland<sup>94</sup>.

A number of countries have centres of expertise for rare diseases which are recognised by reputation only, sometimes self-declared as centres of expertise: Bulgaria, Estonia, Finland, Latvia, Lithuania, Poland, Slovak Republic and Slovenia.

A number of European countries plan to elaborate designation procedures for centres of expertise for rare diseases in the future, mostly within the scope of a future national plan/strategy for rare diseases: Austria, Belgium, Bulgaria, Czech Republic, Cyprus, Finland, Germany, Hungary, the Netherlands, Portugal, Romania, Slovak Republic, Slovenia and Turkey.

In conclusion, the area of centres of expertise for rare diseases in Member States is heterogenous in terms of the process to designate these centres.

## 2.2. European Reference Networks (ERNs)

As aforementioned, the work of the HLG and RDTF included the development of a number of criteria for centres of expertise, to be applied to centres participating in European Reference Networks. This working group also developed some principles regarding European Reference Networks (ERNs) for rare diseases. The main concept is that the expertise, rather than the patients, should travel, although patients should also be able to travel to the centres if they need to.

A number of pilot ERNs for rare diseases have been awarded financing for a three-year duration by the European Commission in the context of the Community action programme on rare diseases, including genetic diseases (1999-2007) and the Second Programme of Community Action in the Field of Health (2008-2013): Dyscerne (European network of centres of expertise for dysmorphology), ECORN-CF (European centres of reference network for cystic fibrosis), Paediatric Hodgkin Lymphoma Network (Europe-wide organisation of quality controlled treatment), NEUROPED (European network of reference for rare paediatric neurological diseases), EUOHISTIONET (A reference network for Langerhans cell histiocytosis and associated syndrome in EU), TAG (Together Against Genodermatoses – improving healthcare and social support for patients and families affected by severe genodermatoses), PAAIR (Patients' Association and Alpha-1 International Registry Network), EPNET (European Porphyria Network - providing better healthcare for patients and their families), EN-RBD (European Network of Rare Bleeding Disorders) and CARE-NMD (Dissemination and Implementation of the Standards of Care for Duchenne Muscular Dystrophy in Europe project), ENERCA (European network for rare and congenital anaemia – Stage 3).

The EUCERD Scientific Secretariat carried out a *Preliminary Analysis of the Outcomes and Experiences of pilot European Reference Networks for Rare Diseases*<sup>95</sup> in late 2010 which was presented and discussed at

<sup>93</sup> Further details concerning the designation processes in these countries can be found in the relevant country section in this report.

<sup>94</sup> These countries also often have self-declared centres of expertise/centres with a reputation for expertise.

<sup>95</sup> <http://www.eucerd.eu/upload/file/Reports/2011ERNAnalysis.pdf>

a EUCERD workshop on 8-9 December 2010. The report has since been approved by the EUCERD, and yields a number of initial conclusions.

This document will contribute to the reflection on criteria for ERNs for rare diseases of the Cross-Border Healthcare Expert Group. Their work will be carried out in the context of the implementation of the European Cross-Border Health Care Directive, in which ERNs for rare diseases are explicitly mentioned in Article 12<sup>96</sup>: *“The Commission shall support Member States in the development of European reference networks between healthcare providers and centres of expertise in the Member States, in particular in the area of rare diseases.”* The same article of the Directive states that European reference networks shall have at least three of the following objectives:

- a) to help realise the potential of European cooperation regarding highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and health technologies;
- b) to contribute to the pooling of knowledge regarding sickness prevention; to facilitate improvements in diagnosis and the delivery of high-quality, accessible and cost-effective healthcare for all patients with a medical condition requiring a particular concentration of expertise in medical domains where expertise is rare;
- c) to maximise the cost-effective use of resources by concentrating them where appropriate;
- d) to reinforce research, epidemiological surveillance like registries and provide training for health professionals;
- e) to facilitate mobility of expertise, virtually or physically, and to develop, share and spread information, knowledge and best practice and to foster developments of the diagnosis and treatment of rare diseases, within and outside the networks;
- f) to encourage the development of quality and safety benchmarks and to help develop and spread best practice within and outside the network;
- g) to help Member States with an insufficient number of patients with a particular medical condition or lacking technology or expertise to provide highly specialised services of high quality.

To prepare these acts, the Commission will carry out appropriate consultations and has thus set up the aforementioned Cross-Border Healthcare Expert Group which will assist the Commission on this task. In the case of the implementing acts the Commission will be assisted by the Committee on Cross-Border Healthcare composed of Member States representatives created on the 21 June 2011.

The EUCERD plans to elaborate recommendations on European Reference Networks for rare diseases in 2012.

### 2.3. Expert clinical laboratories

Expert clinical laboratories and diagnostic tests are part of quality healthcare in the field of rare diseases. Major progress in gene identification has been translated into diagnostic tests. These tests are now offered internationally, through both public and private sector genetic testing services. Physicians prescribing these tests and biologists receiving the samples need to know which tests are available, where they are performed and whether identified laboratories meet quality standards. To fulfill this need, Orphanet<sup>97</sup> set up a database of medical laboratories in the field of rare diseases in 1997. Data was collected in 1 country in 1997, 15 in 2003, 26 in 2006 and in 36 countries in 2011, with resources from the DG Public Health. In collaboration with the EuroGentest<sup>98</sup> Network of Excellence (financed by DG Research and Innovation), information on quality management has been added to the Orphanet database over the past five years. Information on genetic testing in Orphanet can be searched by disease name or by gene (symbol or name in English) as well as by laboratory or by professional. The information provided on laboratories includes data on quality management. Information is freely accessible online and access to all data can be granted upon request.

<sup>96</sup> <http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf>

<sup>97</sup> [www.orpha.net](http://www.orpha.net)

<sup>98</sup> <http://www.eurogentest.org/>

In 2011<sup>99</sup>, 1 056 laboratories offering tests for 1 811 genes were registered in Orphanet. According to an analysis of Orphanet data in September 2011<sup>100</sup>, the test offer differs greatly from one large country to another (Figure 4): Germany (1 449 genes), France (1 129 genes), Spain (1 081 genes), the Netherlands (760 genes), Italy (793 genes), United Kingdom (541 genes).

The test offer in medium and small-sized countries now ranges from 1 to 355 genes<sup>101</sup>. This situation explains the large cross-border flow of specimens, highlighting the need to provide access to services in other countries when necessary, especially for very rare diseases. According to available data, only testing for Cystic fibrosis is provided by every country.

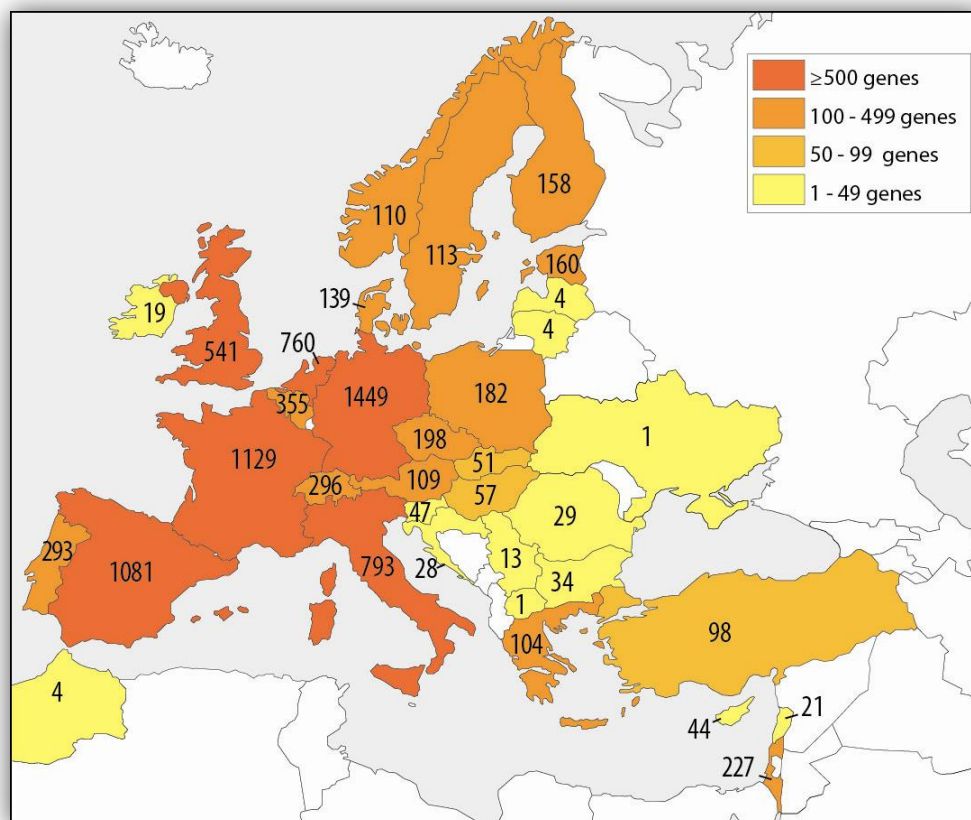


Figure 4: Number of genes tested in laboratories located in each country (Orphanet data extraction, September 2011)

An analysis of Orphanet database<sup>102</sup> shows that 641 rare diseases are tested in laboratories located in one country only in Europe (30% of diseases for which there is a test for the gene), and 1 931 rare diseases are tested in 10 or less countries in Europe, with 1 547 rare diseases tested in 5 or less countries in Europe.

<sup>99</sup> Figure from Orphanet data, September 2011

<sup>100</sup> Figures from Orphanet data, September 2011.

<sup>101</sup> Figure from Orphanet data, September 2011.

<sup>102</sup> Data extracted from Orphanet database in September 2011.

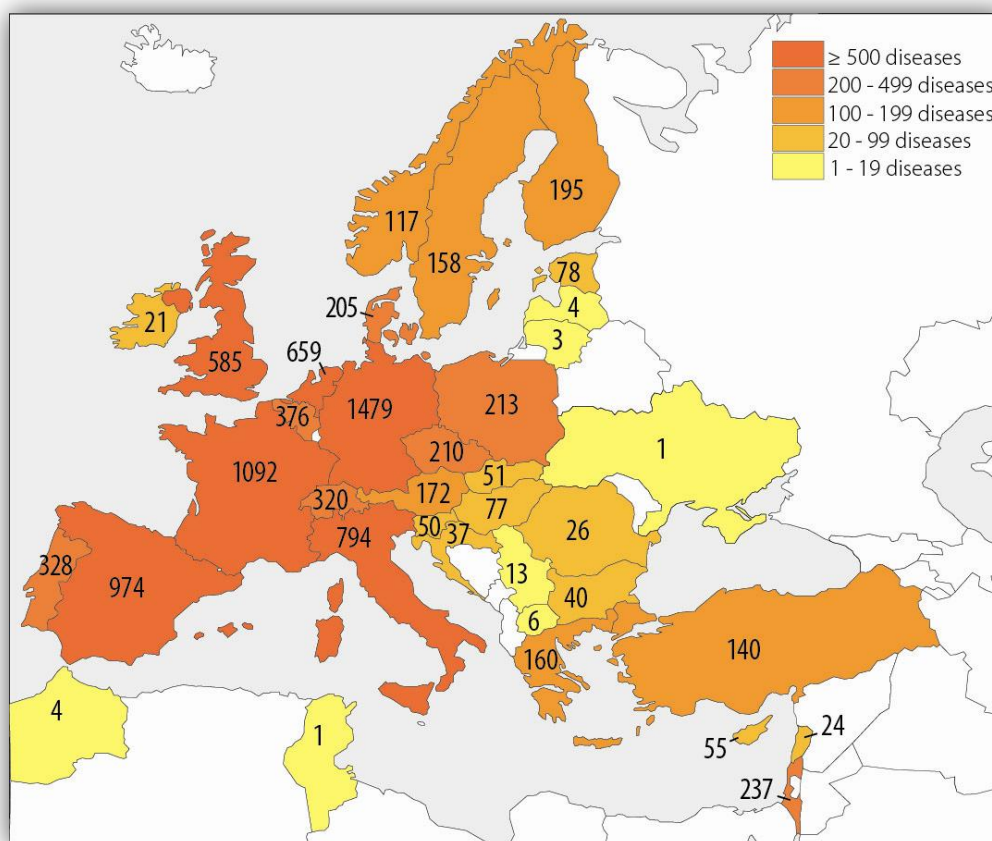


Figure 5: Number of rare diseases tested in laboratories located in each country (Orphanet data extraction, September 2011)

The situation described above reflects the low prevalence of these diseases. As this situation is unlikely to change in the coming years, there is a need for coordination at European level, and for the provision of cross-border services, especially in the case of very rare diseases.

Indeed, there is a need for coordination at International level, outside of Europe. A comparison of the Orphanet (covering Europe) and Genetests<sup>103</sup> (covering the USA) data in September 2011 shows that 584 genes are only tested in Europe, out of the total offer of 1 812 genes tested in Europe, whereas 71 genes are only tested in USA, out of the total offer of 1 299 genes tested in the USA. A total of 1 228 genes are tested both in Europe and USA, with a total of 1 883 genes able to be tested in EU and/or the USA.

### 3. Research and development

There is a great need for research into rare diseases as, so far, most patients' medical needs are not being met. It is considered as an area requiring specific initiatives to attract interest from researchers and from Industry. It is also an area where experts are very rare. Indeed, in terms of academic research in the field of rare diseases there is less interest for clinical studies, fewer funding opportunities, and a disadvantage for researchers at evaluation due to the presumed low societal impact. In terms of industry research, rare diseases represent a small, niche market, and there is a recent shift towards leaving basic research to academic teams. Thus rarity has a real impact on research and R&D, which can meet a range of bottlenecks: a lack of necessary collaborative efforts, limited access to platforms, the need for an alternative design for clinical trials and a

<sup>103</sup> <http://www.ncbi.nlm.nih.gov/sites/GeneTests/query>

limited number of patients for clinical research, as well as the problems posed by the additional difficulties met due to innovative approaches.

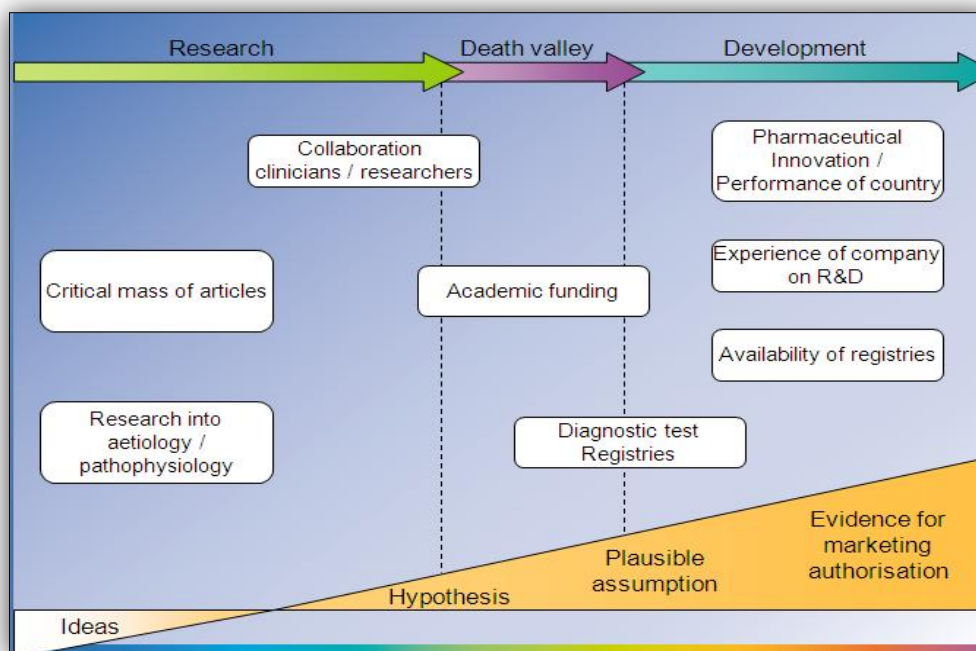


Figure 6: Schema representing the bottlenecks between research and development of therapies for rare diseases<sup>104</sup>.

The field of rare diseases, however, provides a range of opportunities to drive forward research and R&D in general (section 3.1.) Indeed, the R&D landscape in the field of rare diseases is highly contrasted. Rare diseases were instrumental in establishing the Human Genome mapping during the 1990s, then again in cloning genes, as most rare diseases are Mendelian disorders. Even today, high impact journals continue publishing articles on new genes identified by exome sequencing, mostly related to RD. Therefore it can be said that rare diseases are not orphan when it comes to identifying the underlining genetic mechanism, as it is still of high interest for the biomedical research community to dissect genetic mechanisms. This translates in an improvement in the testing possibilities for many rare diseases.

In contrast, the natural history of rare diseases is very often poorly understood, due to the rarity of patients which is an obstacle to collecting enough data to conduct a proper study, due to the high phenotypic heterogeneity of RD and the lack of scientific interest for this stage in research. It is difficult to use medical records data to conduct clinical studies as RD are invisible in health information systems due to the lack of specific codes in the International Classification of Diseases (ICD10) (see section 3.3.). For a few rare diseases only, a systematic collection of clinical data is taking place, at regional, national, European or global level. This situation is an obstacle to the development of therapies and to the establishment of good clinical practice guidelines.

The field of rare diseases can also help drive forward research and R&D in general as rare diseases are models for common diseases. Most rare diseases result from a dysfunction of a single pathway due to a defective gene: understanding the impact of a single defect may therefore yield insights into the more complex pathways involved in common diseases which are generally multifactorial. Therefore, stimulating rare diseases research can lead to scientific breakthroughs applicable to common conditions.

<sup>104</sup> Graphic courtesy of Ségolène Aymé.

Death valley – This part of the research and development process is the ‘translation gap’ where there is no obvious funding body. This is the grey zone between basic research which is supported by academic funding and development which is supported by Industry funding : it is a moment when it is too early for Industry to invest, and too early for the acquisition of knowledge.

Performance of a country – Performance of a country measured by indicators of innovation performance as described in H.E. Heemstra et al, Drug Discovery Today, 2008 Aug;13(15-16):670-6. Epub 2008 Jun 24.



This has translated into the involvement of the pharmaceutical and of the biotechnology Industry in developing new treatments where there are unmet needs. Both innovative therapies (gene and cell therapy, enzyme-replacement therapy, exon-skipping approach) and classical ones with small molecules prove to be efficient in treating rare diseases.

Research in the field of rare diseases is also one of the main priorities of the Council Recommendation (8 June 2009). This text recommends the following actions to Member States:

- Identify ongoing research and research resources in the national and Community frameworks in order to establish the state of the art, assess the research landscape in the area of rare diseases, and improve the coordination of Community, national and regional programmes for rare diseases research.
- Identify needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them, and promote interdisciplinary co-operative approaches to be complementarily addressed through national and Community programmes.
- Foster the participation of national researchers in research projects on rare diseases funded at all appropriate levels, including the Community level.
- Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.
- Facilitate, together with the Commission, the development of research cooperation with third countries active in research on rare diseases and more generally with regard to the exchange of information and the sharing of expertise.

### **Report on Rare Disease Research, Its Determinants in Europe and the Way Forward**

The RareDiseasePlatform project<sup>105</sup> (RDPlatform), a three-year (2008-2011) support action project of the European Union's Seventh Framework Programme (HEALTH-F2-2008-201230), has produced an inventory of publicly funded research projects in the field of RD and orphan medicinal products, accessible through the research tab of the Orphanet website<sup>106</sup>. The RDPlatform project analysed the data collected by Orphanet and carried out a review of the relevant literature, to establish a state of the art of the research activities in the field of rare diseases in order to propose areas for action in the future. The report published as a result, "*Report on Rare Disease Research, Its Determinants in Europe and the Way Forward*<sup>107</sup>", was published in January 2011. This report sheds light on where research and development (R&D) in the field of rare diseases has been - and where it needs to go next. The report presents a compilation of data gathered within the RDPlatform project. As such it offers readers an inventory of publicly-funded research initiatives on the national and international levels in the field of rare diseases and orphan medicinal products. The data, accessible on pan-European rare disease and orphan drug informational portal Orphanet, encompasses ongoing research projects, clinical trials, and registries. Other areas covered in the report include testing, therapeutic development, and R&D determinants (such as prevalence and medical area). The rare disease ontologies, data repositories and bioinformatic tools are given special emphasis in the report.

## **3.1. Research funding**

### **3.1.1. At Member State level**

#### **a) National rare disease research programmes**

Very few countries have specific funding programmes for research in the field of rare diseases. Amongst the countries which have established (both on-going or finished) specific rare disease funding programmes/calls are: France, Germany, Hungary, Italy, the Netherlands, Portugal, Spain and Switzerland. Many other countries fund rare disease projects through generalised research funding programmes.

<sup>105</sup> <http://www.rdplatform.org/>

<sup>106</sup> <http://www.orpha.net>

<sup>107</sup> [http://asso.orpha.net/RDPlatform/upload/file/RDPlatform\\_final\\_report.pdf](http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf)

A few countries (such as France, Germany, Italy, the Netherlands and Spain) also have, or have had, specific initiatives and incentives in place to boost R&D in the field of orphan medicinal products and other innovative therapies at national level.

“Telethon” initiatives provide/have provided funding for rare diseases projects in countries such as Cyprus, France, Italy, Luxembourg, Spain and Switzerland. In many other countries disease-specific charities raise funds for research.

**b) E-Rare: European coordinated rare disease research programmes**

E-Rare is an FP6, and now FP7, funded ERA-Net programme for research on rare diseases<sup>108</sup>. ERA-Nets aim to step up the cooperation and coordination of research activities carried out at national or regional level in the Member States and Associated States through the networking of research activities conducted at national or regional level, and the mutual opening of national and regional research programmes. The scheme aims to help develop a European Research Area by improving the coherence and coordination across Europe of such research programmes. The scheme will also enable national systems to take on tasks collectively that they would not have been able to tackle independently. Both networking and mutual opening require a progressive approach. The ERA-Net scheme therefore has a long term perspective that must also allow for the different way that research is organised in different Member States and Associated States.

The E-Rare project now has 16 partners from 12 countries: Austria, Belgium, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and Turkey. Poland is an observer in E-Rare 2.

The first E-Rare project launched two Joint Transnational Calls in the first phase of the project (2006-2010). The aim of the first call was to enable scientists in different countries to build an effective collaboration on a common research project based on complementarities and sharing of expertise. Six E-Rare partnering countries joined the first call in 2007 (France, Germany, Italy, Israel, Spain and Turkey). These National Institutions funded multilateral transnational research projects on rare diseases. The partners of E-Rare, ERA-Network for research programmes on rare diseases, launched the second joint transnational call (JTC) at the end of 2008/beginning of 2009. The ten countries that joined the 2<sup>nd</sup> Transnational Call are France, Germany, Israel, Spain, Turkey, the Netherlands, Portugal, Italy, Austria and Greece: 4 additional funding organisations from 4 Member States joined the 2<sup>nd</sup> JTC. The financial input of each partner research funding agency/ministry has allowed for the funding for 16 transnational research consortia with 75 participating research teams from 10 countries for a total research budget of €9.6 million. A list of funded projects is available<sup>109</sup>.

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<sup>108</sup> <http://www.e-rare.eu/>

<sup>109</sup> <http://www.e-rare.eu/content/funded-projects-joint-transnational-call-2009>

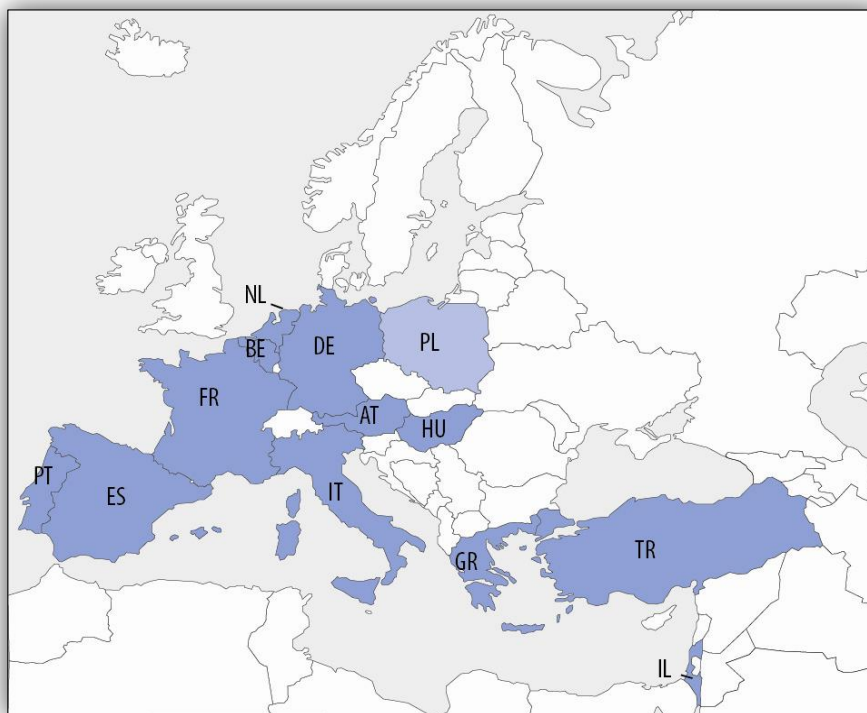


Figure 7: Countries with national research agencies participating in the E-Rare (2) ERANET for rare diseases

The new E-Rare project (E-Rare-2) (2010-2014) aims at deepening and extending the cooperation established by the first project. At the end of 2010 E-Rare-2 launched its third Joint Transnational Call for proposals with closed at the end of January 2011. Research groups from nine countries (Austria, Belgium, France, Germany, Greece, Israel, Italy, Spain and Turkey) were eligible to participate in this call that seeks to promote transnational research collaboration on rare diseases.

Transnational research proposals must have covered at least one of the following areas:

1. Definition of new nosological entities, epidemiological studies, genotype/phenotype correlations, natural history of diseases
2. Characterisation of the genetic/molecular basis of specific diseases
3. Pathophysiological and genetic studies of rare diseases
4. Diagnostic and therapeutic research (interventional clinical trials are excluded).

Following the evaluation process, 13 consortia with foreseen budget of about €9 million were selected for funding. The funded projects cover a wide range of rare diseases including hematologic, metabolic, neurologic and dermatologic diseases as well as congenital malformations while addressing potential therapeutic options using state-of-the-art techniques like pluripotent stem cells, gene therapy vectors and customised animal models. A list of funded project is available<sup>110</sup>.

In late 2011 E-Rare launched its 4<sup>th</sup> Joint Transnational Call issued a call entitled “European Research Projects on Rare Diseases driven by Young Investigators”<sup>111</sup>. The aim is to provide to young, independent investigators the opportunity of building transnational collaborations in the field of rare disease research. The transnational project should be based on complementarities and sharing of expertise, demonstrating a clear added value of the cooperation and impact of the expected results on patients affected by rare diseases. Eligible under this call will be young investigators who have been awarded their first PhD/MD or equivalent of doctoral degree since at least 2, and up to 10, years.

E-Rare issued its very first newsletter<sup>112</sup> and made over its website in 2011.

<sup>110</sup> <http://www.e-rare.eu/content/funded-projects-joint-transnational-call-2011>

<sup>111</sup> <http://www.e-rare.eu/content/joint-call-european-research-projects-rare-diseases-driven-young-investigators-jtc-2012>

<sup>112</sup> <http://www.e-rare.eu/newsletter/subscriptions>

### 3.1.2. At European level (European Commission Directorate General Research and Innovation)

At European level, research on rare diseases is being addressed as one of the priority areas in the health field under the EU Framework Programmes for Research and Technological Development (FP) since the early 1990s.

During the Fifth Framework Programme for Research (FP5: 1998-2002) the thematic programme “Improving the quality of life and management of living resources” included, amongst other topics, fundamental and clinical research in the field of rare diseases. Support was provided for multinational research into rare diseases, applying advances in modern technology to diagnosis, treatment, prevention and surveillance through epidemiology. Forty seven projects were funded for about €64 million in total.

Under the subsequent Sixth Framework Programme for Research (FP6: 2002–2006), one of the seven thematic areas supported projects focusing on “Life sciences, genomics and biotechnology for health”. This thematic area stimulated and sustained multidisciplinary research to exploit the full potential of genome information to underpin applications to human health. In the field of applications, the emphasis was on research aimed at bringing basic knowledge through to the application stage (translational approach), to allow real, consistent and coordinated medical progress at European level and to improve the quality of life. This thematic area was twofold, one of the aspects being the fight against major diseases, including rare diseases. FP6 saw a significant increase in the funding for rare disease projects: around €230 million for a total of 59 projects, also including an ERA-Net project (E-Rare). Overall this allowed for the mobilisation of researchers to tackle the fragmentation of research and the production of new knowledge, but also a better coordination of research at EU level, and the fostering of dialogue with all stakeholders, including patients.

The Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7, 2007-2013<sup>113</sup>). Rare disease research specifically features under the heading of the Health theme, one of ten themes proposed under the specific programme on “Cooperation”. This specific programme is designed to gain or strengthen leadership in key scientific and technological areas by supporting trans-national cooperation between universities, industry, research centres, public authorities and stakeholders across the European Union and the rest of the world. The European Commission has already published several calls for proposals covering research on rare diseases in various thematic areas of FP7. For the period 2007–2011, 66 research projects with an EU contribution of over €325 million are being supported. They will ultimately lead to better diagnostic methods, new treatments, better care and prevention strategies for rare diseases. Of these, 17 projects are specifically devoted to support research on the natural history and the pathophysiology of rare diseases (for a total of €71 million), and 8 projects cover the preclinical and clinical development of orphan medicinal products (for a total of €36 million). The “Cooperation” 2010 work programme of the Health Theme<sup>114</sup> also called for an ERA-Net on rare diseases (E-Rare-2<sup>115</sup>, see section 3.1.1).

The European Commission released on 20 July 2011 the content of a new call for proposals<sup>116</sup> which opened several opportunities for rare diseases in the HEALTH theme of the work programme for 2012. The indicative budget for the rare disease activities is €108 million.

A full list of projects concerning rare diseases supported by the Framework Programmes is available in the Orphanet Report Series (European collaborative research projects funded by DG Research and Innovation and by E-Rare in the field of rare diseases and European clinical networks funded by DG Health and Consumers and contributing to clinical research in the field of rare diseases)<sup>117</sup>. The list

<sup>113</sup> [http://cordis.europa.eu/fp7/home\\_en.html](http://cordis.europa.eu/fp7/home_en.html)

<sup>114</sup> [ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/health/a\\_wp\\_201001\\_en.pdf](ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/health/a_wp_201001_en.pdf)

<sup>115</sup> <http://www.e-rare.eu/>

<sup>116</sup> [http://ec.europa.eu/research/participants/portal/page/cooperation;efp7\\_SESSION\\_ID=QJMWPGCQHMZgQwqLihGhQY2XH6RRrITxDH4hWkvQBz3NBsYrW!1086760178?callIdentifier=FP7-HEALTH-2012-INNOVATION-1](http://ec.europa.eu/research/participants/portal/page/cooperation;efp7_SESSION_ID=QJMWPGCQHMZgQwqLihGhQY2XH6RRrITxDH4hWkvQBz3NBsYrW!1086760178?callIdentifier=FP7-HEALTH-2012-INNOVATION-1)

<sup>117</sup> “European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases & European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases”, Orphanet Report Series, Rare Diseases Collection, November 2010 <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

contains projects that have been funded thanks to specific calls on rare diseases and also projects on rare diseases that have been funded through non-specific calls.

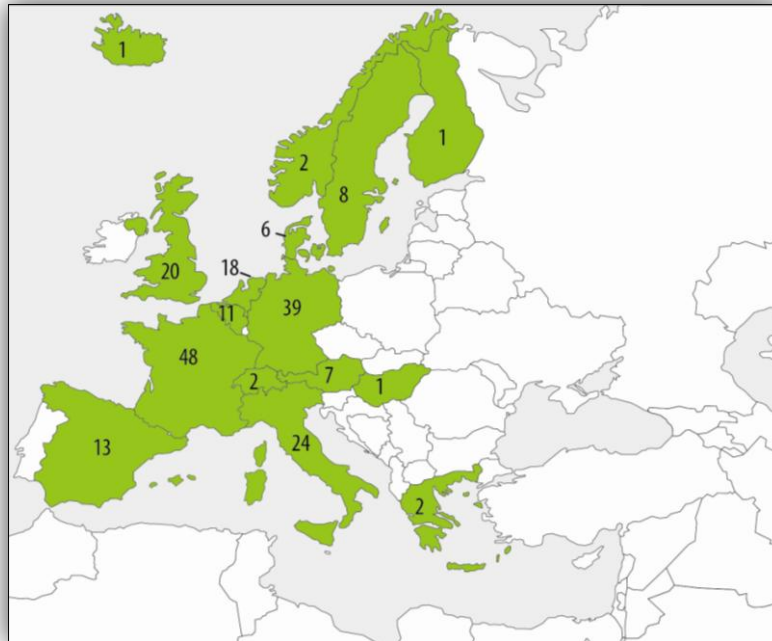


Figure 8: Number of FP5, FP6 and FP7 rare disease related projects in which research groups in European countries have participated as leading partner (December 2011)<sup>118</sup>

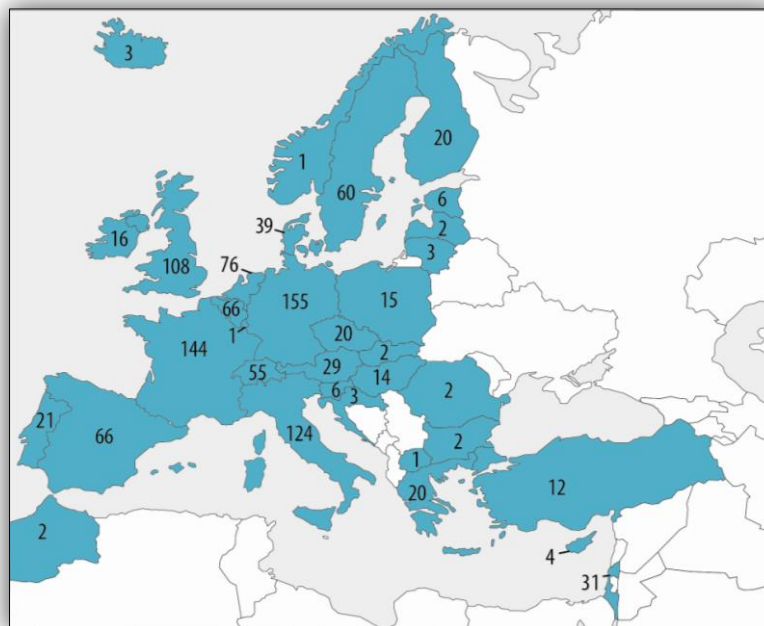


Figure 9: Number of FP5, FP6 and FP7 rare disease related projects in which research groups in European countries have participated (December 2011)<sup>119</sup>

<sup>118</sup> Based on information presented in « European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases & European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases », Orphanet Report Series, Rare Diseases Collection, November 2010 <http://www.orpha.net/orpha.com/cahiers/docs/GB/Networks.pdf> updated with results of the E-Rare 2 3<sup>rd</sup> Transnational Call.

<sup>119</sup> Based on information presented in « European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases & European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases », Orphanet Report Series, Rare Diseases collection, November 2010 updated with results of the E-Rare 2 3<sup>rd</sup> Transnational Call. <http://www.orpha.net/orpha.com/cahiers/docs/GB/Networks.pdf>

### 3.1.3. At International level – The International Rare Diseases Research Consortium (IRDiRC)

Maximising scarce resources and coordinating research efforts are key elements for success in the rare diseases field. Worldwide sharing of information, data and samples to boost research is currently hampered by the absence of an exhaustive rare disease classification, standard terms of reference and common ontologies, as well as harmonised regulatory requirements.

The International Rare Disease Research Consortium (IRDiRC<sup>120</sup>) was launched in April 2011 to foster international collaboration in rare diseases research. The European Commission and the US National Institutes of Health initiated the discussions, and other stakeholders, including other funding agencies, were also invited to join the consortium. In October 2011 there was a meeting to identify principal research topics and regulatory challenges in this international context, as well as to establish the governance of the consortium.

IRDiRC will team up researchers and funding agencies in order to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and diagnostic tools for most rare diseases.

A number of great challenges will need to be addressed through collaborative actions to reach these 2020 goals:

- establish and provide access to harmonised data and samples,
- perform the molecular and clinical characterisation of rare diseases,
- boost translational, preclinical and clinical research,
- streamline ethical and regulatory procedures.

This collaboration will also require harmonisation of policies related to research use, standardisation, and dissemination. A policy agenda is currently in development.

The IRDiRC will be governed by an Executive Committee, three Scientific Committees and a number of working groups. The Executive Committee involves representatives of funding members and three patients' organisations, namely EURORDIS, NORD and the US Genetic Alliance. There will be three Scientific Committees, one each for Diagnostics (including sequencing and characterisation), Therapies (including pre-clinical and clinical development) and Interdisciplinary aspects of rare diseases research (including ontologies, natural history, biobanking, registries etc). The Scientific Committees will advise the Executive Committee on research priorities and progress made from a scientific viewpoint. The first members of the Scientific Committees were appointed on 29 February 2012<sup>121</sup>.

The IRDiRC Working Groups will be composed of representatives of all projects funded within the scope of IRDiRC. They will cooperate to ensure synergies between all research projects within the scientific area of the working group, by exchanging results, expertise, experiences and information.

The funding agencies now committed<sup>122</sup> to the IRDiRC are from the following countries: Australia, Canada, Italy, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States, in addition to the European Commission.

The EC announced its commitment to supporting the logistical organisation of IRDiRC activities through a dedicated support action topic in the FP7-HEALTH-INNOVATION<sup>123</sup> call for proposals (Work Programme 2012).

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<sup>120</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html)

<sup>121</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/governance\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/governance_en.html)

<sup>122</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members_en.html)

<sup>123</sup> <http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-1> and <http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-2>

### 3.2. Disease registries

Patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrollment of patients.

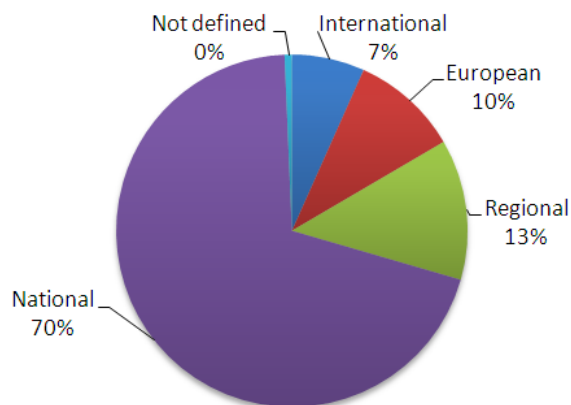


Figure 10: Geographical coverage of rare disease registries registered in the Orphanet database (May 2012)

According to the data in the Orphanet database<sup>124</sup>, there are 597 disease registries in Europe (59 European, 40 International, 417 national, 77 regional, 4 undefined).

Almost all of these registries concern diseases or groups of diseases for which there is an innovative treatment either in development or already on the market. This is not surprising as registries of patients treated with orphan medicinal products are particularly relevant: they allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing.

Most of the registries are established in academic institutions. A minority of them are managed by pharmaceutical or biotech companies, with others being run by patient organisations.

### 3.3. State of the art of the coding and classification of rare diseases

The International Classification of Diseases (ICD) is used worldwide and by a wide range of stakeholders. Most rare diseases are absent in ICD10 and those with a specific code are often misclassified. As a consequence, morbidity and mortality due to rare diseases is invisible in health information systems. To overcome this difficulty, Orphanet has established a partnership with WHO to ensure a fair representation of rare diseases in general. In order to prepare the proposal, Orphanet has collected all published expert classifications and established a database of phenotypes indexed with ICD10 codes, MIM codes, genes, mode of inheritance, age of onset and class of prevalence. Phenotypes are assigned to as many classification systems as necessary to represent them. The visualisation of the classification systems and of the place of each disease within the classification is available on the Orphanet website. This work is currently supported by the Joint Action EUCERD: Working for Rare Diseases (N° 2011 22 01). The Orphanet nomenclature of rare diseases is a stable one, directly exploitable by information systems and available on request. It will soon be released as an open-source service.

<sup>124</sup> Data extracted from Orphanet, 15 May 2012

A Topic Advisory Group on rare diseases has been established to manage the revision process at WHO. The whole community of experts is involved in the validation process. Revised chapters follow a primarily clinical approach, only secondarily an aetiological one, up to the gene level. When several names are possible for a disease, descriptive names formed in accordance with a clinical approach are preferred. Every entity is assigned a unique identification number. Rare diseases affecting several body systems are included in every relevant chapter, as ICD11 will be poly-axial, but a main code is proposed to allow for linearisation, according to the most severe involvement and/or the specialist most likely to be relied on for the management of the disease. In some cases, the choice is open to debate. The rare disease community is invited to take an active part as the results will condition the visibility of all activities in the field. The ICD-11 draft is open for comments and available at <http://apps.who.int/classifications/icd11/browse/f/en>.

In addition to this effort to update ICD, the Orphanet inventory of diseases is cross-referenced with other nomenclatures, namely SnoMed-CT and MeSH, through a collaboration with the University of Manchester. The list of rare diseases, the classifications and the cross-referencing with other terminologies is available on [www.orphadata.org](http://www.orphadata.org).

## 4. Orphan medicinal products and other therapies for rare diseases

The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000)<sup>125</sup> was adopted in December 1999 and came into force in the European Union in 2000. The Regulation addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides incentives for products receiving an orphan designation (e.g. protocol assistance, market exclusivity, centralised procedure). The incentives contained in the legislation aim to assist sponsors receiving orphan medicinal product designations in the development of medicinal products with the ultimate goal of providing medicinal products for rare diseases to patients.

Since 2000, there is a Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). The Commission adopts decisions on designation based on an opinion from the COMP. The COMP is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products.

### 4.1. Orphan designated products at European level

Since its implementation, the Regulation on Orphan Medicinal Products has yielded more than 1 005 positive opinions for orphan product designation, adopted from 1 449 applications reviewed since 2000. To date, the distribution of the prevalence of conditions for which the designations have been adopted shows that the most frequently designated conditions have been those that affect between 1 and 3 in 10 000 patients, that is between approximately 50 000 and 150 000 people (receiving 52% of all orphan designations). Indeed, 37% of the orphan medicinal products having obtained market authorisation in the EU, are for the treatment of diseases affecting less than 1 in 10 000 patients (approximately 50 000 persons).

<sup>125</sup> This section reproduces information from [http://ec.europa.eu/health/rare\\_diseases/orphan\\_drugs/strategy/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/orphan_drugs/strategy/index_en.htm)



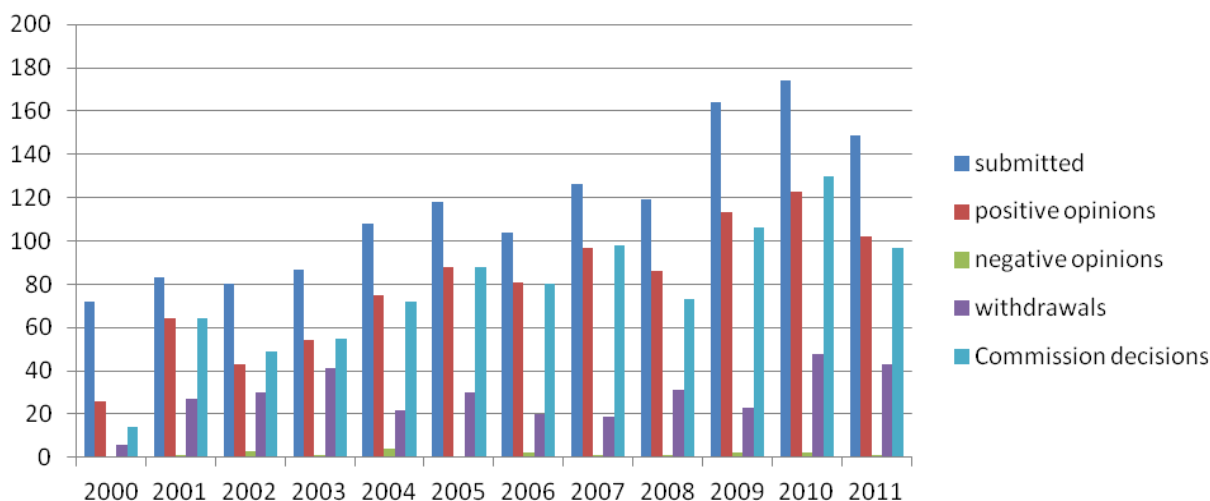


Figure 11 : Status of orphan designation applications<sup>126</sup>

The number of applications has increased steadily each year during the first decade of the Regulation with 166 applications received in 2011. Sixty-eight designated products had received marketing authorisation by the end of 2011<sup>127</sup>, of which oncology is by far the most common therapeutic area (35%). Interestingly, the average time span between designation and authorisation is only 2.8 years, indicating that designated products were at an advanced developmental stage.

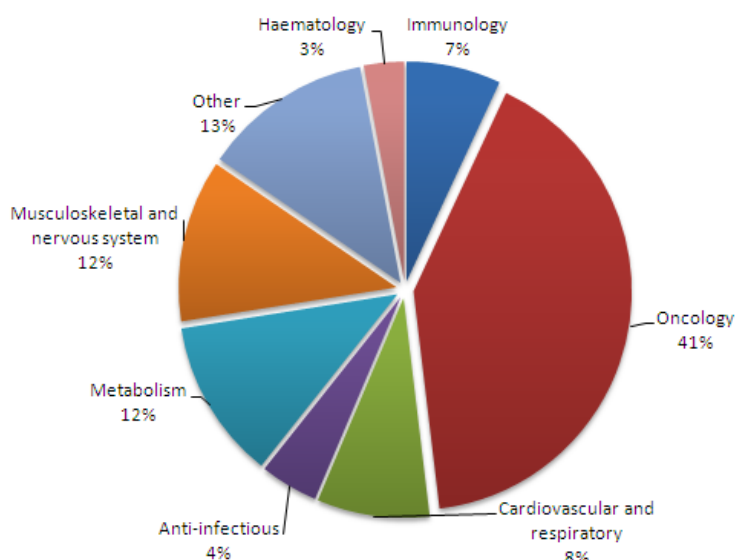


Figure 12: Distribution of orphan designation positive opinions by therapeutic area<sup>128</sup>

In 2011 alone, the COMP adopted 111 positive opinions on orphan designations. Over eighty diseases are covered by these designations. The European Commission then granted 107 of these orphan designations in 2011. Five orphan medicinal product products received marketing authorisation in 2011. This information can be accessed via the European Community Register of Medicinal Products<sup>129</sup>.

The COMP has also granted orphan medicinal product designations to various innovative product types (i.e. fusion proteins, monoclonal antibodies, cell and gene therapy products, tissue-engineered products, oligonucleotides): at the end of 2011, the COMP has given more than 70 positive opinions for advanced therapy products out of a total of 1 005 positive opinions for orphan medicinal product designation.

<sup>126</sup> Courtesy of the European Medicines Agency, 16 December 2011

<sup>127</sup> This figure is for initial applications. Variations are not included.

<sup>128</sup> Courtesy of the European Medicines Agency, 16 December 2011

<sup>129</sup> [http://ec.europa.eu/health/documents/community-register/html/index\\_en.htm](http://ec.europa.eu/health/documents/community-register/html/index_en.htm)

The Orphan Medicinal Product Regulation has thus, via its incentives, resulted in the development and marketing of medicinal products for rare diseases which would perhaps not have been developed or marketed without such an initiative.

## 4.2. Availability of orphan medicinal products at Member State level

Charting which products are available, in which countries and at what price is a difficult task and stakeholders from many different strands of the rare disease community lament the lack of transparency in this area. To begin with, one must define what is meant by “available”.

The information provided at Member State level in this report aims to describe as explicitly as possible what “availability” means when data has been obtained by national sources concerning the drugs “available” at national level (i.e. that it is registered at national level and/or marketed at national level, etc). In some cases national sources have provided additional information concerning the list of reimbursed orphan medicinal products, and in these cases this is explicitly stated.

“Availability” is the term generally used to describe when an orphan medicinal product has obtained marketing authorisation through a centralised procedure, and has been launched/marketed by the company with the marketing authorisation in a given country. It is important to highlight that if an orphan medicinal product has obtained marketing authorisation, this does not necessarily mean that it is launched (i.e. marketed or commercialised) immediately by the market authorisation holder in all Member States.

“Accessibility” is a different concept: for a drug to be “accessible” it has to be “available” according to the aforementioned definition, and available to the patient without unacceptable financial and administrative hurdles, i.e. through general out-patient reimbursement systems (for example, inclusion of the orphan medicinal product in the country’s positive list(s), national formulary or in the general reimbursement scheme), or through an in-patient system (for example, in a centre of expertise, or inclusion, of the medicine in a hospital formulary/positive list). In some instances, derogatory reimbursement procedures can be used to obtain access to orphan medicinal products. It is also possible in some Member States for orphan medicinal products without market authorisation to be accessed via one or more of the following initiatives: a compassionate use procedure (in the case of drugs which have applied for market authorisation or which are undergoing a clinical studies), an off-label use procedure (in the case of the prescription of an already authorised medicine for an un approved indication, dose, mode of administration, age group), or on a named-patient basis (in the case of a drug without market authorisation, when a doctor or centre of expertise requests supply of a drug directly from a manufacturer for a specific patient under their direct responsibility).

In addition, the Working Group “Mechanism of coordinated access to orphan medicinal products (MoCA OMP)”, one of the groups of the Platform on Access to Medicines in Europe (part of the ongoing Process of Corporate Social Responsibility initiated by Commissioner Tajani) has developed a definition of “coordinated real life access”. The term “coordinated real life access” refers to when:

- The product is available on the EU market:
  - through receiving EMA marketing authorisation (in exceptional cases products without marketing authorisation can be dispensed, e.g. via compassionate use);
  - by launch of the product in one or several Member State;
- The product is affordable (e.g. funded through public funds) with no unacceptable financial or administrative hurdles for the patient;
- The product is (physically) reachable for the patient, e.g. through the most accessible/appropriate healthcare provider, specific hospital or national/regional centre of expertise.

Early dialogue between stakeholders and Member States can contribute to this goal of improving coordinated real life access.

As part of the European Medicine Information Network (EMINet) project, a report was published in 2011 on an *Initial Investigation to Assess the Feasibility of a Coordinated System to Access Orphan Medicines*<sup>130</sup>. This new report, commissioned by the European Commission DG Enterprise and Industry, presents a country-by-country survey of accessibility to orphan medicines, with an emphasis on product distribution through Centres of Expertise and derogatory procedures for accessing products in situations of restricted availability (typically Compassionate Use-type programmes). Taking Pompe disease and pulmonary arterial hypertension as examples, the EMINet report surveys both the availability of treatments across Europe and the distribution of centres of expertise for the diseases. The EMINet findings, combined with the results of the Ernst & Young CAVOD tender report, which focuses on developing a coordinated approach to providing orphan medicinal product information to all Member States prior to price negotiation in order to streamline health technology assessment and facilitate pricing decisions, contribute to the debate on efficient and equitable distribution of orphan medicinal products. Both reports seek to further the understanding of product access and availability for rare disease treatments across Europe. This feeds in to the reflection on a coordinated system for accessing orphan medicinal products.

## 5. Patient organisations

According to the Council Recommendation (8 June 2009), the WHO has defined the empowerment of patients as a “pre-requisite for health” and encourages a “proactive partnership and patient self-care strategy to improve health outcomes and quality of life among the chronically ill”<sup>131</sup>. In this sense, the role of independent patient groups is crucial both in terms of direct support to individuals living with the disease and in terms of the collective work they carry out to improve conditions for the community of rare disease patients as a whole and for the next generations. The Council also recommends that Member States “consult patients and patients’ representatives on the policies in the field of rare diseases and facilitate patient access to updated information on rare diseases” as well as “promote the activities performed by patient organisations, such as awareness-raising, capacity-building and training, exchange of information and best practices, networking and outreach to very isolated patients”.

### 5.1. EURORDIS

EURORDIS<sup>132</sup> is an international, non-governmental, non-profit, patient-driven alliance of patient organisations and individuals active in the field of rare diseases, dedicated to improving the quality of life of all people living with rare diseases in Europe. It was founded in 1997; it is supported by its members and by the French Muscular Dystrophy Association (AFM), the European Commission, corporate foundations and the health industry. EURORDIS represents more than 500 rare disease organisations in 48 countries (of which 24 are EU Member States), covering more than 4 000 different rare diseases. It is therefore the voice of the 30 million patients affected by rare diseases throughout Europe.

EURORDIS’ principal missions are to build a strong pan-European community of patient organisations and people living with rare diseases, and to be their voice at the European level and - directly or indirectly - fight against the impact of rare diseases on their lives. EURORDIS aims at improving the quality of life of people living with rare diseases in Europe through advocacy at the European level, support for research and drug development, networking patient groups, raising awareness and other actions designed to fight against the impact of rare diseases on the lives of patients and families.

EURORDIS is actively involved in the work carried out by the European Medicines Agency (EMA) and the European Commission in the field of health research and healthcare. EURORDIS has 10 representatives on EMA scientific committees and Working Party: the Committee for Orphan Medicinal Products (COMP), the

<sup>130</sup> [http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access\\_orphans\\_initialinvest\\_052011\\_en.pdf](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access_orphans_initialinvest_052011_en.pdf)

<sup>131</sup> <http://www.euro.who.int/Document/E88086.pdf>

<sup>132</sup> [www.EURORDIS.org](http://www.EURORDIS.org)

Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO), the Patients’ and Consumers’ Working Party (PCWP). It has also 4 representatives and their alternates on the EUCERD.

## 5.2. National alliances of rare disease patient organisations

National alliances of rare disease patient organisations are important structures for this key group of stakeholders at Member State level, serving to provide patients with a common voice and the presence needed to have an impact on national policy. Indeed, many of these national alliances have played (or are playing) key roles in elaborating the national plans or strategies for rare diseases already in place. Many also have a place on official committees treating issues directly related to the needs of rare disease patients.

An increasing number of National Alliances of rare disease patient organisations have been created in Europe. The Member States where National Alliances have been established include: Austria, Belgium, Bulgaria, Cyprus, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Portugal, Romania, Slovak Republic, Spain, Sweden and the United Kingdom. In addition, Alliances have been established in Croatia in 2006 and in Switzerland in 2010. In 2012, two new National Alliances have been formally established in the Czech Republic and Finland.

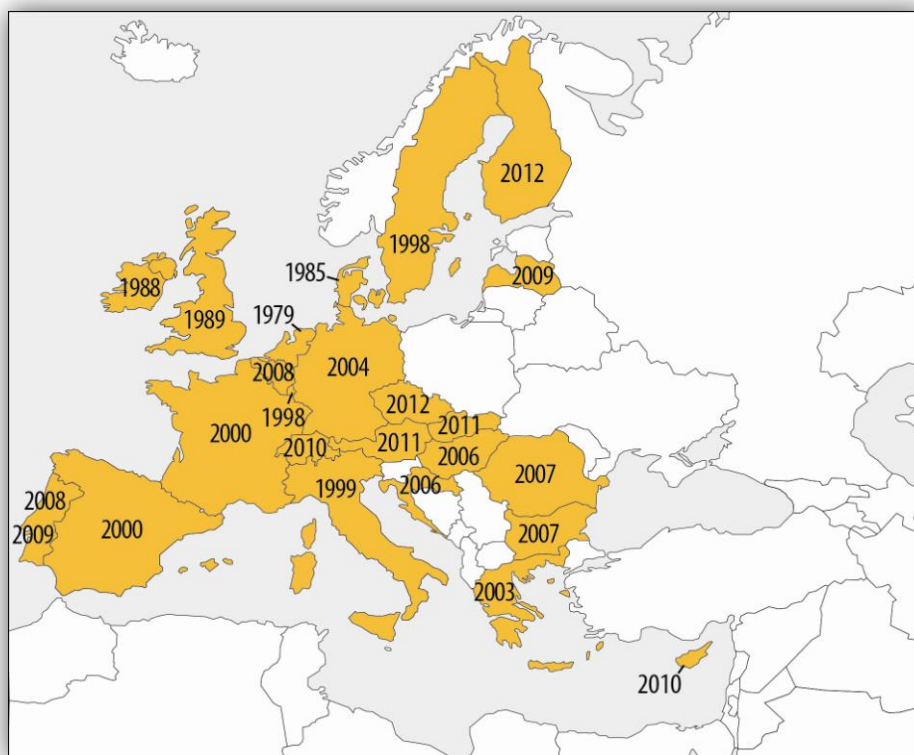


Figure 13: Countries in Europe with a national alliance for rare disease patient organisations and year founded

EURORDIS runs the Council of National Alliances of rare disease patient organisations (CNA) bringing together the majority of Alliances in Europe as well as Alliances in the USA and Canada. The Council allows national representatives of rare diseases to work together on common European and international actions, for instance the Rare Disease Day (see section 5.4).

EURORDIS and the National Alliances also work together to help translate European directives or recommendations into national policies such as adopting a national plan for rare diseases and implementing the EU Directive on cross-border healthcare.

### 5.3. Disease-specific patient organisations in the field of rare diseases

In 2011, 2 376 disease-specific patient organisations were registered in the Orphanet database<sup>133</sup>. Of these, 1 885 were national disease-specific patient organisations, 122 were regional disease-specific organisations, 70 were European disease-specific patient organisations, and 45 were international disease-specific patient organisations.

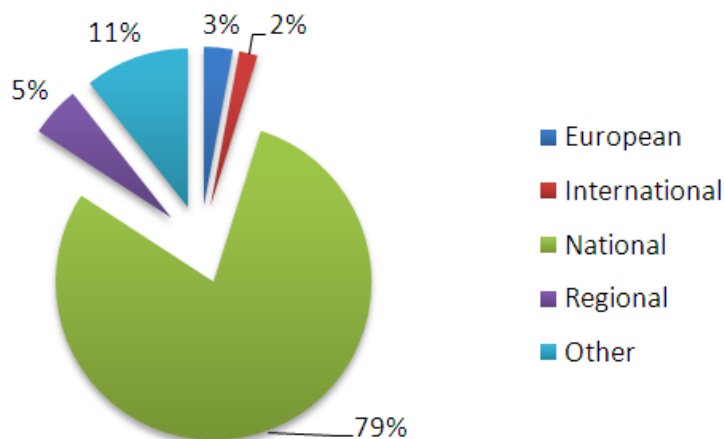


Figure 14: Geographical coverage of disease-specific patient organisations in the Orphanet database (July 2011)

In parallel to the Council of National Alliances, EURORDIS has created the Council of European Federations and Networks for disease-specific patient organisations (CEF). This Council provides a platform for exchanging experiences and information across federations working for specific diseases or groups of diseases. The objectives of the CEF are to share information and experience relevant to common activities and issues concerning specific rare diseases at the European level, to enhance or build capacities as European federations, to gather together patient groups from different countries for specific diseases or group of diseases, and to foster a voice at European level for respective diseases. In particular, this Council concentrates on promoting exchanges and developing collaboration with existing pilot and prospective European Reference Networks of centres of expertise for rare diseases.

### 5.4. Rare Disease Day

Rare Disease Day is an annual event initiated by EURORDIS, which started on 29 February 2008 as a European event. The success of that day meant that the participants decided that from that year on it should be observed on the last day of February and that it should grow to being a world awareness day. This annual event has since served to help raise awareness for patients, families and carers living with rare diseases worldwide.

The campaign targets primarily the general public and policy makers but anyone is welcome to join: patients and their families, patient organisations, health professionals, researchers, drug developers, public health authorities.

Since Rare Disease Day was first launched by EURORDIS and its Council of National Alliances in 2008, thousands of awareness-raising activities have taken place throughout the world reaching hundreds of thousands of people and generating a great deal of media attention.

The political momentum resulting from the Day has also served for advocacy purposes. It has notably contributed to the advancement of national plans and policies for rare diseases in a number of countries.

<sup>133</sup> Data extracted from the Orphanet database in July 2011.

The campaign, which started as a European event, has progressively become a world event, with the US joining in 2009 and a total of 63 countries participating in 2012.

EURORDIS coordinates the campaign at international level and National Alliances coordinate events at the national level. Together they decide on a common annual theme and common actions. EURORDIS provides a communication material tool kit and animates the rare disease day website ([www.rarediseaseday.org](http://www.rarediseaseday.org)) and social media channels.

## 6. Information services

### 6.1. Orphanet

Orphanet<sup>134</sup> is the reference portal for information on rare diseases and orphan drugs in Europe. Orphanet was established in 1997 by the French Ministry of Health (*Direction Générale de la Santé*) and the INSERM (*Institut National de la Santé et de la Recherche Médicale*). Both agencies are still funding the core project. The European Commission funds the encyclopaedia and the collection of data in European countries (since 2000 with DG Health and Consumers grants and since 2004 with DG Research funding). Orphanet data is collected in each European Member State and is expert validated.

Orphanet is accessed by 20 000 users each day from over 200 countries. To resolve the issue of information dispersion Orphanet provides direct online access to all stakeholders to: an inventory of rare diseases and an encyclopaedia in 6 languages (English, French, Spanish, German, Italian and Portuguese). Each European country will soon have an access point to Orphanet in their national language(s).

Each disease in Orphanet has a unique identifier and is placed in a poly-hierarchy classification system. All the classifications of diseases can easily be displayed on the website. Orphanet has also developed an encyclopaedia published in an electronic, open-access journal, the Orphanet Journal of Rare Diseases<sup>135</sup>. To help physicians diagnose rare diseases, Orphanet provides a query system of signs and symptoms. The possible diagnoses are listed in order of probability. To support appropriate referrals, Orphanet has developed a continuously updated directory of expert clinical centres and expert clinical laboratories in 38 countries. To promote quality services, data on quality management of clinical laboratories are available on the website. Distinct logos indicate which laboratories are certified, accredited and/or participate in external quality assessment. This information is gathered and validated in partnership with EuroGentest. To facilitate collaboration between researchers and between researchers and Industry, Orphanet lists all ongoing national and European-level funded research projects by type of research and by disease. The licensing opportunities are displayed, as well as the patient registries, biobanks and highly specialised platforms and know-how, which may be of interest in R&D. To help patients establish contact with other patients, Orphanet provides information on existing patient organisations. In addition to these services, Orphanet provides an inventory of orphan drugs in Europe. To support policy-makers, Orphanet regularly publishes reports in a collection entitled “Orphanet Report Series”: reports in the series include lists of rare diseases with their prevalence<sup>136</sup>, lists of orphan drugs in Europe<sup>137</sup>, lists of rare disease registries in Europe<sup>138</sup> and lists of collaborative research projects and clinical networks in the field of rare diseases funded by the European Commission<sup>139</sup>.

The European Commission proposed in 2010 that Orphanet would be funded as a Joint Action between the European Commission and the Member States from April 2011, with a budget of €7.2 million. The expected outcomes of this Joint Action are a comprehensive and complete information will be made available, including: an inventory of rare diseases; an expanded encyclopaedia of rare diseases (translated into French, German,

<sup>134</sup> [www.orpha.net](http://www.orpha.net)

<sup>135</sup> [www.ordj.com](http://www.ordj.com)

<sup>136</sup> [http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence\\_of\\_rare\\_diseases\\_by\\_alphabetical\\_list.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf)

<sup>137</sup> [http://www.orpha.net/orphacom/cahiers/docs/GB/list\\_of\\_orphan\\_drugs\\_in\\_europe.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf)

<sup>138</sup> <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

<sup>139</sup> <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

Spanish, Italian and possibly more) a directory of expert clinics, medical laboratories, networks, registries and patient organisations; and information on orphan medicinal products. The Orphanet dataset will be available for re-use in different formats to ensure dissemination of the Orphanet nomenclature of rare diseases and maximise the use of collected information on expert services. Customised websites at national level in national language(s) will be available in order to disseminate national data at MS level. Orphanet will have the governance needed to ensure its mission at international level. The Kick-Off Meeting of the Orphanet Joint Action, gathering all national country coordinators and Member State health representatives took place on 7 and 8 June 2011 in Paris.

The Orphanet network will soon expand at the International level: Canada joined Orphanet in 2011 and negotiations have started with Argentina, Australia, Brazil, China and Japan.

Because of the growing number of requests for data, to ensure dissemination of the Orphanet nomenclature of RD and to maximise the use of collected information on expert resources, orphadata.org was created. On this website, the whole Orphanet dataset is directly accessible in a reusable format since June 2011 at [www.orphadata.org](http://www.orphadata.org). The dataset is a partial extraction of the data stored in Orphanet and is updated monthly. It is freely accessible in six languages (English, French, German, Italian, Portuguese and Spanish).

The dataset encompasses:

- An inventory of rare diseases, cross-referenced with OMIM, ICD-10 and with genes in HGNC, OMIM, UniProtKB and Genatlas;
- A classification of rare diseases established by Orphanet, based on published expert classifications;
- Epidemiology data related to rare diseases in Europe (class of prevalence, average age of onset, average age at death) extracted from the literature;
- A list of signs and symptoms associated with each disease, with their frequency class within the disease.

It is also possible, on request, to access other types of Orphanet data, including:

- An inventory of orphan drugs at all stages of development, from EMA (European Medicines Agency) orphan designation to European marketing authorisation, cross-linked with diseases;
- Summary information on each rare disease in six languages (English, French, German, Italian, Spanish, Portuguese);
- URLs of other websites providing information on specific rare diseases;
- A directory of specialised services, providing information on expert centres, medical laboratories, research projects, clinical trials, patient registries, mutation registries, and patient organisations in the field of rare diseases, in each of the countries in the Orphanet consortium.

Orphadata provides a guide for users that defines and describes the elements of the dataset. Orphadata is intended to contribute to accelerating R&D and to facilitate global adoption of the Orphanet nomenclature.

There are currently 3 000 downloads per month.

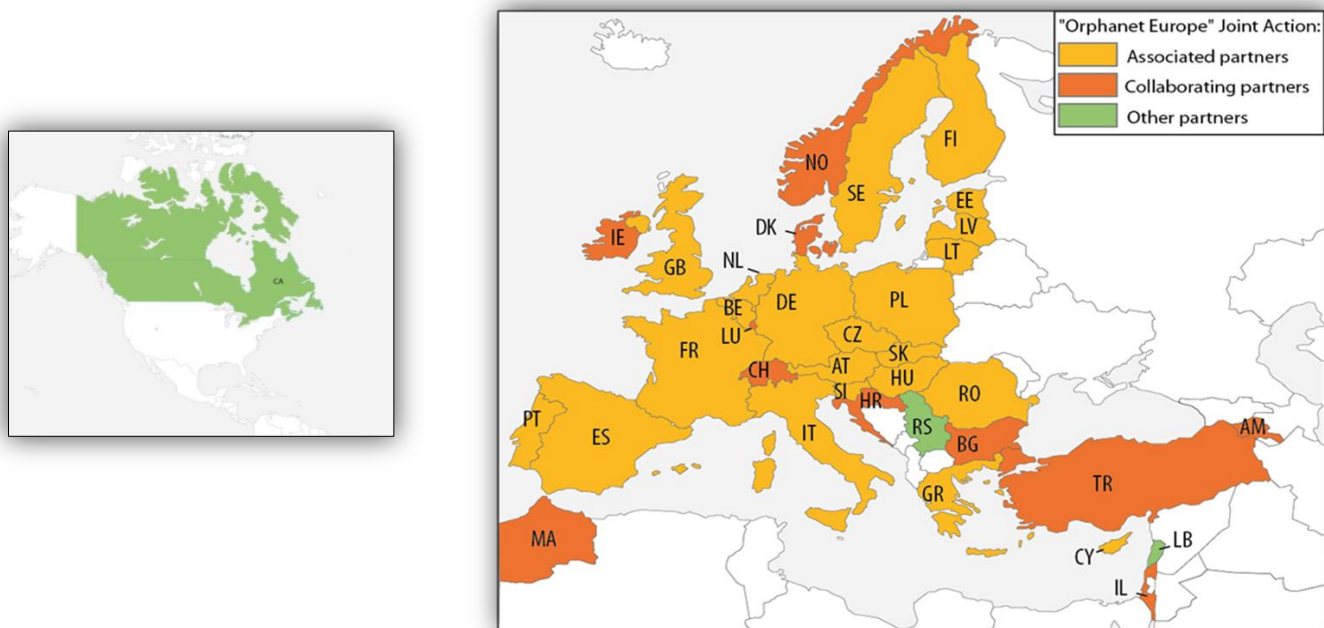


Figure 15: Participating countries in the Orphanet Joint Action<sup>140</sup> (2011-2013)

## 6.2. Official information services/centres at Member State level

Apart from the information on national expert services provided by Orphanet, a number of Member States have established official information services or information centres specifically concerning rare diseases at Member State level. Official rare disease information services are those designated and/or funded by national authorities. The countries having established these services/centres are: Austria, Bulgaria, Denmark, France, Italy, Romania and Sweden. Norway's centres of expertise also play the role of official information centres for rare diseases.

In addition, Rarelink<sup>141</sup> is a web resource providing information on rare diseases which has developed through collaborations between the Center for Små Handicapgrupper (Denmark), the Department for Rare Disorders in the Directorate for Health and Social Affairs (Norway), and the Swedish National Centre for Rare Diseases (Sweden), with the recent collaboration of Harvinaiset (Finland). These government bodies have for several years made a joint effort at disseminating knowledge regarding rare disorders. A key element of this effort has been the publication of information on the internet. Rarelink is available in Norwegian, Swedish, Danish, Finnish and Icelandic.

<sup>140</sup> As of December 2011.

<sup>141</sup> [www.rarelink.org](http://www.rarelink.org)



### 6.3. Official rare disease helplines at Member State level

A few European countries have official rare disease-specific helplines aimed at providing information to patients, families and professionals alike. Official rare disease helplines are those designated/accredited and/or funded by national authorities. These countries are: Bulgaria, Denmark, France, Italy, Norway, Portugal, Romania, Sweden, Spain and the United Kingdom. Some additional countries have non-official helplines, notably those run by national alliances of rare disease patient organisations, and the remaining countries often maintain non rare-disease specific helplines to help orientate users of national health systems, with patient organisations often also providing support by telephone.

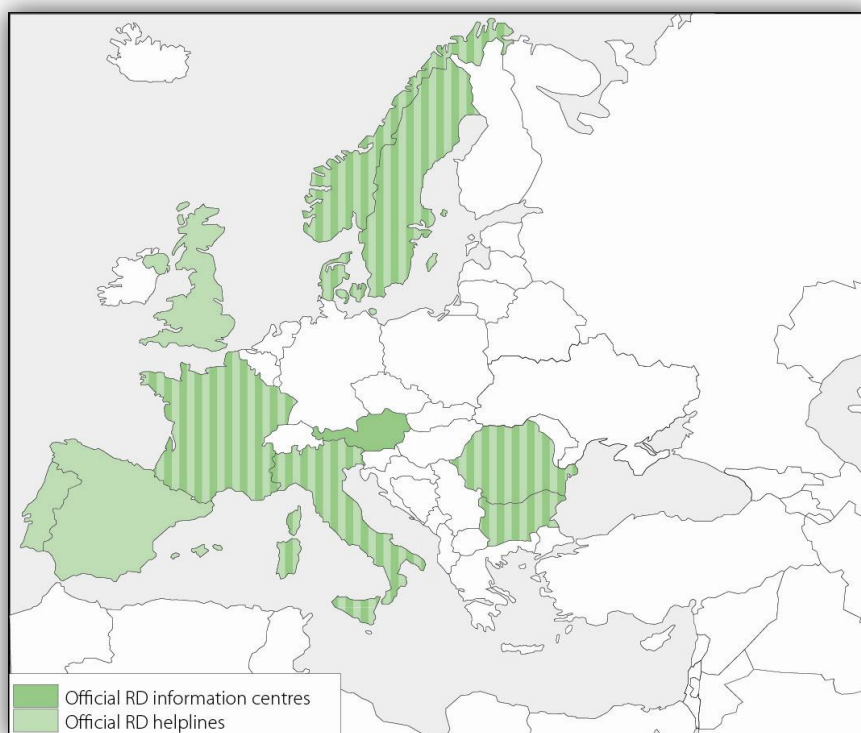


Figure 16: Countries in Europe with official information centres and helplines on rare diseases (December 2011)

### 6.4. OrphaNews Europe

OrphaNews Europe is the electronic newsletter of the European Union Committee of Experts on Rare Diseases (formerly the European Commission's Rare Diseases Task Force), which is published on-line, and sent to over 13'000 subscribed readers, twice a month. OrphaNews Europe was launched on the 15 June 2005 and over 80 issues of the newsletter have since been published.

Every issue of the newsletter presents news and views on rare diseases and orphan drugs in Europe and contains the following sections: Editorial; EU Committee of Experts on Rare Diseases news; EC policy news; other International news; Spotlight on an EU-funded project; New Rare Diseases; New Genes; New Basic Discoveries; New Clinical Research Outcomes; New Public Health Research Outcomes; New Orphan Drugs; Job and Funding Opportunities; News from patient organisations; New Publications; Calendar of Events. The newsletter, produced in English, aims to reach all sectors of the rare disease and orphan drugs community across Europe, ensuring that all those concerned are informed of important developments and new initiatives in the field.

The publication of OrphaNews Europe is supported by the AFM (Association Française contre les Myopathies) and a Joint Action to support the scientific secretariat of the RDTF/EUCERD (Joint Action N° 2008 22 91<sup>142</sup>). National editions of the newsletter are available when national funding is available: this is the case in France (since 2003) and in Italy (since 2011).

## 6.5. Eurobarometer European Awareness of Rare Diseases Report (2011)

Published on 28 February 2011, in honour of the fourth International Rare Disease Day, the *European Awareness of Rare Diseases Report*<sup>143</sup> presents the results of a Eurobarometer survey conducted by TNS Opinion & Social at the request of the Directorate General for Health and Consumers (DG Sanco) and coordinated by Directorate General Communication.

Seeking to gauge the awareness for rare conditions as well as the level of public support for European-level measures, the survey found that “[...]approximately 2 out of every 3 respondents know that rare diseases affect a limited number of people and require very specific care. Almost 1 in every 5 personally knows of someone suffering from a rare disease”. While there were “significant differences” in awareness between the Member States, some “[...] 95% of respondents believe there should be more European cooperation in this area and that rare disease patients should have the right to access appropriate care in another Member State”.

The survey, in the form of questionnaire, was undertaken in each of the 27 European Union Member States, with approximately 1 000 citizens from each country participating, for a total of 26 574 interviews. The release of the report coincided with the formal adoption of the Cross-Border Healthcare Directive – legislation of particular relevance to rare disease patients and their families. In a press release, John Dalli, European Commissioner for Health and Consumer Policy, stated: “I am encouraged to see that EU citizens want more European co-operation on rare diseases. This is important, because the required medical expertise may not be available within national borders. [...]I want to stress that the European Commission is engaged in added value action to help citizens access the care they need across the EU”.

While the results of the Eurobarometer survey are clearly encouraging, rare disease stakeholders cannot rest on their laurels. The assessment found that detailed knowledge of rare diseases and available resources was scant, despite support for national and European-level action as well as improved research, access to care and awareness-raising. Nevertheless, the key finding of the survey is that “[...]the European public almost unanimously supports a coordinated EU strategy for improving the treatment of people suffering from rare diseases. It is only within the context of other major national health issues that respondents are slightly less supportive although even here the majority of Europeans are still willing to make rare diseases a priority”. The full Eurobarometer report<sup>144</sup> is available in English, French and German. Fact-sheets for each of the Member States are available in the country's EU language and also in English.

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<sup>142</sup> This Joint Action finished in February 2012 : the newsletter will be supported by the EUCERD Joint Action : Working for Rare Diseases N° 2011 22 01 from March 2012.

<sup>143</sup> [http://ec.europa.eu/health/rare\\_diseases/eurobarometers/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/eurobarometers/index_en.htm)

<sup>144</sup> [http://ec.europa.eu/health/rare\\_diseases/eurobarometers/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/eurobarometers/index_en.htm)

## LIST OF CONTRIBUTIONS<sup>145</sup>

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Patient Organisation for Rare Diseases (*Pro Rare*)

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The revision and the validation of the report was carried out by the Public Federal Service of Health in collaboration with the National Institute for Health and Disability Insurance and the Institute of Public Health as well as the Regions and the Communities.

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<sup>145</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.

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<sup>146</sup> Disclaimer: the European Commission is not responsible for the completeness and correctness of the information included in this report.

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<http://www.enfermedades-raras.org/>

- Europlan Spanish National Conference Final Report  
[http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/final\\_report\\_spain\\_%20europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_spain_%20europlan.pdf)

#### Sweden

- Swedish Information Centre for Rare Diseases  
<http://www.socialstyrelsen.se/>
- Agrenska  
<http://www.agrenska.se/en/>
- National Quality Register  
<http://www.kvalitetsregister.se/>
- Orphanet Sweden national website  
<http://www.orphanet.se/national/SE-SV/index/hemsida/>
- Rare Diseases Sweden  
<http://www.sallsyntadiagnoser.se/>
- Medical Products Agency  
[www.mpa.se](http://www.mpa.se)
- Rarelink Sweden  
[www.rarelink.se](http://www.rarelink.se)
- Europlan Swedish National Conference Final Report  
[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_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Sweden%20EUROPLAN%20NC%202010.pdf)

#### Switzerland

- Swiss Telethon  
<http://www.telethon.ch/>
- Orphanet Switzerland national website  
<http://www.orpha-net.ch/?lng=EN>
- Proraris  
[www.proraris.ch](http://www.proraris.ch)
- Gebert RUF Stiftung Foundation  
<http://www.grstiftung.ch/en.html>
- Black Swan Foundation  
<http://www.blackswanfoundation.ch/>
- Association Enfance et Maladies Orphelines  
<http://www.aemo.ch/index.php?page=news/afficher&idNew=22>

#### Turkey

- Turkey Health Transformation Program  
<http://www.saglik.gov.tr/EN/BelgeGoster.aspx?17A16AE30572D313AAF6AA849816B2EF1DACD7356F6C2568>
- Orphanet Turkey national website  
<http://www.orpha.net/national/TR-TR/index/orphanet-t%C3%BCrkiye/>

#### United Kingdom

- National Commissioning Group  
[www.ncg.nhs.uk](http://www.ncg.nhs.uk)
- Advisory Group for National Specialised Services (AGNSS)  
<http://www.specialisedservices.nhs.uk/info/agnss>
- UK Genetic Testing Network  
<http://www.ukgt.nhs.uk/gtn/Home>
- Screening Programmes in the UK  
<http://www.screening.nhs.uk/programmes>
- Orphanet UK national website  
<http://www.orphanet.co.uk>
- Genetic Alliance  
<http://www.geneticalliance.org.uk/>
- Rare Disease UK  
<http://www.raredisease.org.uk/>
- Contact A Family  
<http://www.cafamily.org.uk/index.php?section=861>
- Consultation – UK Plan for Rare Diseases  
<http://www.dh.gov.uk/health/2012/02/consultation-rare-diseases/>

- Europlan UK National Conference Final Report  
[http://download.EURORDIS.org/europlan/2\\_EUROPLAN\\_Guidance\\_Documents\\_for\\_the\\_National\\_Conference/final\\_report\\_uk\\_europlan.pdf](http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_uk_europlan.pdf)
- Rare Disease UK Report: *Improving Lives, Optimising Resources: A Vision for the UK Rare Disease Strategy*  
[www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf](http://www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf)
- Specialised Healthcare Alliance Report: The Challenge of rarity  
<http://www.shca.info/PDF%20files/The%20challenge%20of%20rarity%20-%20FINAL.pdf>
- Specialised Healthcare Alliance Report: *Leaving No One Behind: Delivering High Quality, Efficient Care for People with Rare and Complex Conditions*  
<http://www.shca.info/PDF%20files/SHCA%20Report%202011%20low%20res.pdf>

#### 4. OTHER DOCUMENTS/SITES

- **EPPOSI**  
Archive of EPPOSI workshop reports in the field of rare diseases  
<http://www.epposi.org/index.php/programmes/rare-diseases>
- **European Conference on Rare Diseases 2007**  
ECRD 2007 Final Report  
<http://www.rare-diseases.eu/2007/IMG/File/ECRD%202007%20report.pdf>
- **European Conference on Rare Diseases 2010**  
ECRD 2010 Final Report  
<http://www.rare-diseases.eu/2012/ECRD-2010-Krakow>
- **Rare Disease Day**  
<http://www.rarediseaseday.org>



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