



**2011 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 AND KEY DEVELOPMENTS IN 2010**

**Joint Action to Support the Scientific Secretariat of the Rare Diseases Task Force/
European Union Committee of Experts on Rare Diseases (N° 2008 22 91)**



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More information on the European Union Committee of Experts on Rare Diseases can be found at www.eucerd.eu.

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GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), formerly the Scientific Secretariat of the European Commission's Rare Diseases Task Force (RDTF), through the Joint Action to support the Scientific Secretariat of the former-RDTF/EUCERD (N° 2008 22 91), which covers a three year period (January 2009 – December 2011).

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 drugs up to the end of 2010. A range of stakeholders in each Member State 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 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 or national health authorities

The report is split into three parts:

Part I: Overview of Rare Disease Activities in Europe and Key Developments in 2010

Part II: European Commission and other European activities

Part III: Activities in EU Member States and other European Countries

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 this 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, in addition to data provided by the EUROPLAN associated and collaborating partners in response to the EUROPLAN questionnaire, past reports published by the European Commission (including past reports of the working groups of the Rare Diseases Task Force and EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan drugs, 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 Health¹ and Directorate General Research CORDIS website² as well as the site of the European Medicines Agency³, in particular the pages of the COMP⁴ (Committee of Orphan Medicinal Products).

¹ http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

² http://cordis.europa.eu/home_fr.html

³ www.ema.europa.eu

⁴ 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 Europe⁵ newsletter for the period 2007-2010 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 France⁶ (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.

- **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*⁷ 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*⁸, as well as the *RDTF Final Report – State of the Art and Future Directions – March 2008*⁹.

- **EUCERD Publications**

Parts II and III 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*¹⁰ (July 2010). The methodology for the production of this previous report is outlined in the introduction. Information on the state of the art of centres of expertise at MS level was also collected during the EUCERD workshop on national centres of expertise and ERNs for rare diseases (8-9 December 2010¹¹ and 21-22 March 2011¹²).

- **Minutes of the EUCERD**

The minutes of the first meeting of the EUCERD held on 9-10 December 2010 (and previous minutes of the RDTF meetings) was 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 2010.

- **Reports on orphan drugs**

The information provided for each Member State concerning the state of affairs in the field of Orphan Drugs is taken, when referenced, from 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*¹³ 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*)¹⁴. This report notably provided information for the

⁵ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

⁶ <http://www.orpha.net/actor/cgi-bin/OAhome.php>

⁷ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>

⁸ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

⁹ <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

¹⁰ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

¹¹ <http://www.eucerd.eu/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf>

¹² <http://www.eucerd.eu/upload/file/EUCERDReport220311.pdf>

¹³ http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

¹⁴ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*
http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646

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 drug availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Information for the overview was also taken from 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*¹⁵.

- **Eurordis website and websites of patient organisation alliances**

The site of the European Organisation for Rare Diseases¹⁶, 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 EurordisCare¹⁷ 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 2010 site¹⁸, maintained by Eurordis, also provided information on events at Member State level¹⁹ concerning Rare Disease Day.

- **EUROPLAN questionnaire to collect information on rare disease activities**

In the context of the European Project for National Plans Development (EUROPLAN), the partners of the project (who include representatives of national health authorities, expert researchers and clinicians, national alliances of rare disease patient organisations from all MS, and a number of other experts from national health authorities) were addressed a questionnaire and asked to provide detailed information, especially information from sources in their languages, which is more difficult to access on the state of rare diseases activities in their country. The structure of the questionnaire (a sample of this questionnaire is included in Annex IV of the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*²⁰) followed the structure of the Commission Communication on an action in the field of rare diseases²¹: 19 main questions were formulated in order to collect key data on a number of actions in their country. Since the detail of the answers to these questionnaires varied depending on the information available and the actions specific to the country, a session of telephone interviews was also carried out to improve the information available, where appropriate. The collection of the information was concluded in October 2009.

- **EUROPLAN national conferences final reports**

In the context of the EUROPLAN project, 15 national conferences were organised in collaboration with Eurordis and national rare disease patient alliances in 2010 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 diseases²² and its application at national level. These conferences were attended by a range of stakeholder groups at national level and the final reports²³ 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.

¹⁵ <http://www.ncbi.nlm.nih.gov/pubmed/21532564>

¹⁶ <http://www.eurordis.org/secteur.php3>

¹⁷ http://www.eurordis.org/article.php3?id_article=1960

¹⁸ <http://www.rarediseaseday.org/>

¹⁹ <http://www.rarediseaseday.org/country/finder>

²⁰ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

²¹ Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on “Rare Diseases: Europe's challenges” (COM(2008) 679 final)

²² http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf

²³ <http://www.eurordis.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN%20%20National%20Conference%20Final%20Reports>

- **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 and rare disease/orphan drug policies outside of Europe for Part I. Orphanet also provides links²⁴ 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 project²⁵, in particular the report *Rare diseases research, its determinants in Europe and the way forward*²⁶ 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 conferences, as well as participation in Rare Disease Day events and partnerships. This surveillance at national level yielded information for the events section for each Member State.

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

2. REPORT PREPARATION, REVISION AND VALIDATION

The present report provides a compilation of information from the previous report 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 EUCERD*) elaborated in 2010, which has been updated in 2011 to take into account advances and activities in the field of rare diseases and orphan drugs at EU and MS level in 2010.

Although, in the previous report, information was structured to provide a retrospective of actions at EU level and the state of affairs in the field in each EU Member State (i.e. pre-2009), as well as an inventory of initiatives and incentives undertaken in 2009 at EU and MS level, it was decided in consultation with the EUCERD to take a different approach to this year's report. The current report has merged the information from 'retrospective' and '2009' sections of the previous report and updated it to provide an overview of the state of the art of rare diseases activities in Europe which takes into account the advances up to the end of 2010 whilst providing background information to set these activities in context in order to provide a view of the evolution of activities. The EUCERD also decided that this year's report should include a shorter overview of EU and MS activities in the field of rare diseases (Part I) in addition to the broader 'background' document (Parts II and III).

Once this information was merged and updated using the sources cited above, a draft of each country section was sent in April to a range of key stakeholders in each respective country for their input along with a guidance document providing an explanation of the type of information to include if available for each category. The stakeholders identified for each country included: the MS representatives at the EUCERD and their alternates, the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, the partners of the E-Rare consortium, MS representatives on the COMP, representatives of national competent authorities and other rare diseases experts identified at national level. The collected feedback was integrated into the country reports to elaborate the final drafts which were sent at the end of May 2011 to the EUCERD MS representatives for their final validation, to the best of their knowledge, of the information concerning their respective country.

Part II 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, Research and Innovation, Enterprise and Industry, as well as the EMA: this process was carried out in May/June 2011 by the

²⁴ http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN

²⁵ <http://www.rdplatform.org/>

²⁶ http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

Scientific Secretariat of the EUCERD. The European Commission is not responsible, however, for the completeness and the accuracy of the information presented in this report.

Part I was the last part of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe and key developments in 2010 is the result of an analysis of the information collected for Parts II and III. Part I was drafted by the Scientific Secretariat of the EUCERD before validation by the Bureau of the EUCERD acting as the Editorial Board for the present report.

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 as well as a short summary of key developments at EU and MS level in 2010; Part II concerns activities at EU level; Part III 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 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 and key developments in 2010 at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts II and III, 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 drugs and therapies for rare diseases, patient organisations and information services.

Part II of the report on activities at EU level is organised slightly differently to the last edition of the report where activities were presented in sections corresponding to the European Commission Directorates General (DG) of the European Commission implicated in the field of rare diseases. In the present report, activities concerning rare diseases and orphan drugs at EU level are 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 drugs and therapies for rare diseases
4. Other European rare disease activities (i.e. meetings at European level and selected transversal EU activities)

The sub-section concerning the EC activities actions in the area of Public Health is divided into three parts: an overview of EC 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 5th, 6th and 7th 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.

The sub-section concerning EC activities in the area of orphan drugs and advanced therapies for rare diseases is organised accordingly: European legislation concerning orphan medicinal products and related activities, 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 drugs, EU-

USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan drugs.

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 2010.

Part III concerns the activities in the field of rare diseases in each of the 27 Member States plus Norway and Switzerland as EEA 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 expertise²⁷
- Registries
- Neonatal screening policy
- Genetic testing²⁸
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines;
- Best practice guidelines
- Training and education initiatives
- Europlan national conference
- National rare disease events in 2010²⁹
- Hosted rare disease events in 2010³⁰
- Research activities and E-Rare partnership
- Participation in European projects³¹
- Orphan drugs (Orphan drug committee, Orphan drug incentives, Orphan drug availability³², Orphan drug reimbursement policy, Other initiatives to improve access to orphan drugs, Orphan drug pricing policy)
- Orphan devices
- Specialised social services

The choice of categories of information for inclusion in this year's report were discussed by the EUCERD at their first meeting (9-10 December 2010): categories new to this year's edition include genetic testing, Europlan national conferences, orphan devices, other initiatives to improve access to orphan drugs and orphan drug pricing policy. The categories for which information is provided depends 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.

²⁷ The term "official centre of expertise" used in this report means officially designated via a (ministerial) procedure.

²⁸ This section contains data extracted in May 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).

²⁹ As announced in OrphaNews Europe.

³⁰ As announced in OrphaNews Europe.

³¹ Past and ongoing participation in pilot European Reference Networks, DG Research and Innovation financed projects, EUROPLAN and European registries. Some countries have added information on additional European projects.

³² Contacts were asked to provide information on availability of orphan drugs (i.e. which drugs are registered/marketed at national level): 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.

ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG- Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area (Iceland, Switzerland, Norway)
EMA - European Medicine's 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 Rare Diseases Patient Organisation
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
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

INTRODUCTION: OVERVIEW OF RARE DISEASE ACTIVITIES IN EUROPE AND KEY DEVELOPMENTS IN 2010

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 prevalence³³ 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 5 in 10000 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 products³⁴. 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)³⁵ 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 2010 unless otherwise stated.

³³ 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, May 2011, Number 1 : Listed in alphabetical order of diseases,

http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

³⁴ http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

³⁵ 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 1999³⁶, 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 drugs, 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. Now, in 2010, 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 systems³⁷”.

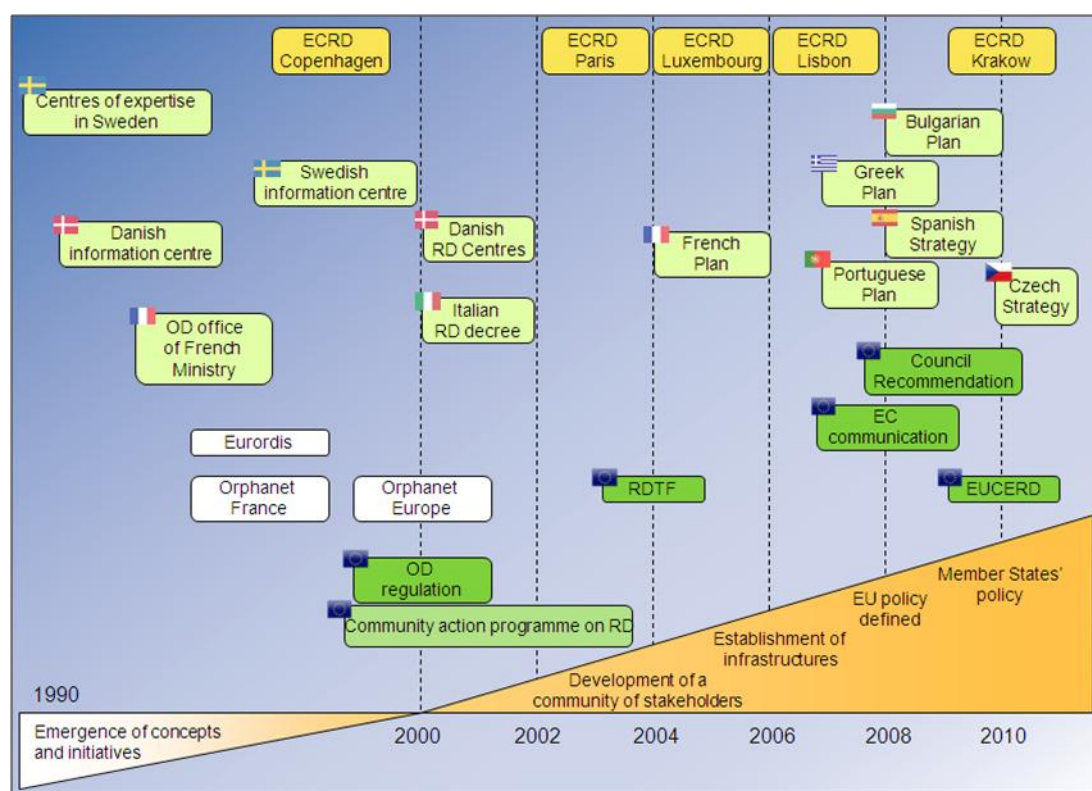


Figure 1: Emergence of concepts and initiatives surrounding rare diseases in Europe³⁸

³⁶ http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

³⁷ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

³⁸ ECRD – European Conference on Rare Diseases

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)** 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 shall 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. This EU policy for orphan drugs has been heralded as a success (see section 4.1). However, Member States do not yet ensure full access to each authorised orphan drug approved.
- b) **The Commission Communication on Rare Diseases: Europe's challenge**³⁹, 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**⁴⁰ 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.

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

³⁹ http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

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

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)**⁴¹ was formally established via the European Commission Decision of 30 November 2009 (2009/872/EC)⁴². This committee 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.

The activities of the EUCERD are currently supported by Joint Action N° 2008 119 (Support to the Scientific Secretariat of the RDTF/EUCERD) and will be supported by a new Joint Action as of 2012.

The European Commission has also funded The European Project for Rare Diseases National Plans Development (EUROPLAN), a three-year project which began in April 2008. The main goal of the project is 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 are composed of three documents focused on defined priority areas: a Guidance document on recommendations for the

⁴¹ The EUCERD www.eucerd.eu replaces the European Commission's Rare Diseases Task Force www.rdtf.org (2004-2009).

⁴² <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:315:0018:0021:EN:PDF>

definition and implementation of National Plans and Strategies for rare diseases⁴³; a joint report with the RDTF on initiatives and incentives in the field of rare diseases in Europe⁴⁴; and a document on the recommended set of indicators for monitoring and evaluating the implementation of national initiatives⁴⁵. 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 and aimed both to raise awareness of the Council Recommendation and to move forward the process of developing a national strategy for rare diseases in each particular country.

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 EU Health Programme 2008-2013**⁴⁶. 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 2007-2013⁴⁷) 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.

⁴³ http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf

⁴⁴ <http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

⁴⁵ <http://www.europlanproject.eu/public/contenuti/files/EP-D6-Indicators.pdf>

⁴⁶ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>

⁴⁷ 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.

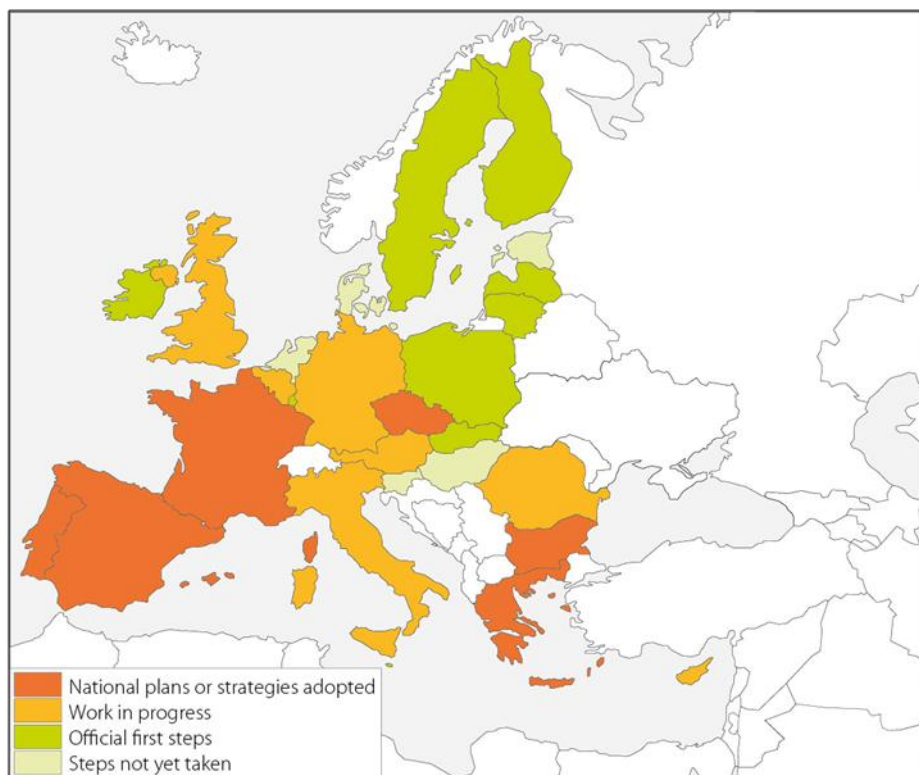


Figure 2: Current stages of development of national plans or strategies for rare diseases in EU MS (in December 2010)

Only a few Member States have currently adopted a national plan/strategy for rare diseases: France, Portugal, Greece, 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.

a) France

France was the first EU country to put in place a comprehensive rare disease plan (2004-2008) with allocated funding. The axes of this plan were to:

- Increase knowledge of the epidemiology of rare diseases;
- Recognise the specificity of rare diseases;
- Develop information for patients, health professionals and the general public concerning rare diseases;
- Train professionals to better identify rare diseases;
- Organise screening and access to diagnostic tests;
- Improve access to treatment and the quality of healthcare provision for patients;
- Continue efforts in favour of orphan drugs;
- Respond to the specific needs of accompaniment of people suffering from rare diseases and develop support for patients' associations;
- Promote research and innovation on rare diseases, notably for treatments;
- Develop national and European partnerships in the domain of rare diseases.

The second French National Plan for Rare Diseases⁴⁸ was elaborated during 2009-2010 and was launched on 28 February 2011 on the occasion of Rare Disease Day with a budget of €180 million. The second plan has been streamlined to function as efficiently as possible while retaining all of the elements essential to adequately care for the country's over three million rare disease patients. The ten axes of the first plan have been consolidated into 3 main axes: improve the quality of health care for rare diseases patients, develop research on rare diseases, and increase European and international cooperation in the field of rare diseases.

b) Portugal

On 12 November, 2008, the Portuguese Minister of Health approved a national plan for rare diseases for Portugal. The plan adheres closely to the structure outlined during the European Conference on Rare Diseases, which took place in Lisbon in 2007. The "*Programa Nacional de Doenças Raras*", which has already undergone a period of public consultation, delineates two general and seven specific objectives and was supposed to have been implemented within an initial timeframe running from 2008-2010, followed by a consolidation period stretching from 2010 to 2015.

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; and 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 RD and accessibility to orphan drugs;
- assuring cooperation at national and international level, including the countries in the EU and the Community of countries with Portuguese 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.

c) Greece:

A commission composed of government officials, health professionals and patient representatives was formed in 2007 following requests by the Greek Alliance for Rare Diseases (PESPA) to help draft the Greek National Plan for Rare Diseases. PESPA members presented a draft to the Committee, which was then modified by officials of the Greek Ministry of Health and Social Solidarity to the format of the current Plan. An outline for this National Plan of Action for Rare Disorders (to run over the period 2008-2012⁴⁹) was presented by the Greek Minister for Health in February 2008: this document identified and outlined eight strategic priorities:

- Acknowledgement of the specificity of rare diseases (registration on the list of chronic long-term disorders),
- Increase the knowledge of the epidemiology of rare diseases and establish a National Registry of Rare Disorders,
- Develop information for patients, health professionals and the general public concerning rare diseases,
- Upgrade services for diagnosis, therapy and rehabilitation of rare diseases patients (training for health care professionals to improve diagnosis and access to quality health care),
- Organise screening and access to diagnostic tests,
- Promote research and innovation regarding rare diseases and specifically effective new therapies,
- Respond to the specific needs of people living with rare diseases,
- Generation of an integrated platform for action in the field of rare diseases at a national level and the development of European partnerships.

⁴⁸ http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf

⁴⁹ http://www.ygeianet.gov.gr/HealthMapUploads/Files/SPANIES_PATHISEIS_TELIKO_LOW.pdf

Although an initial estimate for the budget required was made, no funding has been officially allocated to the National Plan of Action for Rare Disorders, and none of the eight strategic priority actions have yet started. As of yet, there is no legal framework for the Plan.

d) 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). 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.

e) Spain:

The Spanish National Health System Rare Diseases Strategy was approved by the Interterritorial Council of the Spanish NHS on 3 June 2009⁵⁰. 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 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 participants of the Strategy decided, by consensus, to establish the following strategic lines: Information on rare diseases, Prevention and early detection, Healthcare, Therapies, Integrated health and social care, Research and Training.

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

1. Information on RD (specific information on the disease and on the available care resources).
2. Prevention and early detection of RD.

⁵⁰<http://www.msc.es/organizacion/sns/planCalidadSNS/docs/enfermedadesRaras.pdf> and http://ec.europa.eu/health/ph_threats/non_com/docs/rare_strategy_spain_en.pdf

3. Health care (coordination among health care different levels).
4. Therapies: orphan drugs, 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 the Autonomous Communities (regional governments), the Strategy will act as a framework and a set of recommendations for the different regions, who will in turn be in charge of implementation.

f) Czech Republic:

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

The following Member States are currently in the process of elaborating a national plan/strategy for rare diseases: Austria, Belgium, Cyprus, Germany, Italy, Romania and the United Kingdom.

The following Member States have taken some official first steps towards a national plan/strategy for rare diseases: Finland, Ireland, Latvia, Lithuania, Luxembourg, Malta, Poland, Slovak Republic and Sweden.

The remaining Member States (Denmark, Estonia, Hungary, Netherlands and Slovenia) have not yet taken official first steps towards a national plan/strategy for rare diseases.

14 European Member States have held in 2010 a Europlan conference (see section 1.1): these conferences provided the opportunity to bring together a range of stakeholders at national level to raise awareness of the Council Recommendations and discuss national plans/strategies in place, or not yet developed, at national level. The countries that have held a Europlan conference are: Bulgaria, Denmark, France, Germany, Greece, Hungary, Ireland (in 2011), Italy, Netherlands, Poland, Romania, Spain, Sweden and the United Kingdom. Croatia also held a conference in 2010.

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 drugs⁵¹. Policies for orphan drugs 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 drugs. In addition, the European Council Recommendation on an action in the field of rare diseases and the successful termination of the first term of the French rare disease plan – considered a model - is inspiring other countries around the world to reflect on the elaboration of national plans/strategies for rare diseases. Below, a few examples of political frameworks in the field of rare diseases are presented in other world regions outside of Europe.

⁵¹ Information provided by Orphanet http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN

a) North America

a. USA

The Office of Rare Diseases⁵² (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 Act⁵³ 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': 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 OOPD⁵⁴ (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:

- 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.

b) Asia

a. 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)⁵⁵. 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.

⁵² <http://rarediseases.info.nih.gov/>

⁵³ <http://history.nih.gov/research/downloads/PL107-280.pdf>

⁵⁴ <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

⁵⁵ <http://www.nanbyou.or.jp/english/index.htm>

- 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.

b. 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 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.

c. Taiwan⁵⁶

In Taiwan the Rare Diseases and Orphan Drugs Act was adopted in 2000⁵⁷. 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 organizations, and the subsidised supply of specific pharmaceuticals and special nutrients.

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.

d. Korea⁵⁸

Although there is currently no rare disease/orphan drug 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

⁵⁶ 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 (accessed 21 June 2011)

⁵⁷ http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html

⁵⁸ Information from presentation at the 2009 ICORD conference by 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=0CC0QFjAC&url=http%3A%2F%2Fficord.se%2Fdocuments%2Fficord_2009%2Fpresentations%2FKoo.ppt&rct=j&q=korea%20rare%20diseases%20center&ei=8m8ATtnqNla2hAefp4S8DQ&usg=AFQjCNEQ6r3z5e0UuYx3KBHv839W3MSgpw&sig2=LRZURh40JbNM8yLdaQT_Ig&cad=rja

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 2006⁵⁹) 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 service for patients. 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 clinical research network with around 5.5 million USD.

c) Australasia

a. 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.

⁵⁹ <http://helpline.cdc.go.kr/cdchelp/index.gst>

2. Expert services in Europe

2.1. National centres of expertise

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 2006⁶⁰ based on the experience of countries with designation processes already in place:

- appropriate capacities for diagnosing, following-up and managing patients, with evidence of good outcomes, where applicable.
- sufficient activity and capacity to provide relevant services at a sustained level of quality;
- capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control;
- demonstration of a multi-disciplinary approach;
- high level of expertise and experience, as documented through publications, grants or honorific positions, teaching and training activities, etc.;
- strong contribution to research;
- involvement in epidemiological surveillance, such as registries;
- close links and collaboration with other expert centres at national and international level, and capacity to network;
- close links and collaboration with patient associations, where they exist.

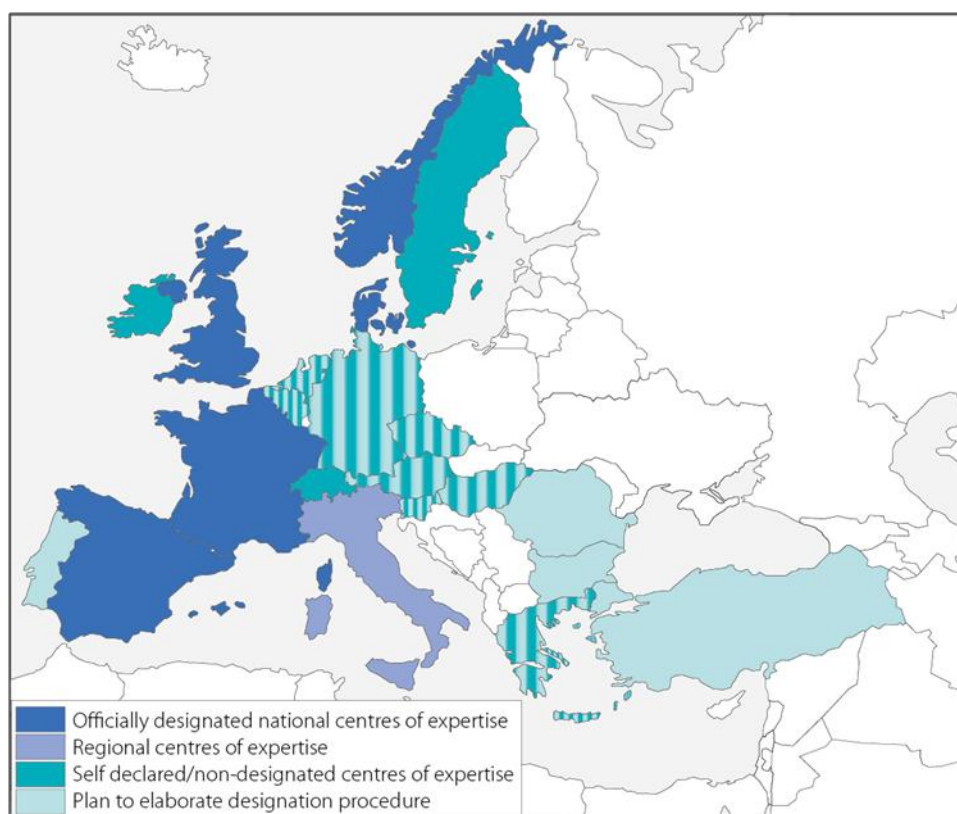


Figure 3: State of the art of centres of expertise at national level in Europe (December 2010)

⁶⁰ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

Few countries currently have officially designated national centres of expertise for rare diseases (i.e. selected and financed by health authorities): Denmark, France, Norway, Spain and the United Kingdom⁶¹. Italy has regional centres of expertise for rare diseases (represented in a lighter blue in Figure 3). It should be highlighted that the designation criteria vary from country to country, even if these criteria are reflected by the recommendations of the HLG and RDTF.

A number of countries have self-declared/non-designated centres of expertise for rare diseases which are acknowledged by authorities to varying degrees: Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Ireland, the Netherlands, Slovenia, Sweden and Switzerland.

A number of European countries plan to elaborate designation procedures for national 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, Germany, Greece, Hungary, the Netherlands, Portugal, Romania, Slovenia and Turkey.

In conclusion there is a great heterogeneity in the area of national centres of expertise for rare diseases in Europe, both in terms of the initiatives already in place, and the state of advancement of MS in the provision of expert care for rare diseases. It is important to highlight that in 2011 the EUCERD will working on a EUCERD recommendation on quality criteria for national centres of expertise for rare diseases. The homogeneity of quality criteria for national centres of expertise will be a key concept and concern in the context of the future implementation of the EU Cross-Border Health Care Directive⁶², in which rare diseases are specifically mentioned.

2.2. European Reference Networks (ERNs)

As aforementioned, the work of the HLG and RDTF developed a number of criteria for national 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), 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) 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*⁶³ in late 2010 which was presented and discussed at a EUCERD workshop on 8-9 December 2010. The report has since been approved by the EUCERD, and

⁶¹ Further details concerning the designation processes in these countries can be found in the relevant country section in this report.

⁶² <http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf>

⁶³ <http://www.eucerd.eu/upload/file/Reports/ERNAnalysis2011.pdf>

yields a number of initial conclusions concerning the experience of EC-funded pilot European Reference Networks and other EC-funded networks for rare diseases:

- a) The activities of pilot ERNs reflect some of the specific actions needed at European level in order to improve the situation for patients suffering from a specific disease/group of diseases across Europe. As a result, the activities and aims of ERNs are extremely heterogeneous. The geographical coverage of these networks is also heterogeneous due to the choice of partners identified for the pilot and the availability/organisation of expertise from country to country. Despite this variability, the actions of these pilot ERNs have a European added-value in the field of rare diseases as their actions would not have been possible without European collaboration and networking. The pilot ERNs have thus explored various networking possibilities and the benefits of networking in the field of rare diseases. Due to the variability of these networks' aims, it is very challenging to establish a common definition of ERN based on these experiences and to establish criteria for carefully selecting, creating or assessing ERN in a field where resources are limited. The experiences of the pilot ERN should be taken into account to assess the suitability of the criteria defined by the HLG/RDTF, and possibly revise these criteria.
- b) The analysis of the networks previously and currently funded by DG Sanco shows that the most valuable resources developed by these ERNs are:
 - Shared databases/registries
 - Shared tools for teleexpertise
 - Guidelines and information
 - Training tools and training sessions
- c) The analysis shows previously and currently funded pilot European Reference Networks are primarily networks of experts. These networks can include designated national centres of expertise, centres which are recognised as having expertise but without designation, laboratories and patient organisations.
- d) This analysis has highlighted that the pilot ERNs have varying objectives and activities. Up to now, research networks have been funded at European level by DG Research, and DG Sanco funds public health networks, as stated in the *2008 RDTF Report European Reference Networks in the Field of Rare Diseases: State of the Art and Future Directions*⁶⁴. In fact, networking is a process, and there is a natural progression in the networking process:
 1. Basic research networks
 2. Clinical research/trials networks
 3. Clinical care networks
 4. Information networks for patients/public
 5. Comprehensive networks
- e) Pilot ERNs do not currently follow this schema in developing their networks, but some comprehensive networks have developed from DG Research funded networks in this way. There is thus a need to harmonise and coordinate the approaches of DG Sanco and DG Research.
- f) The analysis also shows that much of the networking currently practiced by ERNs and other networks with similar activities is virtual: expertise is shared at distance (teleexpertise) rather than physically (patients do not travel to expert centres in the network to receive care). Pilot ERNs practice teleexpertise, but not yet telemedicine as recommended by the Council Recommendation (§14) 'when necessary'. The exception to the virtual/physical mobility of expertise trend is that some networks promote travel by expert professionals to countries which lack certain expertise in order to share their experiences and certain specific treatment techniques, and many networks organise regular meetings of network partners in order to strengthen communication and cooperation in the network. Pilot ERNs, therefore follow the recommendation of the Council and the HLG/RDTF that expertise should travel rather than patients whenever possible, but they have not yet fully explored the potential of telemedicine.

These types of infrastructures require long-term funding which is difficult to envisage with the current instruments.

⁶⁴ <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

Further reflection on ERNs for rare diseases will be necessary in the context of the future implementation of the European Cross-Border Health Care Directive, in which ERNs for rare diseases are explicitly mentioned in Article 12⁶⁵: “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:

- 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;
- 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;
- to maximise the cost-effective use of resources by concentrating them where appropriate;
- to reinforce research, epidemiological surveillance like registries and provide training for health professionals;
- 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;
- to encourage the development of quality and safety benchmarks and to help develop and spread best practice within and outside the network;
- 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.

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, Orphanet⁶⁶ 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 now in 36 countries in 2011, with resources from the DG Public Health. In collaboration with the EuroGentest⁶⁷ Network of Excellence (financed by DG Research), 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.

Currently⁶⁸, 1'049 laboratories offering tests for 1'764 genes are registered in Orphanet. According to an analysis of Orphanet data in May 2010⁶⁹, the test offer differs greatly from one large country to another (Figure 4): Germany (1'244 genes), France (902 genes), Spain (594 genes), Netherlands (600 genes), Italy (643 genes), United Kingdom (416 genes).

The test offer in medium and small-sized countries now ranges from 1 to 344 genes⁷⁰. This situation explains the large cross-border flow of specimens, highlighting the need to provide access to services in other countries

⁶⁵ <http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf>

⁶⁶ www.orpha.net

⁶⁷ <http://www.eurogentest.org/>

⁶⁸ Figure from Orphanet data, June 2011.

⁶⁹ Figures from Orphanet data, May 2010.

⁷⁰ Figure from Orphanet data, June 2011.

when necessary, especially for very rare diseases. According to available data, only testing for Cystic fibrosis is provided by every country.

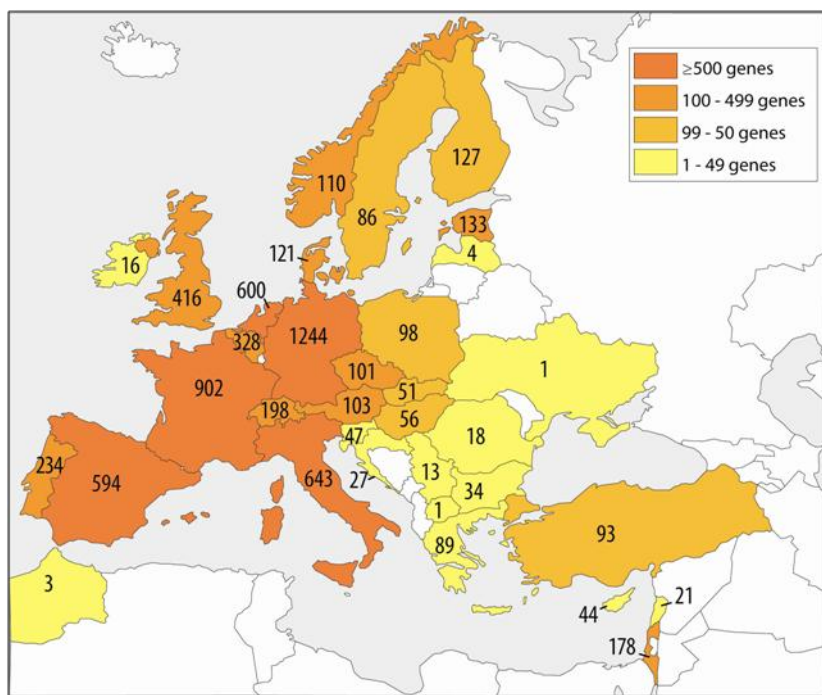


Figure 4: Number of genes tested in each country (Orphanet data extraction May 2010)

An analysis of the Orphanet database⁷¹ shows that 297 genes are tested in one laboratory only in the EU (19% of genes), 1'189 genes are tested in less than 10 laboratories in the EU (76% of genes), 1'088 genes are tested in less than 5 countries (69% of genes), and 395 genes are tested in one country only (25% of genes).

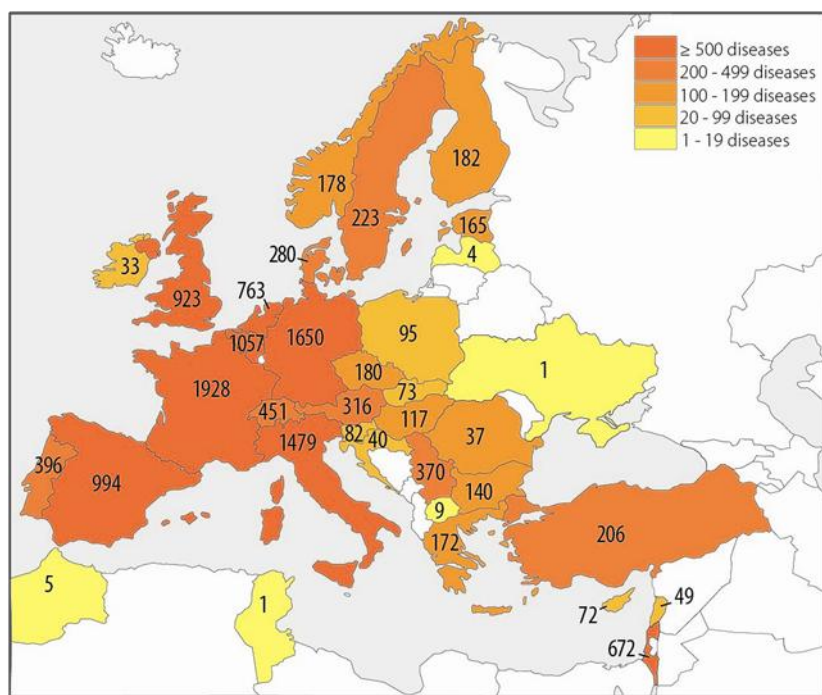


Figure 5: Number of rare diseases tested in each country (Orphanet data extraction May 2010)

⁷¹ Data extracted from Orphanet database in May 2010.

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.

In terms of quality assurance of genetic services, an analysis of the Orphanet database⁷² shows that 107 laboratories in Europe are accredited for at least some part of their diagnostic activities, with 432 laboratories participating in at least one External Quality Assessment scheme during the previous 5 years through 46 different EQA organisations.

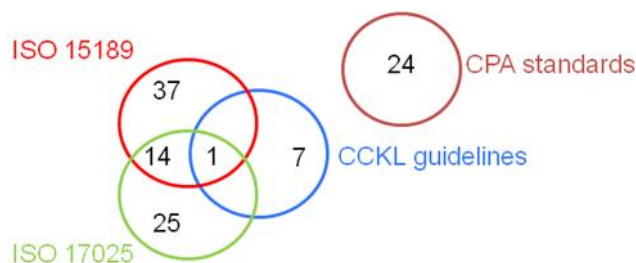


Figure 6: Number of laboratories with quality assurance accreditation for part of their activities⁷³.

⁷² Data extracted from Orphanet database in May 2010.

⁷³ **ISO 17025:** 2005 are the general requirements for the competence of testing and calibration laboratories. This international standard contains all of the requirements that testing and calibration laboratories have to meet if they wish to demonstrate that they operate a quality system, are technically competent and are able to generate technically valid results. Accreditation bodies that recognize the competence of testing and calibration laboratories should use this International Standards as a basis for their accreditation.

ISO 15189: 2007 are the particular requirements for quality and competence for medical laboratories. While ISO 17025 is simply recognition of competency of testing and calibration laboratories, this international standard provides requirements for competence and quality that are particular to medical laboratories. Medical laboratory services have to meet the needs of all patients and the clinical personnel responsible for the care of those patients.

CCKL Guidelines are Dutch guidelines based on the ISO 15189 standard and applies to medical laboratories.

CPA (Clinical Pathology Accreditation) Standards are the national guidelines for accreditation of medical laboratories in the United Kingdom.

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

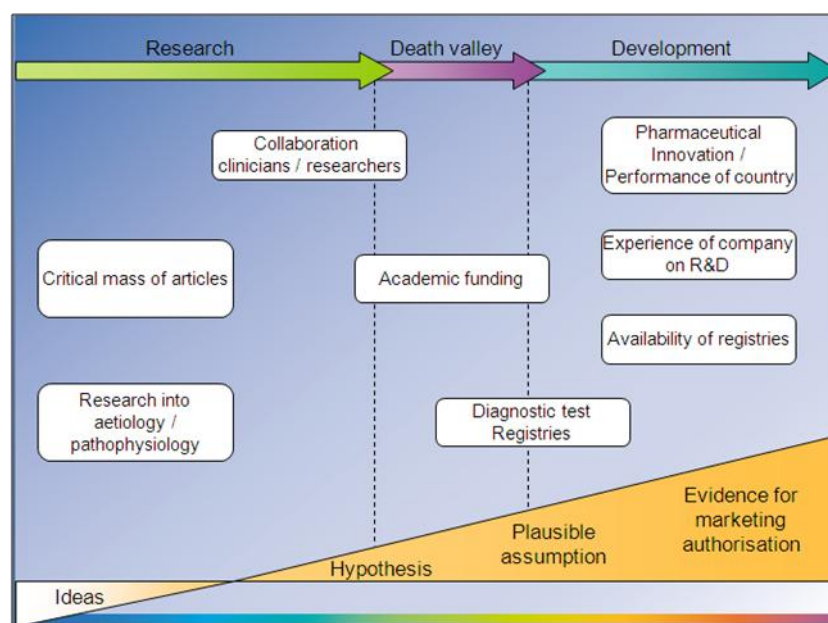


Figure 7: Schema representing the bottlenecks between research and development of therapies for rare diseases.

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 3.5). 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.

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.

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 currently, or previously, have established specific rare disease funding programmes/calls are: France, Germany, Hungary, Italy, the Netherlands, Portugal, Spain, Switzerland. Many other countries fund rare disease projects through generalised research funding programmes.

A few countries (such as France, 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 at national level.

“Telethon” initiatives provide funding for rare diseases projects in countries such as Cyprus, France, Italy, Luxembourg, Spain, 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 diseases⁷⁴. It aims 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

⁷⁴ <http://www.e-rare.eu/>

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 project now has 16 partners from 12 countries: Austria, Belgium, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and Turkey.

E-Rare 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 2nd 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 2nd 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 available⁷⁵.

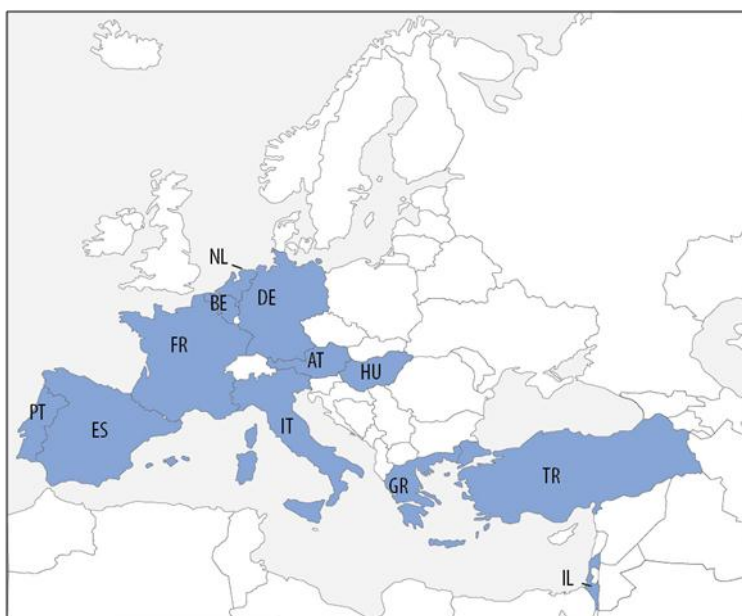


Figure 8: Countries participating in the E-Rare (1) ERANET for rare diseases

A 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. 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.

⁷⁵ <http://www.e-rare.eu/images/stories/e-rarejtc2009fundedprojects.pdf>

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 mobilization 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, 2007-2013⁷⁶). 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 2007–2010, 50 research projects with an EU contribution of over €237 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 drugs (for a total of €36 million). The “Cooperation” 2010 work programme of the Health Theme⁷⁷ also called for an ERA-Net on rare diseases (E-Rare-2⁷⁸, see section 3.1.1).

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 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)⁷⁹. The list 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.

⁷⁶ http://cordis.europa.eu/fp7/home_en.html

⁷⁷ ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/health/a_wp_201001_en.pdf

⁷⁸ <http://www.e-rare.eu/>

⁷⁹ “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>

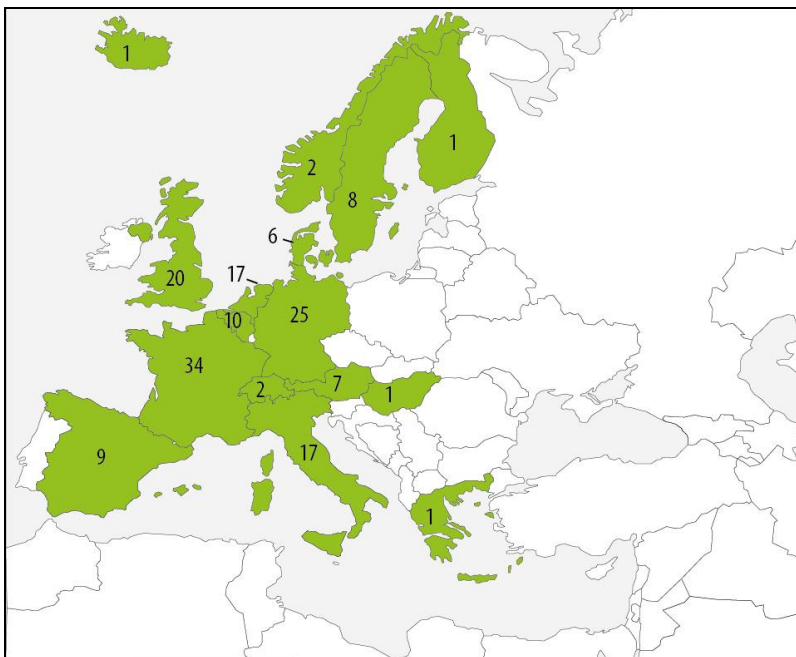


Figure 9: Number of FP5, FP6 and FP7 rare disease related projects in which Member States have participated as leading partner (November 2010)⁸⁰

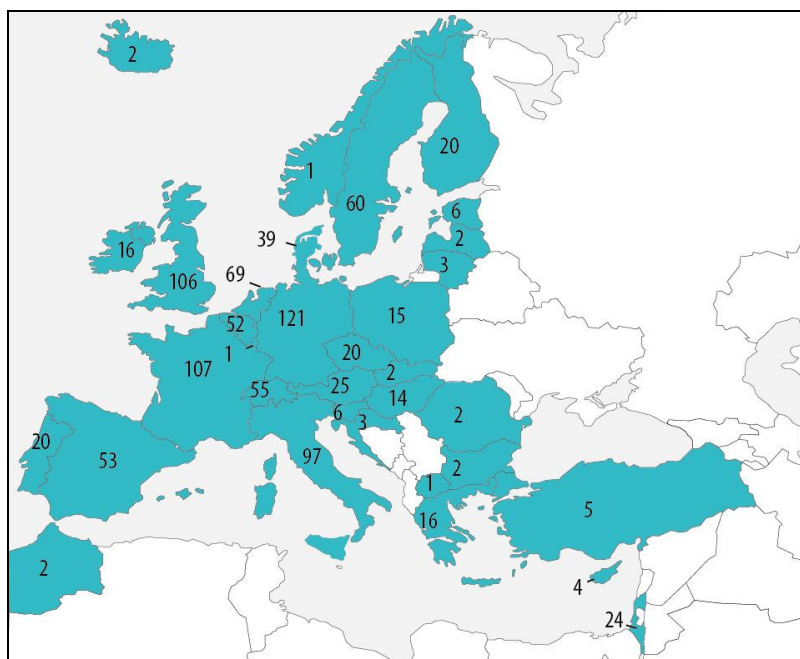


Figure 10: Number of FP5, FP6 and FP7 rare disease related projects in which Member States have participated (November 2010)⁸¹

⁸⁰ 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/orphacom/cahiers/docs/GB/Networks.pdf>

⁸¹ 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/orphacom/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 (IRDiRC⁸²) 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, have also been invited to join the consortium. Several national agencies have already expressed their intent to join.

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 under development and a short summary of overarching policies will be available by June 2011.

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.

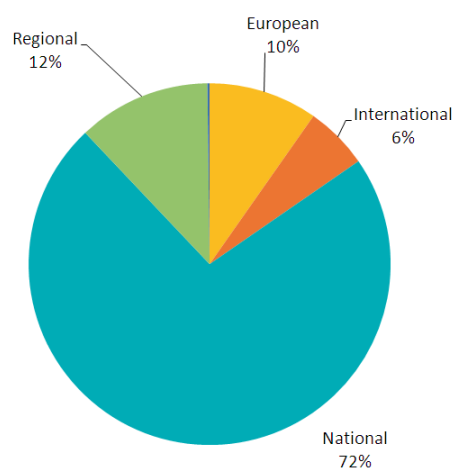


Figure 11: Geographical coverage of rare disease registries registered in the Orphanet database (January 2011)

⁸² http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html

According to the Orphanet database accessed in December 2010, there are 514 disease registries in Europe (50 European, 29 International, 373 national, 61 regional, 1 undefined). The complete list is provided in the Orphanet Report Series “Disease Registries in Europe”⁸³.

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 drugs 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 rare disease research activities in Europe

The RareDiseasePlatform project⁸⁴ (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 drugs, accessible through the research tab of the Orphanet website⁸⁵. 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.

So far the Orphanet database contains 4’212 ongoing research projects for about 2’131 different rare diseases⁸⁶. These research projects are conducted in 27 countries. Among these projects, 232 do not concern a particular stage of research and correspond to an activity of coordination of research projects. A hundred of the research projects registered in the Orphanet database belongs to socio-economical category of research projects (public health, health economy and health sociology). These projects usually have a wide scope and do not consider a particular disease or group of diseases. We could thus more accurately estimate that there are 3’880 research projects for 2’100 rare diseases in 27 countries. These projects have been classified as follows (see Figure 12):

Stage of research	Number of Projects
Basic research	2750
Pre-clinical research	331
Clinical research	487
Diagnostic & Biomarkers	312

Figure 12: Number of research projects by stage of research⁸⁷

The “Basic research” category gathers research projects such as gene search, mutation search, gene expression profile, genotype-phenotype correlation, in vitro functional study, animal model and human physiopathological study. “Pre-clinical research” covers areas of drug development, gene therapy, cell therapy and medical devices development. This step is often performed by Industry and thus data is not fully accessible, which can explain

⁸³“Disease Registries in Europe”, Orphanet Report Series, *Rare Diseases collection*, January 2011 - <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

⁸⁴ <http://www.rdplatform.org/>

⁸⁵ <http://www.orpha.net>

⁸⁶ Figures from the RDPlatform report “Rare Diseases Research, its determinants in Europe, and the way forward” (January 2011), http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

⁸⁷ Figures from the RDPlatform report “Rare Diseases Research, its determinants in Europe, and the way forward” (January 2011), http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

the low number of projects in Figure 12. The category “clinical research” includes non-therapeutic clinical research, epidemiological research and excludes clinical trials. “Diagnostic and biomarkers” concerns studies that are conducted with the goal to identify biomarkers and/or to develop a diagnostic test that is not already available in clinical laboratories.

The category represented the most is “Basic research” a highly active field representing many challenges and considerable consequences as the outcomes concern both rare and common diseases, with rare diseases often being used as model for more common disorders.

In terms of R&D, Orphan designations act as a proxy when considering potential products in development: according to an analysis⁸⁸ carried out by Orphanet, there are 581 orphan designations to potentially treat 343 diseases, affecting a total 8.2 million people in Europe. This analysis of the Orphanet database also shows that there are 666 ongoing, unique clinical trials for potentially 312 rare diseases. There are 99 marketed drugs for the treatment of 141 diseases. There are 62 drugs with EU market authorisation and orphan designation for 82 diseases, and 44 drugs with market authorisation but without orphan designation for 74 diseases. In terms of R&D by medical domain, the analysis of number of medical products in development or with Marketing Authorisation shows that the greatest number of products have been developed for solid tumours, followed by neurology, haematology, metabolism, dermatology and endocrinology.

3.4. 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. 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.

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. All the revised chapters open for comments are available on the EUCERD website (www.eucerd.eu).

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 alignment of the Orphanet nomenclature with OMIM poses the question of the fair representation of genetic diseases and of the genetic contribution of genomics to disease definition, in relation with the needs of the end-users.

⁸⁸ Figures from the RDPlatform report “Rare Diseases Research, its determinants in Europe, and the way forward” (January 2011), http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

4. Orphan medicinal products and other therapies for rare diseases

The orphan medicinal product regulation (Regulation (EC) No 141/2000)⁸⁹ was adopted in December 1999 and came into force in the European Union in 2000. The Orphan Drug 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 drug 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 level⁹⁰

The first decade of the Orphan Drug Regulation has yielded more than 850 positive opinions for orphan product designation, adopted from 1235 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 less than 1 in 10'000 patients (receiving 52% of all orphan designations). Indeed, 51% 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.

The number of applications has increased steadily each year during the first decade of the Regulation with 174 applications received in 2010. Sixty-three designated products had received marketing authorisation by the end of 2010, of which oncology is by far the most common therapeutic area (41%). Interestingly, the average time span between designation and authorisation is only 2.8 years, indicating that designated products were at an advanced developmental stage.

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 2010, the COMP has given 64 positive opinions for advanced therapy products out of a total of 850 positive opinions for orphan medicinal product designation.

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

Orphanet regularly updates an Orphanet Report Series listing orphan drugs with orphan designation and European market authorisation and orphan drugs with European market authorisation without prior orphan designation⁹¹.

⁸⁹ This section reproduces information from

http://ec.europa.eu/health/rare_diseases/orphan_drugs/strategy/index_en.htm

⁹⁰ Source: *Nature Reviews: Drug Discovery* "European regulation on orphan medicinal products: 10 years of experience and future perspectives" COMP/EMA Scientific Secretariat, Volume 10, May 2011:

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

⁹¹ http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

4.2. Availability of orphan drugs at Member State level

Trying to chart what 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, marketed at national level, etc). In some cases national sources have provided additional information concerning the list of reimbursed orphan drugs, and in these cases this is explicitly stated.

“Availability” is the term generally used to describe when an orphan drug 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 drug 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 it has to be available according to the aforementioned definition, and available to the patient without administrative hurdles, i.e. through general out-patient reimbursement systems (for example, inclusion of the orphan drug 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 procedure can be used to obtain access to orphan drugs. It is also possible in some Member States for orphan drugs 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).

Eurordis, the European rare disease patient alliance, has recently made available the results⁹² of a survey launched in 2010 involving ten European countries that attempts to demonstrate the price and access to orphan drugs at the national level. Working with the national rare disease alliances of Belgium, Denmark, France, Greece, Hungary, Italy, the Netherlands, Romania, Spain and Sweden, the Eurordis study demonstrates the complexity of the process through which approved orphan products are brought to market across Europe. The survey reveals that while patient organisations can access information about the availability of the medicinal products used by their members, other data – particularly pricing information - remains inconclusive, as data on the official prices in individual countries as well as the actual prices paid by their healthcare system are not easily obtained. The information presented shows the diversity of product availability between countries and identifies Denmark, France and the Netherlands amongst the countries enjoying wide access to orphan drugs, in contrast to Greece, Romania or Spain, which have a limited number of the 60 EU approved orphan drug products available. What is now required is full access to the hard pricing and reimbursement data and the national decision-making processes in order to better identify the bottlenecks that are preventing full and equal access to all the EU market-approved orphan drugs.

⁹² http://img.eurordis.org/newsletter/pdf/mar-2011/ERTC_13122010_YLeCam_Final.pdf

5. Patient organisations

According to the Council Recommendation (8 June 2010), 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'⁹³. 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

EURORDIS⁹⁴ 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 479 rare disease organisations in 45 different countries (of which 25 are EU Member States), covering more than 4,000 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.

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 European countries have established national alliances of rare disease patient organisations. The Member States having established these alliances include: Belgium, Bulgaria, Cyprus, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Portugal, Romania, Spain, Sweden and the United Kingdom. In addition, two alliances have been established in Croatia and in Switzerland and one is in the process of being established in Russia.

⁹³ <http://www.euro.who.int/Document/E88086.pdf>

⁹⁴ www.eurordis.org

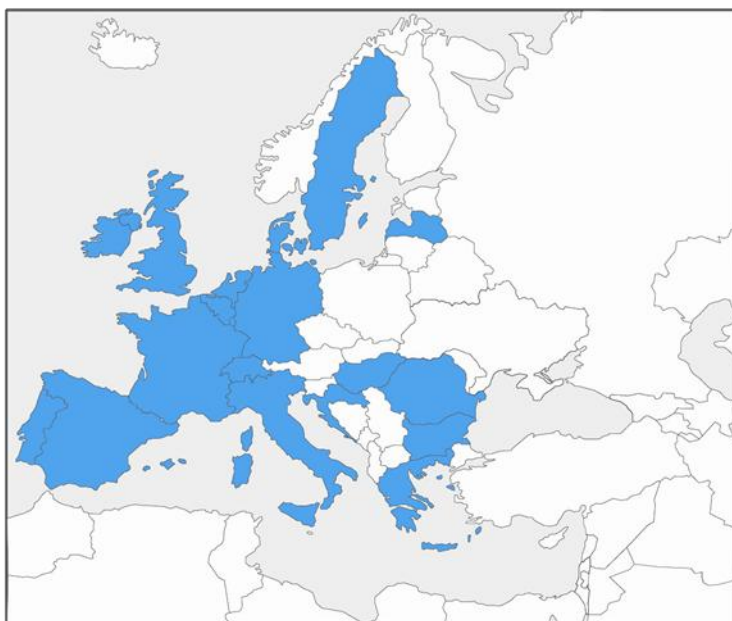


Figure 13: Countries in Europe with a national alliance for rare disease patient organisations

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, Canada and Latin America. This structure 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

There are 2376 disease-specific patient organisations registered in the Orphanet database⁹⁵. Of these, 1885 are national disease-specific patient organisations, 122 are regional disease-specific organisations, 70 are European disease-specific patient organisations, and 45 are international disease-specific patient organisations.

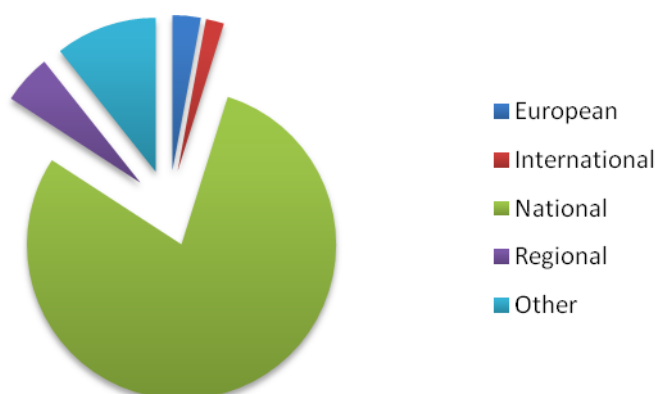


Figure 14: Geographical coverage of disease-specific patient organisations in the Orphanet database (July 2011)

⁹⁵ Data extracted from the Orphanet database in 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 with the idea being the 'Rare Day for special people'. 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. Now participants in over thirty-five countries on six different continents have signed up to host events in celebration of the Day: these events are most often planned by the national alliances at National level, and the day is increasingly used for announcements of national and European initiatives in the field of rare diseases.

The National Alliances are highly involved in Rare Disease Day and together adopt a common annual theme. EURORDIS provides a tool kit and hosts the rare disease day website (www.rarediseaseday.org).

6. Information services

6.1. Orphanet

Orphanet⁹⁶ 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 Public Health 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 Diseases⁹⁷. 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

⁹⁶ www.orpha.net

⁹⁷ www.orjd.com

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 prevalence⁹⁸, lists of orphan drugs in Europe⁹⁹, lists of rare disease registries in Europe¹⁰⁰ and lists of collaborative research projects and clinical networks in the field of rare diseases funded by the European Commission¹⁰¹.

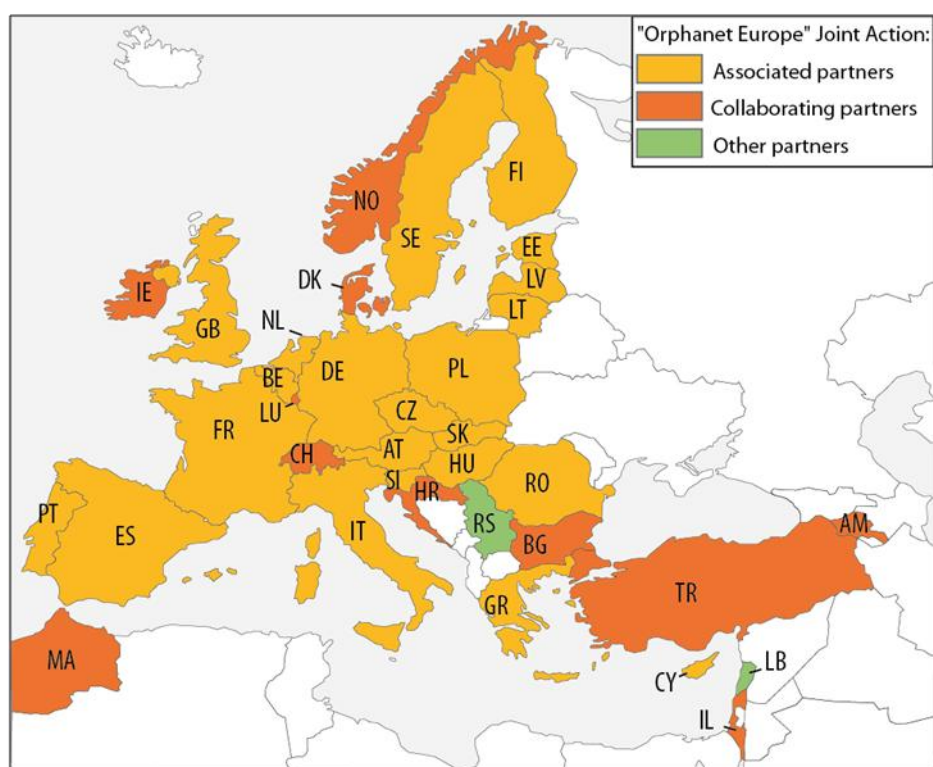


Figure 15: Participating countries in the Orphanet Joint Action (2011-2013)

6.2. Official information services 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: Bulgaria, Denmark, France, Italy, Sweden and Norway.

⁹⁸ http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

⁹⁹ http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf

¹⁰⁰ <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

¹⁰¹ <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

6.3. Rare disease helplines

A few European countries run official rare disease-specific helplines aimed at providing information to patients, families and professionals alike: Bulgaria, Denmark, France, Italy, Norway, Portugal, Sweden, Spain and the United Kingdom. The remaining countries often maintain non rare-disease specific helplines to help orientate users of national health systems, with patient organisations often providing support by telephone.

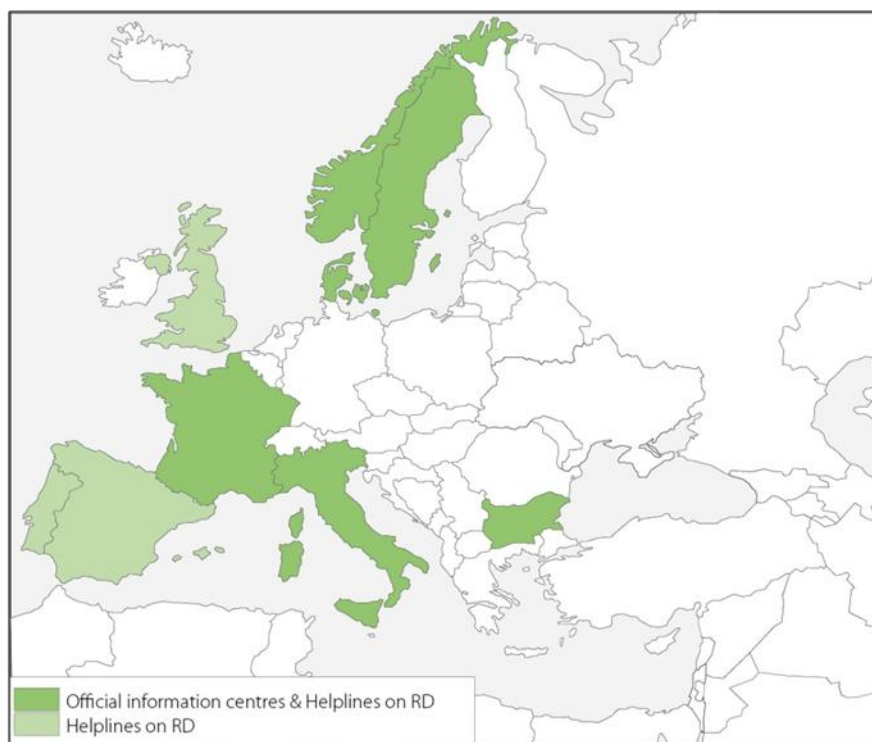


Figure 16: Countries in Europe with official information centres and helplines on rare diseases (December 2010)

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 15th 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 (Joint Action N° 2008 22 91) to support the scientific secretariat of the RDTF/EUCERD.

7. Key developments in 2010

7.1. Key developments at European level

- **European Union Committee of Experts on Rare Diseases - EUCERD¹⁰²**

The European Union Committee of Experts on rare Diseases (EUCERD) established via the European Commission Decision C(2009)9181 (30 November 2009), held its first meeting on 9-10 December 2010 in Luxembourg. During this meeting Members elected the Bureau of the EUCERD and discussed priority topics to be tackled by the Committee¹⁰³. The EUCERD is specifically 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 International Rare Disease Research Consortium - IRDiRC¹⁰⁴**

The first steps towards the establishment of the International Rare Disease Research Consortium were made during a workshop held in Reykjavik, Iceland, on 27-28 October 2010¹⁰⁵, co-organised by the European Commission and the USA's National Institutes of Health. Scientists from leading organisations in the field, industry and patient representatives, and regulatory bodies from both Europe and the USA were brought together to take stock of the ongoing activities on either side, to identify areas that would most benefit from trans-Atlantic and international cooperation, and to reflect on potential strategies and contributors for implementation. A second workshop, devoted to the preparation of the IRDiRC policy framework took place in Washington on 5-8 April 2011¹⁰⁶.

- **Committee for Orphan Medicinal Products' reviews of orphan designation made public**

The European Medicines Agency's Committee for Orphan Medicinal Products (COMP) started to publish summaries of the outcomes of the reviews for orphan designation carried out by the COMP whenever an orphan medicinal product reaches marketing authorisation. This review is carried out to check that the criteria underpinning a medicine's orphan designation still applies, and includes a discussion of the justification of significant benefit over existing authorised treatments. The first review was made public in September 2010 on the website of the EMA¹⁰⁷.

- **Increased collaboration between European Medicine's Agency and United States' Food and Drug Administration**

In February 2010, the European Medicines Agency (EMA) and United States' Federal Drug Administration (FDA) moved their collaborative efforts forward by introducing an agreement permitting one single annual report to be submitted for orphan products designated in both the EU and USA to avoid duplication of efforts. Prior to this, sponsors with designations in both areas were required to submit two separate reports detailing the progress of drug development. Each regulatory body will continue to conduct its own assessment of the reports filed in order to appraise whether information satisfies the legal and scientific requirements of each agency.

¹⁰² www.eucerd.eu

¹⁰³ <http://www.orpha.net/nectasso/EUCERD/upload/file/Meeting/EUCERD/EUCERDPublicSummaryReport101210.pdf>

¹⁰⁴ http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html

¹⁰⁵ http://ec.europa.eu/research/health/medical-research/pdf/reykjavik-workshop-report_en.pdf

¹⁰⁶ http://ec.europa.eu/research/health/medical-research/pdf/rare-diseases/event04/executive-summary_en.pdf

¹⁰⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_review/2010/09/WC500096728.pdf

- **Rare Diseases Day – 28 February 2010**

The third Rare Disease Day¹⁰⁸, organised by EURORDIS, the European Organisation for Rare Diseases, had as its theme “Bridging Patients and Researchers” and sought specifically to promote collaboration between patients and researchers and influence public policy and the European research agenda. A workshop was organised in Brussels, Belgium, on 1 March 2010 with this scope, inviting policy-makers, researchers, patient organisations and members of the industry to identify priorities and means for developing a collaborative framework for advancing research in the field of rare diseases. Thirty-five countries participated in Rare Disease Day 2010 from six different continents.

- **The European Conference on Rare Diseases – 13-15 May 2010, Krakow, Poland**

The 5th European Conference on Rare Diseases¹⁰⁹ held in Krakow, Poland (13-15 May 2010) brought together 600 international stakeholders. The event was organised by the EURORDIS and had as its main theme ‘From Policies to Effective Services for Patients’ with eight separate themes tackling different aspects of this topic, particularly relevant in considering the publication of the Council Recommendation on an action in the field of rare diseases in June 2009.

7.2. Key developments concerning national plans/strategies for rare diseases at Member State/country level

- **Austria**

In 2010, the working group elaborating the future national plan adopted the definition of the strategic priorities to be covered by the national plan.

- **Belgium**

In 2010, phase 1 of the recommendations and proposals were elaborated for the Belgian Plan for Rare Diseases, covering the following four central topics (1) diagnostics and treatment; (2) codification and inventory; (3) information, awareness and patient empowerment; and (4) access and cost.

- **Bulgaria**

The First National Conference for Rare Diseases in Bulgaria (28 to 30 May 2010), organised within the scope of the Europlan project, brought together stakeholders in order to discuss the provisions of the Bulgarian plan for rare diseases (2009-2013) and its implementation.

- **Cyprus**

It was announced on 28 February 2009 that in order to coordinate the best possible existing services for treating rare diseases, and to develop research activities, the Ministry would establish a National Committee for Rare Diseases and apply a strategic plan for rare diseases. The National Steering Committee has since been established and a draft national plan for rare diseases has been elaborated.

- **Czech Republic**

In October 2010, the Czech Republic released for the first time a ten-year strategy (2010-2020) for rare diseases. 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*. A Taskforce has been created which has established dedicated working parties with the aim of establishing the basis for the National Action Plan by 2013.

¹⁰⁸ <http://www.rarediseaseday.org/>

¹⁰⁹ www.rare-diseases.eu

- **Denmark**

On 19 November 2010, Rare Disorders Denmark in collaboration with Eurordis held a National Conference on Rare Diseases in the context of the Europlan project in order to discuss the elaboration of a national plan for rare diseases in Denmark.

- **Finland**

Finland participated in a project (which ran from 2009 to 2010) to publish a report concerning cooperation possibilities between Nordic countries in the field of rare diseases. The project came to the conclusion that cooperation with the Nordic countries should involve continuous exchange of experiences and knowledge of rare diseases through regular conferences and seminars, increasing cooperation with small separate projects in the field of rare diseases, and joint Nordic training in the field.

- **France**

The second French National Plan for Rare Diseases¹¹⁰ was elaborated during 2009-2010 and was launched on 28 February 2011 on the occasion of Rare Disease Day with a budget of €180 million. The ten axes of the first plan have been consolidated into 3 main axes: improve the quality of health care for rare diseases patients, develop research on rare diseases, and increase European and international cooperation in the field of rare diseases.

- **Germany**

The Federal Ministry of Health in Germany initiated a national action league for people with rare diseases - *Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen* (NAMSE) – in Berlin on 8 March 2010. NAMSE is a coordination and communication platform comprising all key bodies and organisations. This platform provides the basis for further concerted action, including the implementation of a National Action Plan on Rare Diseases. All partners, the major institutions and stakeholders of the German health care system, adopted a common declaration to improve the health situation for people with rare diseases in Germany.

- **Greece**

The provisions of the Greek National Plan for Rare Diseases (2008-2010) were discussed in detail during the Greek National Conference on Rare Diseases co-organised by the Greek Alliance for Rare Diseases (PESPA) and Eurordis, was held in Athens (26-27 November 2010) in the framework of the Europlan project.

- **Hungary**

At the Europlan national conference on rare diseases, organised by HUFERDIS on 18-19 October 2010 in Budapest, it was suggested that the issue of rare diseases should be adapted into the present, on-going reorganisation of the health care and social care system.

- **Ireland**

A National Planning Group of stakeholders has been established under the aegis of the Department of Health and Children to work on the development of a national plan, starting with a mapping exercise and focusing on the structure, governance and monitoring of a national strategy.

- **Italy**

An agreement was signed between the Government, the Regions and the special statute Provinces of Trento and Bolzano on the proposal of the Ministry of Labour, Health and Social Policy concerning guidelines for the correct use of bound resources by the special statute Regions and Provinces, as provided in art. 1, par. 34 and 34bis, Law dated 23 December 1996, n. 662, in order to implement the primary and nationally important objectives for year 2010, including the allotment of €20 million for rare diseases. On 11-13 November 2010 the Italian Federation for Rare Diseases (UNIAMO F.I.M.R ONLUS) in collaboration with EURORDIS organised a national conference on rare diseases in Florence in the context of the EUROPLAN project.

¹¹⁰ http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf

- **Latvia**
A working group including the Ministry of Health and specialists has been established with the aim of elaborating a national plan by 2013.
- **Lithuania**
The Ministry of Health Care is currently organising an interdisciplinary working group (including medical professionals, representatives of patient organisations, health care administrators) to develop a National plan for rare diseases.
- **Luxembourg**
A survey analysing the strengths and weaknesses of Luxembourg's healthcare system and the experience of rare disease patients was published on Rare Disease Day 2011. The Task Force on Rare Diseases Luxembourg will proposed a national plan based on the results.
- **Malta**
A Task Force for the implementation of the key requirements for Member States for the Council Recommendations on a European action in the field of rare diseases was set up in October 2010.
- **The Netherlands**
Following the adoption of the European Union Council Recommendation in June 2009, the Dutch government took no immediate initiatives to support a national plan/strategy for rare diseases. Therefore the Steering Committee on Orphan Drugs along with the Dutch Genetic Alliance VSOP and the Forum Biotechnology and Genetics (FBG), lobbied for a national plan to be put on the political agenda, and stated their intention at the Europlan National Conference on Rare Diseases (18-20 November 2010) to cooperate with stakeholders to prepare a national plan. Moreover, the Steering Committee on Orphan Drugs expressed their concerns about the preparation of a Dutch plan to the Minister of Health in December 2010.
- **Poland**
During the 5th European Conference on Rare Diseases in Krakow (13-15 May 2010) several patient organisations and health professionals signed the petition to the Polish Minister of Health requesting the government to initiate the works on the Polish National Plan for rare diseases. A National Conference on Rare Diseases was organised by the Polish Cystic Fibrosis Foundation MATIO and National Forum for the Therapy of Rare Diseases on 22 October 2010 in Krakow in the context of the Europlan project to discuss a broad European strategy for rare diseases and the recommendations of Europlan (see section "National rare disease events").
- **Portugal**
The first meeting of the implementation of National Plan on Rare Diseases was held on 25 January 2010 in order to schedule specific activities and to construct a work plan.
- **Romania**
In 2010 Romanian National Plan for Rare Diseases was elaborated and transmitted to the Health Ministry, and was included in the national strategy for 2011. The next step will be the implementation of the plan.
- **Slovak Republic**
After in depth discussions in 2010, a working group will be established at the start of 2011 at the Ministry of Health, composed of experts in the field of rare diseases to work on the "National plan for development of health care for patients with rare diseases ("NP RD SR"). The NP RD SR should be ready for the end of 2013.
- **Slovenia**
A working group for the development of a national strategy for rare diseases has been established and a draft national plan was discussed in 2010.

- **Spain**

The Europlan Spanish National Conference on Rare Diseases was held in Burgos at the Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias de Burgos (CREER) on 4-5 November 2010 in the context of the Europlan project.

- **Sweden**

In June 2010, the National Board of Health and Welfare presented a report concerning the organisation of national resources for rare diseases to the Ministry of Health and Social Affairs. The government decided to establish a national focal point for coordination in the field of rare diseases, a €300,000 project. The focal point will coordinate rare disease efforts and disseminate knowledge and information within and between health services, NGOs and other stakeholders. The National Board of Health and Welfare is currently finalising the specifications for the national focal point. The decision to establish a national focal point represents an important step towards a better use of the resources available for patients with rare diseases and the patients' relatives.

- **United Kingdom**

A UK National Conference on Rare Diseases, organised by RDUK and Eurordis in the context of the Europlan conference, took place on 16 November 2010 in Manchester (see section on National rare disease events) to examine proposals for a plan.

- **Croatia**

The Ministry of Health and Social Care established the National Commission for Rare Diseases in May 2010 in order to elaborate a National Plan for Rare Diseases. This Committee includes three representatives of civil organisations for rare diseases. The First National Conference on Rare Diseases (17-19 September 2010), organised within the scope of the Europlan conference, allowed stakeholders to meet and discuss priorities for the plan.

- **Norway**

In 2010 the Ministry of Health requested a report on how to reorganise the centres for rare disorders under one administration. The working group led by the Directorate of Health delivered the report on 1 December 2010. The recommendations are supported by the Directorate and the Ministry's approval is expected in 2011.

- **Switzerland**

On 16 December 2010, Ruth Humbel, member of the Health Commission in the Parliament, submitted to the Federal Parliament a postulate for "a national strategy for improving the health situation of people with rare diseases". The decision of the Federal Parliament and the National Council will be announced at the beginning of 2011.

- **Turkey**

In 2010, the Turkish Ministry of Health considered collaboration with Orphanet Turkey in specific projects for the establishment of a National Plan for Rare Diseases and a number of were organised amongst professionals in Turkey in the context of the Europlan project of which Turkey is a collaborating partner. The recognition of a national plan is mandatory for assigning priority actions for rare diseases. Under the "National Health Transformation Programme" the Ministry of Health has suggested developments in medicinal product use, medical and social care, surveillance and other relevant actions.

More detailed information concerning the state of the art of rare diseases activities at European Union and Member State level is available in Parts II and III of this report.

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¹¹² Disclaimer: the European Commission is not responsible for the completeness and correctness of the information included in this report.

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http://ec.europa.eu/health/ph_threats/non_com/docs/rare_spain.pdf
- CISATER – Information Centre for Rare Diseases
http://iier.isciii.es/er/html/er_noant.htm
- IIER – Research Institute for Rare Diseases
<http://www.isciii.es/hdocs/index.jsp>
- FEDER – Spanish Rare Disease Alliance
<http://www.enfermedades-raras.org/>
- Europlan Spanish National Conference Final Report
http://download.eurodis.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/en/rarediseases>
- Agrenska
<http://www.agrenska.se/en/>
- National Quality Register
<http://www.kvalitetsregister.se/>
- Rare Diseases Sweden
<http://www.sallsyntadiagnoser.se/>
- Europlan Swedish National Conference Final Report
http://download.eurodis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/FINAL%20Report_Sweden%20EUROPLAN%20NC%202010.pdf

Switzerland

- Swiss Telethon
<http://www.telethon.ch/>
- Gebert RUF Stiftung Foundation
<http://www.grstiftung.ch/en.html>
- Proraris
www.proraris.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>

United Kingdom

- National Commissioning Group
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>
- Genetic Interest Group

- <http://www.gig.org.uk/>
- Rare Disease UK
<http://www.raredisease.org.uk/>
- Contact A Family
<http://www.cafamily.org.uk/index.php?section=861>
- Europlan UK National Conference Final Report
http://download.eurordis.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_uk_europlan.pdf

3. OTHER DOCUMENTS

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>

Rare Disease Day

<http://www.rarediseaseday.org>

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