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

PART I: OVERVIEW OF RARE DISEASE ACTIVITIES IN EUROPE

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

More information on the activities of the former European Union Committee of Experts on Rare Diseases and the EUCERD Joint Action can be found at www.eucerd.eu.

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ACRONYMS

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

GENERAL INTRODUCTION

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

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

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

The report is split into six parts:

Part I: Overview of rare disease activities in Europe
Part II: Key developments in the field of rare diseases in 2013
Part III: European Commission activities in the field of rare diseases
Part IV: European Medicines Agency activities and other European activities in the field of rare diseases
Part V: Activities in EU Member States and other European countries in the field of rare diseases
Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

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

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

INTRODUCTION: OVERVIEW OF RARE DISEASE ACTIVITIES IN EUROPE

Rare diseases

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, estimated as affecting between 6% and 8% of the population in the course of their lives. In other words, although rare diseases are characterised by low prevalence[1] for each of them, the total number of people affected by rare diseases in the EU is estimated at between 27 and 36 million. Most of them suffer from less frequently occurring diseases affecting one in 100 000 people or less. These patients are particularly isolated and vulnerable. The definition of a rare disease as having a prevalence of not more than 5 in 10 000 first appeared in EU legislation in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products[2]. 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 November 2008)[3] and the Council Recommendation on an action in the field of rare diseases (08 June 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 overview report concerning the state of activities at Member State level concerns the state of activities at the end of the year 2013 unless otherwise stated.

Rare cancers

Rare cancers are rare diseases and the problems associated with rare diseases also apply to rare tumours but there are also some specificities. Although in principle, rare cancers should be defined in the same way as rare diseases, prevalence varies greatly depending on life expectancy, thus experts in the field consider incidence to be a more useful indicator when selecting a threshold for rarity for tumours. A suggested threshold for rarity in

[1] For a list of rare diseases and their prevalence, please consult the Orphanet Reports Series "Prevalence of rare diseases: Bibliographic data", Orphanet Report Series, Rare Diseases collection, Number 1 : Listed in alphabetical order of diseases, http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

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

[3] http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

terms of incidence is less than 6 out of 100 000 persons per year[4]. However, as far as the EU Regulation on Orphan Medicinal Products is concerned, the threshold applied to rare cancers is the same as for rare diseases, i.e. a prevalence of not more than 5 in 10 000 persons. Currently 40% of all orphan medicinal products with market authorisation are for rare cancers[5].

There are a number of initiatives in the field of rare cancers at European level as the significant problem of rare cancers (representing around 22% of new cancers diagnosed every year according to the definition above based on incidence[6]) needs particular coordination.

The European Commission adopted on 24 June 2009 a Communication on Action Against Cancer[7] and created a European Partnership on action against cancer (EPAAC). The Communication refers explicitly to the EU added-value that will represent cooperation on European Reference Networks, taking the example of rare diseases.

The European Partnership on action against cancer (EPAAC)[8], brings together the efforts of different stakeholders into a joint response to prevent and control cancer. In its initial phase, until early 2014, the work of the Partnership is being taken forward through a Joint Action. Following the proposed actions outlined by the Commission, the EPAAC Joint Action has set itself a broad range of goals across different areas of cancer prevention and control: health promotion and cancer prevention, including screening, identification of best practice in cancer-related healthcare, the collection and analysis of comparable data and information and a coordinated approach to cancer research. The Joint Action contributes to the long-term aim of reducing cancer incidence by 15% by 2020, and to the objective that all Member States have integrated cancer plans by the end of the Partnership. The EUCERD Joint Action is also working on common areas for collaboration in the field of rare cancers with the future EPAAC Joint Action, notably in the areas concerning information and data, and measures for rare cancers are often included in National cancer plans rather than in National rare disease plans.

Two projects have been funded by the European Commission concerning rare cancers :

- RareCare[9] (2007-2010) Surveillance of Rare Cancers in Europe, was aimed at estimating the burden of rare cancers in Europe. It provided cancer burden indicators (incidence, survival, prevalence and mortality). The sources of this data were population-based cancer registries;
- RareCareNet[10], starting on 1 May 2012 builds on the experience of the previous project RareCare and, in collaboration with Rare Cancers Europe and many other stakeholders RareCareNet aims at building an information network to provide comprehensive information on rare cancers to the community at large (oncologists, general practitioners, researchers, health authorities, patients and their families).

In addition, the Rare Cancers Europe[11] group is a partnership of cooperating organisations that work together to place the issue of rare cancers on the European policy agenda, to identify and promote appropriate solutions and to exchange best practice.

At National level, some countries (such as France, for example) have already developed national plans for cancers which specificially mention actions concerning rare cancers. The development of such plans is being promoted by the EPAAC.

[4] Gatta et al, "Rare cancers are not so rare: the rare cancer burden in Europe", European Journal of Cancer 2011 Nov;47(17):2493-51, http://www.ncbi.nlm.nih.gov/pubmed/22033323
[5] Source : Committee on Orphan Medicinal Products, see Section 4.1 of this part of the report.
[6] Gatta et al, "Rare cancers are not so rare: the rare cancer burden in Europe", European Journal of Cancer 2011 Nov;47(17):2493-51, http://www.ncbi.nlm.nih.gov/pubmed/22033323
[7] http://ec.europa.eu/health/ph_information/dissemination/diseases/docs/com_2009_291.en.pdf
[8] http://www.epaac.eu/
[9] http://www.rarecare.eu/
[10] http://www.rarecarenet.eu/rarecarenet/
[11] http://www.rarecancerseurope.org/

1. Political framework

Since the 1990s at both European Union (EU) and Member State (MS) level political concepts and initiatives concerning rare diseases have emerged (Figure 1). Indeed, a number of countries led the way in the decade leading up to the first European legislative text concerning rare diseases, the Orphan Medicinal Product Regulation of 16 December 1999[12], and the ensuing Commission Communication (2008) and Council Recommendation (2009). Sweden, for example established the first centres of expertise for rare diseases in 1990 and a rare disease database and information centre in 1999; Denmark established an information centre in 1990 and then centres of expertise for rare diseases in 2001; in Italy, a decree on rare diseases came into force in 2001; and in France, Orphanet was established in 1997 with the support of the French Ministry of Health as the portal for information on rare diseases and orphan medicinal products, followed by the first national plan/strategy for rare diseases in Europe (2004). A number of other countries (Bulgaria, Greece, Portugal and Spain) elaborated a national plan/strategy for rare diseases at the very same time as EU policy in the field was defined through the Commission Communication and Council Recommendation. By the end of 2013, it can be observed that policy at Member State level is gathering momentum in the wake of EU policy, in particular the elaboration of national plans or strategies for rare diseases, in response to the recommendation of the Council to "elaborate and adopt a plan or strategy as soon as possible, preferably by the end of 2013 at the latest, aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems[13]": 16 countries had adopted a plan/strategy by the end of 2013.

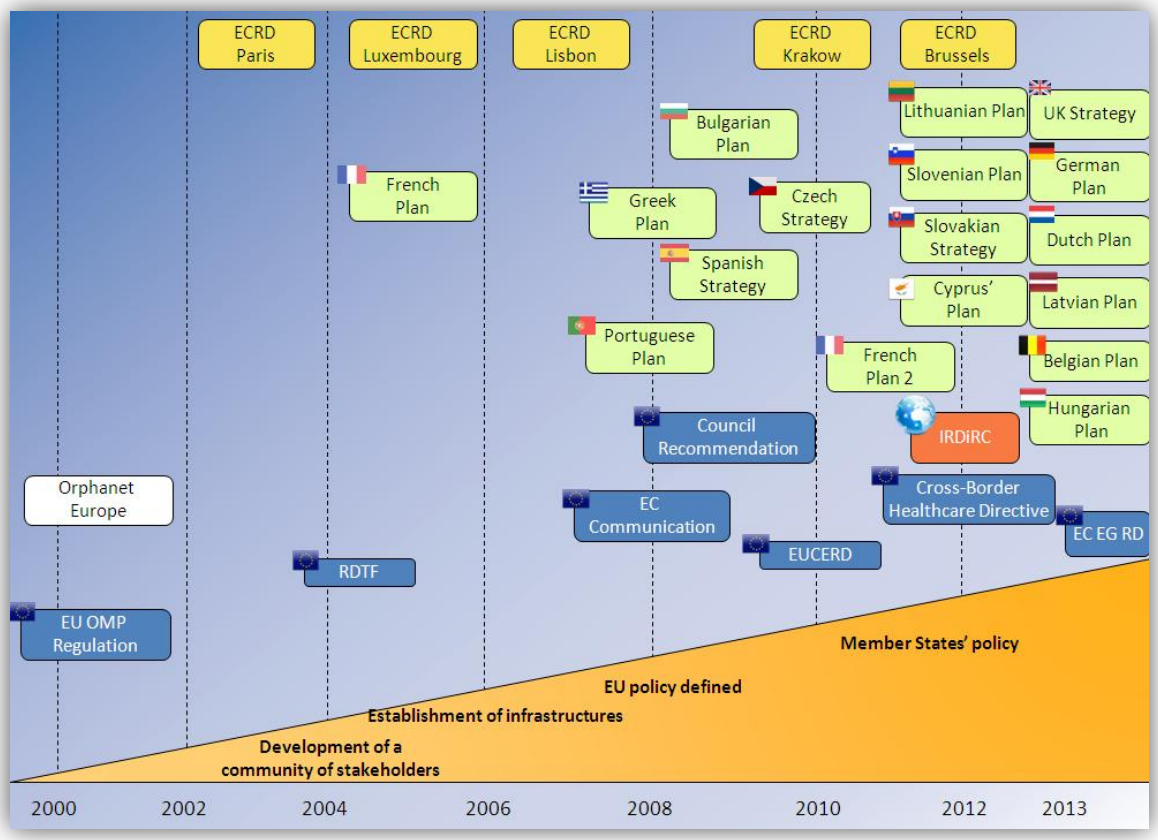

Figure 1: Emergence of concepts and initiatives surrounding rare diseases in Europe (December 2013)[14&15]

[12] http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
[13] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
[14] ECRD – European Conference on Rare Diseases
[15] Graphic courtesy of the EUCERD Joint Action Scientific Secretariat.

1.1. Political framework at European level

1.1.1. Key policy documents

At European level, there are currently four 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)**[16] was proposed to set up the criteria for orphan designation in the EU and describes the incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) to encourage the research, development and marketing of medicines to treat, prevent or diagnose rare diseases. The Regulation provides that a medicinal product can be designated as an 'orphan medicinal product' when intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10 000 persons in the Community when the application is made, and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition. This EU policy for orphan medicinal products has been heralded as a success (see section 4.1). Despite the efforts of Member States to ensure access to orphan medicinal products, not all Member States currently ensure full access to each authorised orphan medicinal product approved.

b) **The Commission Communication on Rare Diseases: Europe's challenge**[17], 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**[18] 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.

[16] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF
[17] http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
[18] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

The seven key themes of the Council Recommendation are:

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

The European Commission will publish in 2014 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)**[19] was formally established via the **European Commission Decision of 30 November 2009 (2009/872/EC)**[20] (see Section 1.1.1.1.).

The European Commission also funded the European Project for Rare Diseases National Plans Development (EUROPLAN[21]) between 2008-2011. The main goal of the project was to provide National Health Authorities with supporting tools for the development and implementation of National Plans and Strategies for rare diseases as recommended by the Council. The supporting tools included a Guidance document on recommendations for the definition and implementation of National Plans and Strategies for rare diseases[22]; a joint report with the RDTF on initiatives and incentives in the field of rare diseases in Europe[23]; and a document on the recommended set of indicators for monitoring and evaluating the implementation of national initiatives[24]. In the context of the EUROPLAN project, national conferences and workshops on the subject of national plans and strategies, took place throughout 2010 in 15 EU MS: these national conferences were organised by National Alliances of rare disease patient organisations under the supervision of EURORDIS. The conferences aimed both to raise awareness of the Council Recommendation and to move forward the process of developing a national strategy for rare diseases in each particular country. The support

[19] The EUCERD www.eucerd.eu replaces the European Commission's Rare Diseases Task Force www.rdtf.org (2004-2009).
[20] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:315:0018:0021:EN:PDF
[21] http://www.europlanproject.eu/
[22] http://www.europlanproject.eu/_newsite_986989/Resources/docs/2008-2011_2.EuroplanRecommendations.pdf
[23] http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf
[24] http://www.europlanproject.eu/_newsite_986989/Resources/docs/2008-2011_3.EuroplanIndicators.pdf

activities of Europlan will continue in the context of the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01 from March 2012 for a 3 year period.

d) **Directive 2011/24/EU on the application of patients' rights in cross-border healthcare**[25], was approved in early 2011 to coincide with Rare Disease Day (28 February 2011). Highly relevant to rare disease patients suffering from scarce and scattered resources for care and diagnostics, the Directive seeks to facilitate access to health care for EU citizens and encourage cooperation between EU Member States in the field of health. Member States will have 30 months to put the provisions of the Directive into national legislation following the publication in the Official Journal of the European Union. The Directive will have no impact on the rights of each Member State to determine which health benefits they will provide. Thus, if a particular treatment is not reimbursed in a patient's home country, it will not be reimbursed if accessed in another Member State. Member States would be able to require prior authorisation for "hospital care" and reimbursement would match the amount that patients would receive in their home country. However, Article 13 of the Directive specifically addresses the commitment of the Commission on behalf of rare disease patients: *"The Commission shall support Member States in cooperating in the development of diagnosis and treatment capacity in particular by aiming to:*

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

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

The focus from 2012 was the implementation of the Directive, led by the Committee on Cross-Border Healthcare, a legal forum where all 27 Member States met discuss general issues concerning the transposition of the directive. On 10 March 2014, two Decisions on European Reference Networks (ERNs) were adopted by the European Commission. In the *Commission Delegated Decision setting out criteria and conditions that European Reference Networks and healthcare providers wishing to join a European Reference Network must fulfil*[26] the certain criteria that a European Reference Network should fulfil in order to efficiently deal with the needs of the patients are outlined. Overall, according to the criteria outlined by the European Commission, European Reference Network should:

- Have the knowledge and expertise to diagnose, follow-up and manage patients with evidence of good outcomes, as far as applicable;
- Follow a multi-disciplinary approach;
- Offer a high level of expertise and have the capacity to produce good practice guidelines and be able to implement outcome measures and quality control;
- Contribute towards research and development;
- Arrange teaching and training activities;
- Work in partnership with other centres of expertise and networks at national and international level.

The accompanying *Implementing Decision*[27] lays down the procedure on how to establish and evaluate the ERNs. Both Decisions are expected to enter into force by the end of May 2014, at the expiry of the two-month period for possible objection to the Delegated Decision by the European Parliament and the Council.

1.1.1.1. The European Union Committee of Experts on Rare Diseases (EUCERD) (2010-2013)

The European Union Committee of Experts on Rare Diseases (EUCERD) was 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

[25] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF
[26] http://ec.europa.eu/transparency/regdoc/rep/3/2014/EN/3-2014-1408-EN-F1-1.Pdf
[27] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2014_147_R_0007

stakeholders acting in the field. The EUCERD fosters exchanges of relevant experience, policies and practices between these parties. The EUCERD was 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 were supported by Joint Action N° 2008 22 91 (Support to the Scientific Secretariat of the RDTF/EUCERD) until February 2012 and are supported by the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01 as of March 2012. The EUCERD Joint Action[28] aims to advance the work of the EUCERD in the areas of:

- Plans and strategies for rare diseases at national level[29];
- Standardisation of rare disease nomenclature at international level[30];
- Specialised social services and integration of rare diseases into mainstream social policies and services[31];
- Quality of care for rare disease[32]s;
- Integration of RD initiatives across thematic areas and across Member States[33].

The EUCERD held two meetings in 2013 in Luxembourg on 31 January – 1 February 2013[34] and 5-6 June 2013[35] (its last meeting). A range of topics were discussed over the year including European Reference Networks, patient registries and databases for rare diseases National Plans and Strategies for Rare Diseases, the activities of the EUCERD Joint Action, Newborn Screening Practices in Europe, and ways to collaborate with other EU initiatives in the field.

In 2013 a number of workshops were held with the support of the EUCERD Joint Action: Workshop on Key indicators for national plans/strategies workshop (25 March 2013, Rome), Workshop on training of social service providers (10-11 October 2013, Copenhagen), and Workshop on registries for rare diseases and the European registry platform (22-23 April 2013, Luxembourg).

To mark Rare Disease Day 2014, an editorial was published in Orphanet Journal of Rare Diseases highlighting the achievements of the EUCERD, entitled "The European Union Committee of Experts on Rare Diseases: three productive years at the service of the rare disease community"[36] .

Three sets of recommendations were adopted by the EUCERD in 2013. The first set was the EUCERD Recommendations on European Reference Networks for Rare Diseases[37]. The recommendations were elaborated by the Committee to feed into the work of the Cross-Border Healthcare Expert Group. European Reference Networks (ERNs) are one of the structures foreseen by the Directive to share knowledge, facilitate the mobility of expertise, and to allow Member States to provide highly specialised services of high quality for patients where this would have been impossible without

[28] http://www.eucerd.eu/?page_id=54
[29] http://www.eucerd.eu/?page_id=280
[30] http://www.eucerd.eu/?page_id=282
[31] http://www.eurordis.org/fr/specialised-social-services
[32] http://www.eucerd.eu/?page_id=284
[33] http://www.eucerd.eu/?page_id=287
[34] http://www.eucerd.eu/wp-content/uploads/2013/03/EUCERD7_ExecutiveSummary.pdf
[35] http://www.eucerd.eu/wp-content/uploads/2013/07/8EUCERD_ExecutiveSummary.pdf
[36] http://www.ojrd.com/content/9/1/30
[37] http://www.eucerd.eu/?post_type=document&p=2207

European networking, such as in the case of rare diseases. Member States are also encouraged in the Council Recommendation on an action in the field of rare diseases (8 June 2009) to help foster the participation of centres of expertise in these ERNs. The EUCERD has already elaborated recommendations concerning centres of expertise for rare diseases which describes how these centres could participate in such networks. The recommendation is addressed to the European Commission and the Member States and includes 21 individual recommendations covering a range of aspects including the mission, vision and scope of ERNs, their governance, their composition, their funding and evaluation, as well as their designation.

The second set of recommendations was the EUCERD's Core Recommendations on Rare Disease Patient Registration and Data Collection[38]. Rare disease registries are valuable instruments for increasing knowledge on rare diseases, and for supporting fundamental, clinical and epidemiological research, as well as for post-marketing surveillance of orphan medicinal products and medicines used off-label. This data is also crucial for the planning of healthcare services. The recommendation calls for the international operability of registries and databases and use of appropriate coding systems to enable the necessary pooling of data for public health and research purposes, gives advice concerning the establishment of registries and collection of data, highlights the various uses of patient data and how to best share this information, underlines the importance of adherence to good practice guidelines in the field, stresses the need for registries to be adaptable to meet future needs, and emphasises the importance of sustainability for the timespan of the registry's utility.

The third set of recommendations adopted was the EUCERD's Recommendation on Core Indicators for National Plans/Strategies for Rare Diseases[39] . This recommendation provides a list of 21 indicators which are intended to capture relevant data and information on the process of planning and implementing of these plans and strategies on a regular basis. These indicators could provide information notably to the European Commission on the implementation of the Council Recommendation on an Action in the field of Rare Diseases (June 2009) which encourages Member States to establish a national plan or strategy in the field by the end of 2013. They will also serve as a basis for the elaboration of indicators at national level tailored to the specific actions foreseen in the plans/strategies. This set of recommendations will be revised in the future to take into account the experiences of the Member States.

The EUCERD also issued in July 2013 an Opinion on Potential Areas of Collaboration in the Field of Newborn Screening[40] to the European Commission, the Member States and third parties for further consideration.

The mandate of the EUCERD ended in July 2013 and from 2014 onwards was replaced by **the European Commission Expert Group on Rare Diseases**[41].

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 were one of the priorities in the **Second Programme of Community Action in the Field of Health 2008-2013**[42]. 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.

[38] http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf
[39] http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf
[40] http://www.eucerd.eu/wp-content/uploads/2013/07/EUCERD_NBS_Opinion_Adopted.pdf
[41] http://ec.europa.eu/health/rare_diseases/expert_group/index_en.htm
[42] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF

The **Third Programme of Community Action in the Field of Health 2014-2020**[43] entitled **Health for Growth** also cites rare diseases as a priority.

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 previous Framework Programme (FP7 2007-2013[44]) 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. FP7 is succeeded by Horizon 2020[45] the new Framework Programme covering the period 2014-2020: calls related to the field of rare diseases have already been launched at the end of 2013 in the context of this financial instrument. More information on the Framework Programmes is provided in section 3.1.2.

1.2. Political framework at Member State level

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

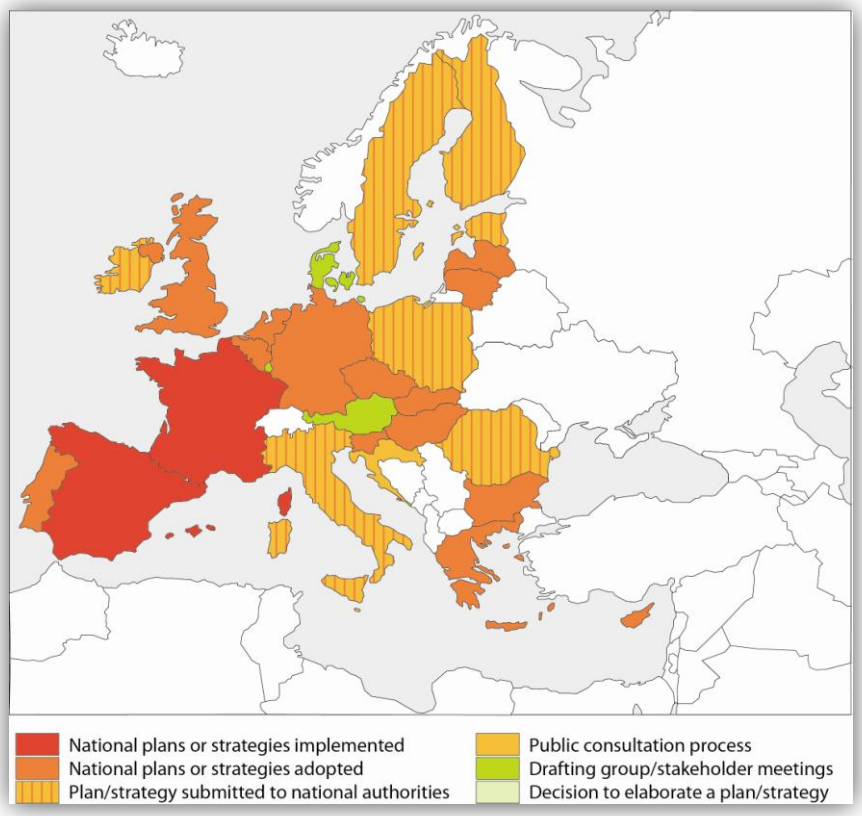

Figure 2a: Stages of development of national plans or strategies for rare diseases in EU MS (December 2013) [46]

[43] http://eur-lex.europa.eu/legal-content/EN/TXT/;jsessionid=5Qj3TvyCyBqbhfLZzzBttjDGh3gyXkQWYrjhrt36mChMJJlp02XX!2060916514?uri=uriserv:OJ.L_.2014.086.01.0001.01.ENG

[44] http://cordis.europa.eu/fp7/home_en.html

[45] http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-establact_en.pdf

[46] Graphic courtesy of the EUCERD Joint Action Scientific Secretariat.

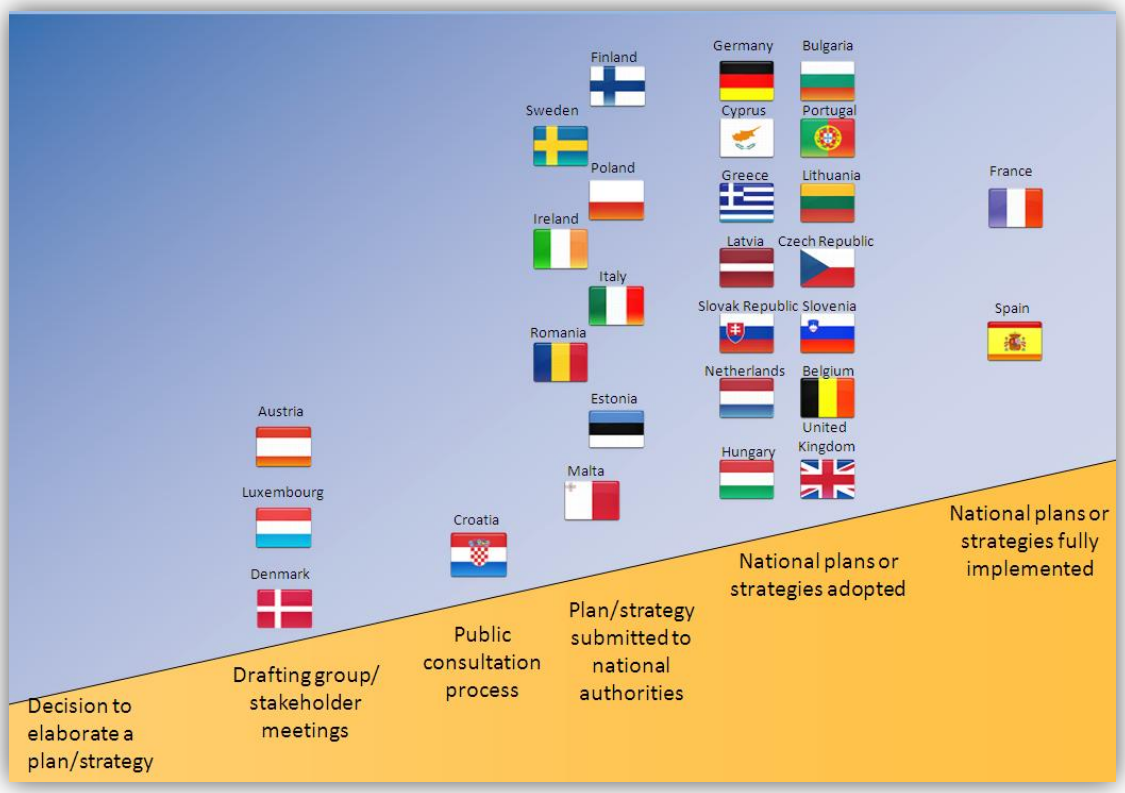

Figure 2b: Stages of development of national plans or strategies for rare diseases in EU MS in December 2013[47]

a) Countries with adopted plans/strategies in 2013

Sixteen Member States had, by the end of 2013, officially adopted a national plan/strategy for rare diseases: Belgium, Bulgaria, Czech Republic, Cyprus, France, Germany, Greece, Hungary, Lithuania, Latvia, the Netherlands, Portugal, Slovenia, Slovakia, Spain and the United Kingdom. By mid-2014 Ireland, Malta and Romania had also adopted a plan/strategy.

These plans/strategies vary in their scope and also their financing, which will ultimately influence the extent of their impact at national level. Belgium, Czech Republic, Cyprus, Germany, Greece, Hungary, Lithuania, Latvia, Netherlands, Portugal, Slovenia, Slovakia, the United Kingdom have adopted their plans/strategies but the level of implementation is highly heterogenous: indeed, in certain countries plans/strategies are still to be detailed in concrete work plans, some countries have adopted a plan/strategy but not yet a budget for the detailed actions, whereas other countries have started to implement elements their plans/strategies. Bulgaria has implemented elements of their plans/strategies and the results are being assessed. France and Spain have fully implemented their national plans for rare diseases and assessed the results.

i. France

France was the first EU country to adopt, at the end of 2004, a comprehensive rare disease plan[48] with allocated funding. This first plan (2005-2008) included 10 objective s:

- Increase knowledge of the epidemiology of rare diseases;
- Recognise the specificity of rare diseases;
- Develop information on rare diseases for patients, health professionals and the general public;
- Train health professionals to better identify rare diseases;

[47] Graphic courtesy of the EUCERD Joint Action Scientific Secretariat.
[48] http://www.orpha.net/actor/EuropaNews/2006/doc/French_National_Plan.pdf

- Organise screening and access to diagnostic tests;
- Improve access to treatment and quality of healthcare provision for patients;
- Continue efforts in favour of orphan medicinal products;
- Respond to the specific needs of accompaniment of patients suffering from a rare disease and develop support for patient organisations;
- Promote research and innovation on rare diseases, in particular on treatments;
- Develop national and European partnerships in the domain of rare diseases.

The second French National Plan for Rare Diseases[49] was elaborated during 2009-2010 by the Ministry of Health with the collaboration of the Ministry of Higher Education and Research from the results of the evaluation of the first plan and from the conclusions of seven working groups, which had gathered during 34 meetings 184 representatives of health professionals, rare disease experts, researchers, patient organisations and administration. The second plan was launched on 28 February 2011 on the occasion of Rare Disease Day, with a budget of €180 million for the period 2011-2014.

The ten objectives of the first plan have been consolidated into three main objectives:
- Improve the quality of care for rare disease patients;
- Develop research on rare diseases;
- Amplify European and international cooperation in the field of rare diseases.

These three objectives encompass actions such as:
- Quality assessment and networking of the existing French Reference Centres;
- Improvement of access to genetic diagnosis;
- Development of neonatal screening of rare diseases;
- Proper use and facilitated access to drugs, orphan medicinal products and any other medical product necessary for patients;
- Information and training of health professionals;
- Information for patients;
- Strengthening of research.

The second plan includes 15 measures and 47 specific actions. The key measures of the plan are:
- Creation of a Foundation for Scientific Cooperation on Rare Diseases (called the *"Fondation maladies rares"*[50]) to coordinate and facilitate research on rare diseases;
- Creation of a National Rare Disease Database (called *"Banque nationale de données maladies rares*" - BNDMR) to allow mapping of patients' needs and delivered healthcare, and to facilitate their recruitment for clinical and epidemiological studies and clinical trials. The national registry BNDMR will be based on the collection of a minimum data set, common to all patients and rare diseases and all the reference and regional centres;
- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature for the patients' follow-up;
- Access to next-generation sequencing (NGS) technology for genetic diagnosis. Most of the French academic laboratories will be equipped at the end of the second year of the plan with NGS facilities to optimise genetic diagnosis of a large set of rare diseases. Various levels of NGS will be implemented during the plan for speeding up and maximal diagnosis coverage;
- Restructuring of rare disease reference and regional centers into a limited number (around twenty) of coherent "national clinical networks" (called *"filières de santé maladies rares"*), gathering all rare disease relevant stakeholders and centered on a homogeneous group of diseases. These networks aim to allow a better and easier orientation of patients towards appropriate diagnosis, treatment, social care and follow-up. These future French clinical networks should be connected to the future European Reference Networks (ERN) concerning rare diseases.
  The additional actions foreseen in the plan to improve the quality of care are:
- Creation of a "permanent working group" for the monitoring of Reference Centres and the future national clinical networks;

[49] http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares.pdf
[50] The "Fondation maladies rares" was created on 6 February and launched officially on 29 February 2012: http://www.fondation-maladiesrares.org

- Measures to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed outside of their marketing authorisation;
- Enhancement of rare disease clinical practice guidelines ("PNDS") development;
- Training of medical doctors and paramedical professionals;
- Better coordination of health care and social care;
- Improvement of information for rare disease patients supporting Orphanet and *Maladies Rares Info Service* and the creation of a European unique number for rare disease help lines.

The implementation and follow-up of plan is the mission of a dedicated Steering Committee (called the *"Comité de suivi et de prospective"*) which held its first meeting on 19 May 2011 and meets at least once a year. Five thematic working groups reporting to the Steering Committee were established to help implement the plan. These include a "permanent working group" dedicated to the definition of a new evaluation process for Reference Centres and the monitoring of Reference Centres and their future networks. The Steering Committee is in charge of the follow up of the plan and its implementation according to schedule, the effective involvement of relevant bodies and institutes in the implementation, and surveying new methods of diagnosis, prevention, treatment and care for patients with rare diseases which would justify the adaptation of the plan during its progress.

ii. Portugal

On 12 November, 2008, the Portuguese Minister of Health approved a national plan for rare diseases for Portugal, the "*Programa Nacional de Doenças Raras*[51]" coordinated, since November 2011, by the Department for Quality in Health at the Directorate-General of Health (*DGS*).

The two main objectives of the National Plan are:

1) to create and improve the national measures in order to satisfy the needs of people with rare diseases and their families in regards to medical services and care;

2) to improve the quality and the equity of the health care measures provided to people with rare diseases.

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 and awareness on rare diseases;
- Promoting innovations in the treatment of rare diseases and accessibility of orphan medicinal products;
- Assuring cooperation at national and international level, including the countries in the EU and the community of countries with Portuguese as their official language.

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

This Plan covered all rare diseases, though it should articulate with other prioritary national plans, namely with the National Plan for Oncologic Diseases *("Programa Nacional para as Doenças Oncológicas"*).

An important step in terms of implementing the National Plan for Rare Diseases took place in 2012: a specific card for the identification of people with rare diseases ("*Cartão para a Pessoa com Doença Rara*") was developed, aiming at disclosing clinical information to medical doctors and also in emergency situations. This card issued by *DGS,* is currently being distributed.

A new Integrated Strategy for Rare Diseases 2014-2020 is currently being finalised, which replaces the previous Programme and aims to ensure that people with rare diseases have better quality of care, based

[51] http://ec.europa.eu/health/ph_threats/non_com/docs/portugal.pdf

on the evidence that science has been producing, as well as greater celerity and variety of social responses adapted to each case. This new strategy further aims to guarantee that, in an inter-ministerial, inter-sectoral, inter-institutional and integrated way, priorities in the global approach to rare diseases be refocused, bringing together the contributions of competences and resources of all relevant sectors, in order to cause, in a progressive way, a real change in the complex conditions of the people who suffer from these diseases.

iii. Greece

An outline for this National Plan of Action for Rare Diseases (to run over the period 2008-2012[52]) 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.

Although an initial estimate for the budget required was made, no funding was officially allocated to the National Plan of Action for Rare Diseases. There is no legal framework for the Plan.

In 2010 the Advisory Scientific Committee for Rare Diseases appointed by KEELPNO together with the office for RD of KEELPNO started to implement the main priorities of national plan for RD that are incorporated in the Greek NHS. The program started in 2011 with two main objectives: i) to develop a national registry of rare diseases and ii) to identify the expertise centres (CEs) involved in the care of patients with rare diseases, within the Greek National Health System (NHS).

In November 2012 a Steering Committee for Rare Diseases was appointed by the General Secretary of the Ministry of Health to review and supplement the plan proposed during the Europlan national conferences and submit it to the Ministry for discussion, adoption and implementation. This Commitee was recently replaced by another one which has not yet started work.

iv. 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 lasted for 5 years. The Plan consists of nine priorities targeting all rare diseases:

- Collection of epidemiological data for rare diseases in Bulgaria by creation of a national register;
- Improvement of the prevention of genetic rare diseases by enlarging the current screening programmes;
- Improvement of the prevention and diagnostics of genetic rare diseases by introducing new genetic tests, decentralisation of the laboratory activities and easier access to medico-genetic counselling;
- Integrative approach to the prevention, diagnostics, medical treatment and social integration of patients and their families;
- Promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases;

[52] http://www.ygeianet.gov.gr/HealthMapUploads/Files/SPANIES_PATHISEIS_TELIKO_LOW.pdf

- Feasibility study on the necessity, possibility and criteria for the creation of a reference centre for rare diseases of functional type;
- Organisation of a national campaign to inform society about rare diseases and their prevention;
- Support and collaboration with NGOs and patient associations for rare diseases;
- Collaboration with the other EU members.

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

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

v. Spain

The Rare Diseases Strategy of the Spanish National Health System was approved by the Interterritorial Council of the Spanish NHS on 3 June 2009[53]. 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 Rare Diseases Strategy of the Spanish National Health System represents a consensus between the Ministry of Health, Social Services and Equality, the Carlos III Health Institute, Autonomous Communities, patient organisations, scientific societies and experts.

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 third part, Monitoring and Evaluation, sets out the process that makes it possible to monitor the proposed actions.

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

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

Given the decentralised health administration of Spain in Autonomous Communities, the Strategy will act as a framework and a set of recommendations for the different regions, which will in turn be in charge of implementation.

[53] http://www.msc.es/organizacion/sns/planCalidadSNS/docs/enfermedadesRaras.pdf and http://www.msc.es/organizacion/sns/planCalidadSNS/docs/RareDiseases.pdf

Funds are allocated through a call for proposals opened to the Autonomous Communities in order to facilitate the implementation of the Strategy. The Strategy for Rare Diseases as well as any other related measures or actions aimed at rare diseases are included in the Spanish National Health Budget.

The first strategy assessment focused mainly on the implementation of the Strategy over the first two years, although it is too soon to measure health related results, this process helped to update recommendations and objectives after consultation with the Stakeholders.

The main achievements have been, amongst others: the establishment of the National Registry for Rare Diseases, availability of an inventory of services and tests of prenatal diagnosis and derivation protocols for pregnant women at risk or foetal RD, to raise awareness and recognition of rare diseases, and to promote socio-health care and research for children under three with rare diseases. Moreover, the evaluation has also showed that it is necessary to implement actions aimed at collecting and disseminating information and resources available on rare diseases, to increase training of primary care professionals on suspected diagnosis of rare diseases and to establish adequate criteria for referral, to improve the availability of basic health information to the teaching staff that attends children with rare diseases, to develop initiatives of joint coordination and planning for the adaptation of jobs and for the management of the reintegration and continued employment of family members of persons affected by rare diseases, to carry out initiatives to facilitate keeping persons with rare diseases in their surroundings such as home care services, home hospitalisation, day centres, and so on, to develop integration activities in the community (leisure activities) for those with rare diseases, and to promote participation of patients associations in participation-decision bodies in the area of health of the Regional Governments.

vi. Czech Republic

In October 2010, the Czech Republic released for the first time a ten-year strategy[54] (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"*.

A dedicated taskforce comprised of leading rare diseases experts, biotech industry, lawyers, the State Institute for Drug Control, medical statisticians and health insurance representatives, has convened every other month since late 2010 and established dedicated working parties with the aim to establish the basis for the National Action Plan. The Czech National Plan for Rare Diseases for 2012-2014[55], was adopted via Decree 633 by the Czech government on 29 August 2012. The plan delineates concrete actions identified in the 2010-2020 Czech National Strategy. Specific areas include: Improving information; Education; Prevention; Improving screening and diagnosis; Improving the availability and quality of care; Improving quality of life and social inclusion; Support for rare disease science and research; Unification and development of data collection and rare disease biological samples; Supporting and strengthening patient organisations; Interdepartmental and interdisciplinary collaboration; and International cooperation. Besides diagnostics and treatment, the Czech National Plan encompasses research, public information, training for health professionals (both paediatric and adult specialists), and quality of life for patients in collaboration with the Ministry of Social Affairs. In order to fulfill the priority aims of the Czech National Plan for 2013 the Taskforce met four times and among others endorsed presentations of representatives of various professional societies for the establishment of respective centers of expertise in the country (e.g. for neurology, endocrinology, rheumatology, orofacial abnormalities, immunedeficiencies, oncology, nephrology, hematology). Based on the endorsements of the Czech Ministry of Health envisages to publish official tenders for their establishment using EUCERD criteria[56].

[54] http://nestor.orpha.net/EUCERD/upload/file/Docs/CZPlan_en.pdf
[55] http://www.eucerd.eu/?post_type=document&p=2105
[56] http://www.eucerd.eu/?post_type=document&p=1224

vii. Lithuania

On 18 October 2012, the national plan for rare diseases[57] was approved by Order No V-938 of the Minister of Health, and a national rare diseases coordination committee was formed, including delegated experts from university hospitals, universities, non-governmental organisations, state institutions representatives to oversee the plan. The plan aims to establish a common approach on rare diseases, to raise public awareness, and to ensure prevention, early diagnosis, efficient treatment, improvement of quality of life and social support for patients suffering from rare diseases. It also includes the optimisation of health care services and rational allocation of available resources, as well as measures for improving the assessment of medicinal products and medical devices. There will be no specific budget for the plan so actions will have to be financed through the existing health budget. There was a Europlan conference[58] on 14 November 2013 under the auspices of the Lithuanian presidency to discuss the implementation of the plan.

viii. Slovenia

In 2012 a national plan for rare diseases was accepted by the Health Council and the next steps will be to elaborate an action plan and its implementation, as well as to identify funding. The Work Plan for Rare Diseases[59] is designed to serve as a roadmap until 2020 and is qualified as *"… an opportunity for better coordination of efforts of all partners involved, establishing health care that will be comprehensive, accessible, timely and patient-focused"*. The major objectives of the plan centre around the identification and monitoring of rare diseases; improving early diagnosis and access to appropriate medical treatments; mechanisms to improve an integrated approach to rare diseases; and improving access to information for patients, the general public, and professionals. Amongst identified actions include the establishment of a national registry for rare diseases; establishment of national reference centres integrated with international networks; examining cross-border cooperation for genetic testing and other services; introducing a system of evidence-based clinical guidelines; defining orphan drug policy and developing decision guidelines for competent authorities; identifying additional funding sources for orphan drugs; establishing an umbrella organisation of patient groups; and establishing a national centre for rare diseases in the country.

ix. Slovak Republic

A strategy including the basic concepts for a national plan on rare diseases was adopted by the Government of the Slovak Republic in 2012[60]. The national strategy for the development of health care for patients with rare diseases in the Slovak Republic for the years 2012-2013 aims to prepare for the development of a national plan for rare diseases and the support of its implementation into health and social care. However, no funding has been allocated for the Plan.

x. Cyprus

The Cyprus National Strategic Plan for Rare Diseases[61] (CNSPRD) was developed by a national steering committee for rare diseases, which consisted of Ministry of Health officials, experts in various fields relating to rare diseases as well as patient representatives, following a public consultation (the second) with local stakeholders including patient's representatives, in March 2012. The CNSPRD was approved by the Council of Ministers of the Republic of Cyprus in November 2012.

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

- Prevention – Early Diagnosis
- Treatment and Management
- Palliative Care / Social Inclusion / Support
- Registries/Epidemiology

[57] http://www3.lrs.lt/pls/inter3/dokpaieska.showdoc_l?p_id=435635&p_query=&p_tr2=2
[58] http://www.eurordis.org/sites/default/files/flags/finalreport-lithuania.pdf
[59] http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf
[60] http://www.europlanproject.eu/_newsite_986989/Resources/docs/NATIONALPLANS_SL_nationalStrategySlovakiaEng.pdf
[61] http://www.moh.gov.cy/MOH/MOH.nsf/All/CD61A07312284C0A422579DC0023AF8A/$file/Strategic%20Plan%20Rare%20Diseases.pdf

- Research

Following the approval of the CNSPRD, the National Committee for Rare Diseases was appointed by the Council of Ministers with the task of implementing as well as monitoring the progress of the plan. In addition, the National Committee for Rare Diseases is responsible for defining a number of priority actions with objectives and follow-up mechanisms. During 2013, the actions of the CNSPRD were prioritised and those requiring little or no budget, such as training initiatives and public awareness raising activities were put into action.

xi. Latvia

In December 2011, the national plan for rare diseases was written and submitted to the Ministry of Health for evaluation. The costs related to rare diseases are currently included in the national health care budget. A public consultation of the plan was launched in 2012 and the results were analysed by the Ministry of Health. A number of meetings with different stakeholders were held, and as a result, the plan was further elaborated. The plan was adopted in 2013, no additional funding has been secured, therefore major activities are related to update of regulations concerning rare diseases[62]. The activities are now being implemented including the approval of an act concerning registries and plans to include Orphacodes and ICD codes in the congenital anomalies and cancer registries.

xii. The Netherlands

A second draft of the National Plan for Rare Diseases was presented on in January 2013. The National Plan for Rare Diseases, having received input from all stakeholders, was then adopted in October 2013[63] and presented on 10 October 2013 by a delegation of The Netherlands Organization for Health Research and Development (ZonMw) to Minister Schippers of Health, Welfare and Sport (VWS). On 14 November 2013 the Minister sent the plan along with her reaction to Parliament. The Dutch National Plan identifies bottlenecks and recommendations, and it encourages field parties to feel responsible. The key bottlenecks for the plan include lack of knowledge about rare diseases, insufficient medical research on causes and course of rare diseases as well as inability of patient organisations to work well together. The plan recommends emphasising knowledge about rare disease through training and establishment of expert centres, make the information widely accessible to diverse audiences; make financial resources available for research and development of treatment as well as maintaining consistent policy for claims and reimbursement of orphan drugs. Finally the plan aims to appoint a director or coordinator to promote all recommendations, and avoid fragmentation and unnecessary duplication within the rare disease field.

xiii. The United Kingdom

The UK Strategy for Rare Diseases was issued by the government in November 2013[64]. The strategy, signed by health ministers of all four countries of the United Kingdom, contains 51 commitments to patients with rare disease. These commitments are wide ranging and include diagnosis, information, healthcare, genomics, registries and research. Health systems and other organisations in the four countries will now develop plans to implement the commitments. A Stakeholder Forum has been established to monitor progress in implementing the strategy.

xiv. Germany

On 8 March 2010 the National Action League for People with Rare Diseases (*Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen* (NAMSE)[65]) was founded at the behest of the German Federal Ministry of Health. Together with the German Federal Ministry for Education and Research (BMBF) and the Alliance of Chronic Rare Diseases (Allianz Chronischer Seltener Erkrankungen, ACHSE e.V.), NAMSE became a national council - a co-ordination and communication platform comprising all key bodies and organisations - responsible for coordinating and publishing the common efforts. The primary goal of

[62] http://www.vm.gov.lv/images/userfiles/reto_slimibu_plans_13_15.pdf
[63] http://www.europlanproject.eu/_newsite_986989/Resources/docs/NATIONALPLANS_NETHERLANDS_nl.pdf
[64] https://www.gov.uk/government/publications/rare-diseases-strategy
[65] http://namse.de/

NAMSE was to prepare suggestions for establishing a National Plan of Action for People with Rare Diseases by 2013 as well as supporting the establishment of national centres of expertise. At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, the German National Plan of Action for People with Rare Diseases[66] was adopted in August 2013. A total of 52 policy proposals have been included in this plan covering 7 action fields. This publication of these policy proposals concludes the first phase of the National Plan of Action for People with Rare Diseases. Now begins the implementation and monitoring phase of the suggested proposals.

xv. Belgium

At the end 2013, a National Rare Diseases Plan[67] was developed based on the analysis by the steering committee of the proposals developed since 2009 and was adopted by the Minister of Public Health. Twenty actions are identified in 4 main categories with specific tasks, budget and leading authorities defined for each point. The four main categories included: the improvement of access to diagnostics and information for patients, the optimisation of health care, the improvement of knowledge generation and the governance and sustainability of the plan.

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

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

xvi. Hungary

By the end of 2012 the National Plan for Rare Diseases was submitted to the Ministry of Health. The fourth Hungarian Europlan conference on 25-26 October 2013, organised with the participation of the Ministry of Health, examined the document and the budgetary question: the conference was a lively one thanks to the signing of National Plan for Rare Diseases by the Minister of Human Resources. The National Plan for Rare Diseases has now been approved (at the end of 2013)[68] and there is an elaborated budgetary plan for the 7 year strategy. The approval of the budget proposal is expected in 2014 in order to finalise the plan. The National Plan for Rare Diseases covers widely the needs of RD patients, extending all important areas and in harmony with the EU recommendations. All stakeholder groups supported the implementation of National Plan for Rare Diseases, including the allocation of a dedicated budget. The implementation of National Plan for Rare Diseases is jeopardized by some uncertainty caused by the prospective MP election, therefore the enhancement of national and international advocacy work is continuously necessary. Beside the National Plan for Rare Diseases the Ministry plans rare disease specific communications in the scope of the project “Development of public health communication” supported by Cohesion Fund.

b) Countries without an adopted plan/strategy in 2013

As previously evoked, the stage of the elaboration of national plans/strategies for rare diseases in the other Member States was varied at the end of 2013, however all Member States have declared their intention to elaborate such a policy[69].

[66] http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf
[67] http://www.laurette-onkelinx.be/articles_docs/Plan_Belge_pour_les_maladies_rares.pdf
[68] http://ec.europa.eu/health/rare_diseases/docs/national_hungary_en.pdf
[69] See Part V of this report for detailed information.

A plan/strategy had been submitted to national authorities by the end of 2013 in Estonia, Finland, Ireland, Italy, Malta, Poland, Romania and Sweden.

A public consultation took place in 2013 in Croatia.

Drafting group meetings/stakeholder meetings to discuss the elaboration of a national plan/strategy have taken place/were taking place by the end of 2013 in Austria, Denmark and Luxembourg. In Austria the draft plan was finalised in 2013 and feedback was collected before submission to the health authorities in 2014. In Denmark, many actions concerning the provision of healthcare for rare diseases were carried out following the recommendations of a report concerning rare diseases issued in 2001. A working group of stakeholders was established in 2012 with the task to elaborate a comprehensive national strategy for rare diseases in Denmark based on the experiences of the implementation of the recommendations the 2001 report and the national designations of centres of expertise in 2010. A Danish Strategy for Rare Diseases was submitted in 2014.

It should be noted that the current economic context is having a negative impact on the development and implementation of these plans: many plans may have insufficient or no funding as a result, thus potentially limiting their impact.

1.3. Political framework in other world regions

Outside of the European region, a number of countries have developed political frameworks in the field of rare diseases. Mostly, these initiatives concern the regulation of orphan medicinal products[70]. Policies for orphan medicinal products started as early as 1983 in the United States with the adoption of the Orphan Drug Act, then in Japan and in Australia in 1993 and 1997. Europe followed in 1999 by implementing a common EU policy on orphan medicinal products. In addition, the European Council Recommendation on an action in the field of rare diseases and the successful completion of the first French National Plan for Rare Diseases – considered a model by other countries – is inspiring other countries around the world to reflect on the elaboration of national plans/strategies for rare diseases. Below, a few examples of existing political frameworks in the field of rare diseases are presented in other world regions outside of Europe.

a) North America

i. USA

The Office of Rare Diseases Research[71] (ORDR) was established in 1993 within the Office of the Director of the National Institutes of Health (NIH). On 6 November 2002, the President established the Office in statute (Public Law 107-280, the Rare Diseases Act of 2002). The Rare Diseases Act[72] 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 Office, 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 of 2002 also takes note of the success of the 1983 US "Orphan Drug Act[73]": this law defines the 'orphan drug' with regard to prevalence (frequency) of the disease for which it is indicated in the American population. In the US, the concept of 'orphan drug' does not simply cover pharmaceutical or biological products. It also covers medical devices and dietary or diet products. The OOPD[74] (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

[70] Information provided by Orphanet http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN
[71] http://www.ncats.nih.gov/research/rare-diseases/ordr/ordr.html
[72] http://history.nih.gov/research/downloads/PL107-280.pdf
[73] http://history.nih.gov/research/downloads/PL97-414.pdf
[74] http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

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.

In 2011 two new bills were introduced on behalf of rare disease patients in the USA. On 27 July 2011, the H.R.2671: CAL Undiagnosed Diseases Research and Collaboration Network Act of 2011[75] was introduced in the House of Representatives to amend the existing Public Health Service Act in order to provide for the establishment and maintenance of an undiagnosed diseases network, and for other purposes. The bill has been referred to the House Committee on Energy and Commerce. Also on 27 July 2011 the H.R. 2672: Preserving Access to Orphan Drugs Act of 2011[76] was also introduced in the US House of Representatives. Seeking to "clarify the orphan drug exception to the annual fee on branded prescription pharmaceutical manufacturers and importers," this motion has been referred to the House Energy and Commerce and the House Ways and Means Committees for consideration.

In addition, a proposed legislative measure is gathering force in the USA seeks to promote low prevalence rare diseases, which the bill promoters assert garner less attention from potential drug developers. The Ultra-orphan Life Saving Treatment Act (ULTRA Act) would cover 83% of all rare diseases, according to a fact sheet[77]. Citing a disease prevalence of 6000 or less (in the USA) the ULTRA Act would tweak the regulatory system, facilitating an accelerated approval system from the FDA for very low prevalence diseases. According to the fact sheet, the ULTRA Act would provide the FDA *"…with the tools necessary to allow for alternative qualification criteria for the rarest diseases that could never have prior clinical data"*. No legislative action has been taken at this time.

In July 2012, President Barack Obama signed into law the U.S. Food and Drug Administration (FDA) Safety and Innovation Act[78], qualified by the USA's National Organization for Rare Disorders stakeholders as *"the most groundbreaking measures for rare disease patients and their families since the Orphan Drug Act of 1983"*. The Act ushers in several significant changes including *"accelerated patient access to new medical treatments; the development of Humanitarian Use Devices, or medical devices for small patient populations; accelerated development of "breakthrough therapies"—those that show early promise; enhanced consultation with rare disease medical experts; a rare paediatric disease priority review voucher incentive program; and resolution of conflict-of-interest issues related to FDA advisory committee participation"*.

The Office of Rare Diseases Research launched in 2012 a pilot project[79] to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR). The goal is to establish a data repository of de-identified patient data, aggregated in a standardised manner, to enable analyses across many rare diseases and to facilitate various research projects, clinical studies, and clinical trials. The aim is to facilitate drug and therapeutics development, and to improve the quality of life for the many millions of people who are suffering from rare diseases. Ongoing activities expanded the initiative to include collaborations with colleagues in the European Union countries, Japan, Australia and other nations.

In 2013, the rare disease community in America celebrated thirty years of the Orphan Drug Act. The success of this program has been dramatic, leading to the approval of hundreds of new therapies for rare diseases. Moreover, Kalydeco-a drug treating cystic fibrosis, made the list of the

[75] http://thomas.loc.gov/cgi-bin/query/z?c112:H.R.2671:
[76] http://www.govtrack.us/congress/billtext.xpd?bill=h112-2672
[77] http://www.kakkis.org/blogs/post/2011/11/29/Ultra-orphan-Life-saving-TReatments-Act-of-2012.aspx
[78] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ucm310927.htm
[79] http://www.grdr.info/index.php?option=com_content&view=article&id=10&Itemid=20

top 50 drugs approved by FDA in 2012. 2013 also marked the 30 year anniversary of the patient organisation National Organization for Rare Disorders (NORD) that made pioneering efforts to increase awareness about rare diseases and continues to provide support to the stakeholders in the rare disease community. In 2013 the FDA made a number of minor revisions[80] to the Act to bring its definitions up to date and to eliminate ambiguity by clarifying the content. The consultation process began in October 2011, with FDA issuing its final rule on the changes. Some of the key changes include refining the definition of an orphan subset to include *"use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug"*. Another important clarification was on whether an orphan drug would still keep its designation and hence the special marketing protection if that drug had more than one indication that finally treated more than 200,000 patients. The final rule concluded that as long as each patient population for which the drug is indicated for is less than 200 000, the drug would still have the protections under the Orphan Drug Act. This, however, does not extend to distinct stages of the same disease (for example, cancer), unless an acceptable justification was provided. The FDA also attempted to address "evergreening" of drugs, where some companies try to obtain extended periods of patent exclusivity that is in excess of the approved 7 years by changing a component of the drug, some of which simply includes a dose change. However, no resolution was obtained on this as according to the FDA some dose changes may be *"eligible for their own seven-year period of orphan exclusive approval"* due to its advanced nature. The final rule also removed language which implied that clinical superiority would require direct comparison with the approved drug such as providing of non-inferiority trial data. FDA also urged sponsors to include only *"relevant"* in vitro laboratory data, and *"clinical experience"* in their application, except in cases of *"well-documented case histories or significant human experience with the drug"*.

In 2013, the FDA awarded 15 grants[81] worth a total of more than $14 million which aim to improve the course of development of products that will be valuable to patients with rare diseases. The grant applications were reviewed by a panel of outside experts with a comprehensive understanding in the disease-related fields that the grants were related to. These grants are administered through the FDA's Orphan Products Grants Program.

In total, $3.623 billion has been earmarked for around 9400 research projects in the field of rare diseases, and $809 million has been committed for orphan drug research (for around 1650 research projects[82]), marking a strong programmatic and financial commitment to rare diseases research in the United States of America.

ii. Canada

In October 2011, the Health Minister of Quebec announced that rare diseases would indeed be "adopted" by Quebec's health system. A specific committee dedicated to rare diseases will be created at Quebec's Institut National d'Excellence en Santé et Services Sociaux. This Institution published in Summer 2011 a French language report[83] on the experiences of countries having developed policies for rare diseases. Until now, Canada's current federal-provincial Health Accord, which expires in 2014, presents a window of opportunity for introducing *"provisions for a federally designed rare disease strategy to be tied to provincial funding"*.

As of 19 January 2011, the province of Ontario will expand its compassionate review policy to allow more patients with *"rare clinical circumstances"* to benefit. The Ontario Public Drug Programs *"…will consider covering drugs that have been reviewed by the Committee to Evaluate Drugs (CED) and where Ontario is in funding negotiations with the manufacturer. Previously, applicants could not be approved for coverage in cases where the CED had made a recommendation, but the ministry was still in negotiations with the manufacturer"*. The expanded

[80] http://www.gpo.gov/fdsys/pkg/FR-2013-06-12/pdf/2013-13930.pdf
[81] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm371503.htm
[82] S. Groft, *A past with uncertainty, a future with hope – rare disease day 2014 from a USA perspective*, *Orphanet Journal of Rare Diseases* 2014, **9**:31 doi:10.1186/1750-1172-9-31, http://www.ojrd.com/content/9/1/31
[83] http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/OrganisationsSoins/ETMIS2011_Vol7_No6.pdf

policy covers *"requests to cover drugs in cases where an individual has been urgently hospitalized due to an immediate life, limb or organ-threatening condition and the requested drug therapy is directly related to the condition that resulted in the hospitalization"*.

In 2012, Leona Aglukkaq, Canadian Minister of Health, announced two initiatives aimed at bringing new hope to Canadians with rare diseases: the Harper Government will create a new approach for the authorisation of "orphan drugs" and the announcement of the Canadian launch of Orphanet, a comprehensive database of information and services for rare diseases. Federal governmental agency Health Canada also announced in 2012 plans to develop a framework for orphan medicinal products that will include the designation, authorisation and monitoring of such products and will foster innovation and research in Canada. The proposed framework, which is based on international collaboration and information sharing, was elaborated with the input of rare disease stakeholders and of help of the Canadian Insitute of Health Research Institute of Genetics.

The Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework was released publicly on 13 December 2013 for review and comment. The objective of the newly proposed framework is to establish a comprehensive framework that will provide access to orphan drugs for Canadians without compromising patient safety. The framework will address the unique challenges of studying small patient populations and align Canadian regulatory activities with those of the international partners. The proposed orphan drug regulatory framework is currently undergoing its final revisions, and is expected to be published by the end of 2014.

b) South America

i. Argentina

Both the Senate and the House representatives of the Argentinean Parliament endorsed the first national law[84] concerning rare diseases on 29 June 2011. Based on proposals elaborated by representatives, the main topics of the act include the definition of a rare disease (Argentina is adopting the same prevalence of no more than 1 person in 2 000 that is used in the European Union). Furthermore, the health system must now provide specific assistance to patients and their care-givers. In addition, public and private social security schemes are obliged to provide specific support. A central multidisciplinary committee is to be created in order to coordinate these actions and will include patient organisations. A national registry of patients will be elaborated, a neonatal screening programme will be considered, along with educational, social and support activities that are all mentioned in the law. All of these activities need governance and different levels of government must be coordinated before the effects of this dramatic development can be felt, but stakeholders believe that a significant first step has been taken.

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

ii. Peru

Peru established its first national law concerning patients with rare diseases in Summer 2011. Law 29698[85] promotes treatments for rare conditions and includes a national strategy encompassing diagnostics, surveillance, prevention, care, and rehabilitation. While Peru has not developed a precise definition based on prevalence, this legislation, a result of efforts from Geiser, Peruvian rare disease patient groups, and policymaker Michael Urtecho, is considered a big step forward for rare disease patients in Peru.

[84] http://www.orpha.net/actor/EuropaNews/2011/doc/ArgentinaLaw.pdf
[85] http://www.orpha.net/actor/EuropaNews/2011/doc/PeruLaw.pdf

iii. Columbia

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

iv. Brazil

The First Ibero-American Congress on Rare Diseases (CIADR), organised by the Associação MariaVitoria (AMAVI) was held on 25 September 2013 in Brasília, Brazil. This event was the first of its kind in Brazil with more than 1 500 participants from all sectors including academia, governmental, industry and patient associations. The focal topic at this conference was the need to create public policies for a population that can reach up to 16 million Brazilian citizens. A working group meeting took place after the CIADR meeting on 25 October 2013 to discuss the creation of policy of care to benefit rare diseases patients. This meeting was attended by 30 stakeholders from different sectors. The working group expressed a deep interest in creating policy that will help creating reference centres for rare diseases. The working group also highlighted the many activities in the area of rare diseases that are underway in Brazil. Additionally, the Minister of Health is already committed to the creation of the Technical Group for Rare Diseases, which was finalised during the event of World Rare Disease Day on 2 February 2012, in Brasilia. AMAVI, promises to seek the necessary actions in the future that will contribute to integration of Brazil in more advanced discussions on rare diseases.

c) Asia

i. Japan

Japan bears the distinction of having the oldest programme for rare disease research and care in the world. Established in 1972, the Medical Care Program for Specific Diseases encompasses "Nanbyo" (Intractable Diseases) and the closely-related "Tokutei Shikkan" (Specified Rare and Intractable Diseases)[86]. 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 subsidiaries 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, including financial subsidies for clinical and non-clinical research, exclusive marketing rights for 10 years and tax credits for research as well as reduction in corporate tax, in addition to priority review, fast track approval, free protocol assistance and user fee waivers. According to these new provisions, orphan drug status can be granted to a drug, provided it fulfils the following two criteria:

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

The Japan Intractable Disease Information Center is a collaborative effort of the MHLW and the Japan Intractable Diseases Research Foundation aimed at dessiminating information about rare diseases in Japan.

[86] http://www.nanbyou.or.jp/english/index.htm

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

The committee for the rare and intractable diseases in Japan generated a proposal for intractable disease for the Commission for Specific Disease Control under the Health Science Council which was accepted on 31 January 2013. The objective of the proposal was to reform the current policies on intractable disease by improving the quality of the development of effective treatment methods, introducing a fair and stable medical expense subsidy system, and enhancing awareness among the public. To accomplish these objectives, the committee recommends increasing the number of reimbursed intractable disease treatments from 56 to 300, and to provide a comprehensive long-term care and social support for patients with intractable disease. To ensure fairness, the committee recommends narrowing the subsidy beneficiaries only to patients facing a severe disruption to lifestyle. The committee also placed great importance to strengthening research and promoting comprehensive and strategic study of intractable diseases.

ii. Singapore

In Singapore, the Orphan Drugs Policy is based upon a Medicine Order ('Orphan drugs Exemption'). The legislation, which came into force at the end of 1991, gave a definition of orphan 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 affecting fewer than 20 000 persons. An orphan drug is a medicinal product which has been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute for the treatment of a rare disease. The product should not hold a previous product licence under the Medicine Act and should be approved by the competent Health Authorities either from the country of origin or from any other country where the orphan drug has been used. Orphan drugs importers must maintain proper records, including:

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

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

iii. Taiwan[87]

In Taiwan the Rare Diseases and Orphan Drugs Act was adopted in 2000[88]. This act comprised 36 articles, detailing resources from the prevention to the treatment of rare diseases. The articles covered: the acquisition of orphan drugs, R&D, manufacturing orphan drugs, diagnosis and treatment of rare diseases, prevention acknowledgement of rare diseases, cooperation with international rare disease organisations, and the subsidised supply of specific pharmaceuticals and special nutrients. It specifies a 10 year marketing exclusivity period in Taiwan for pharmaceuticals approved as orphan drugs. Rare diseases are defined in Taiwan as having a prevalence of less than 1 person in 10 000, being difficultly treatable and genetic in origin.

In Taiwan, to be recognised officially as having a rare disease, patients can apply through their doctors or medical institutions by presenting a rare disorders report sheet (including suspected cases), abstract of the disease and related medical essays to the Bureau of Health Promotion, Department of Health, Executive Yuan to proceed with the application. Patients that have been acknowledged officially as having rare diseases can apply for reimbursement for the medical

[87] 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)

[88] http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html

expenses occurred in local medical centre, or regional teaching hospitals. Expenses include diagnosis, treatment, drugs, and special nutritional supplements. The reimbursement cap is 70% of actual expenses but families that qualify for low-income status can receive reimbursements up to 100% for drugs and nutritional supplements for the patient.

iv. South Korea[89]

Although there is currently no specific rare disease legislation in place in South 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 became the Ministry of Food and Drug Safety in 2013), which supplies medications for rare diseases. The KFDA has also defined, in an official notice, rare diseases as diseases affecting less than 20 000 persons in Korea without appropriate treatment and substitution treatment modalities. An Orphan Drug guideline was established in 2003 which stipulates exclusive marketing rights for 6 years in order to encourage research and development of orphan drugs. The Ministry of Health has also established a Genetic and Rare Disease Centre in 2004 which deals with the subsidies for medical expenses related to rare diseases, organises national reference centres (established in 2006) and research in the field of genetic and rare diseases. The Rare Disease Centre also acts as an information centre, and from 2006 provides a help line[90] service for patients: the centre has produced information on around 800 diseases which is regularly updated. In 2008, a research grant for rare diseases was launched by the Ministry of Health for the period 1 April 2008 to 31 March 2012, to fund basic research and a clinical research network with around 5.5 million USD. There is also a Korean Mutation Database in place with data from 4 major laboratories, and a database of clinical trials in general.

A web-based *"Korean Rare Disease Knowledge Base (KRDK)*[91]*"* has been established with disease summaries and reviews (520 disease summaries and 48 disease reviews), a causal gene list, and a directory of laboratories and clinics. The database intends to add an orphan drug database to its repertoire. Modelled on the genetic database GeneTests (www.genetests.org), this database provides quick querying and prevents the appearance of redundant data. The database uses Orphanet as the main resource for information on rare disease, genetic data and reviews. The database provides a summary of the patient registry - Bio Electronic Medical Record (BioEMR) and is integrated with Genome Research Information Pipeline to provide all information relating to genes.

v. China

In China, a definition of rare diseases was proposed by a group of medical experts on 17 May 2010. This definition is of 1 person in 10 000 covering genetic diseases in infants. An initial list of 23 rare diseases has been proposed. Organisation of care for rare diseases has not yet been included in the national health system and special legislation on orphan medicinal products has not been established; current legislation only sets forth general criteria for the acceleration of regulation and approval of specialised drugs, such as those for rare diseases[92].

The launch of the Chinese Rare Disease Research Consortium (CRDRC) was formally announced on 14 September 2013, during the 1st Chinese Rare Disease Symposium. CRDRC, led by the HUST and the Hong Kong University was accepted as a member of IRDiRC on 5 August 2013. More than 20 universities, colleges and institutes and 50 specialists are now members of this consortium. CRDRC aims to team up with several other researchers and organisations investing in rare disease research in China. The goals of CRDRC are multifold as they include establishing a national registry for rare diseases in China as well as establishing and providing access to harmonized data and samples. Efforts of CRDRC will go towards identifying 5-30 rare disease genes per year and make

[89] Source: 2009 ICORD conference, Soo Kyung Koo of the Genetic and Rare Diseases Centre of the Korea National Institute of Health: http://www.google.com/url?sa=t&source=web&cd=3&ved=0CC0QFjAC&url=http%3A%2F%2Ficord.se%2Fdocuments%2Ficord_2009%2Fpresentations%2FKoo.ppt&rct=j&q=korea%20rare%20diseases%20center&ei=8m8ATtnqNIa2hAefp4S8DQ&usg=AFQjCNEQ6r3z5e0UuYx3KBHv839W3MSgpw&sig2=LRZURh40JbNM8yLdaQT_Ig&cad=rja

[90] http://helpline.cdc.go.kr/cdchelp/index.gst

[91] http://www.snubi.org/software/raredisease/

[92] *Intractable and rare diseases research in Asia*, P Song et al, BioScience Trends, 2012 ; 6(2):48-51

genetic testing based on these genes available for patients as well as performing translational research with newly identified genes and facilitate development of therapeutic strategies. CRDRC will endeavour to provide funding support of rare disease research in China by forming an alliance with the China Natural Science Foundation, the Ministry of Science and Technology, and the Ministry of Health. These will include participating in joint calls or international collaborative funding for rare disease research with the EU, Australia, and other countries. Finally CRDRC will seek to launch a Rare Disease Research Institute in China to centralize the rare disease research efforts in China.

On Rare Disease Day 2013, the China Rare Diseases Prevention and Treatment Alliance was launched in Jinan, China, bringing together 17 medical institutions from 13 provinces in China.

d) Australasia

i. Australia

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

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

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

The Federal Government funds treatments and therapies via the PBS (Pharmaceutical Benefits Scheme). However, treatments for rare diseases do not meet the criteria of listing on the Pharmaceutical Benefits Scheme (PBS), as they do not meet cost effectiveness standard set by the PBS. Much of the treatments for rare diseases are funded by another scheme - the Life Saving Drugs Program (LSDP). This program was set up in 1995 on the back of an Act of Grace as a means of providing much needed treatments to those living with very rare conditions. The LSDP currently funds 10 treatments for 7 rare conditions for which patients must meet an entrance criteria to enable them access to these therapies. This program is carefully managed with advisors for each specific condition listed. All treatments listed on this program must be referred and recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia for listing. In August 2013 the PBAC announced that LSDP will be undergoing a Post Market Review to assess the state of affairs of drugs funded under LSDP.

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

- Raise awareness of the burden of rare diseases on patients, families, health professionals and the community;
- Provide educational resources and networking opportunities for health professionals to allow them to better identify and manage rare diseases;
- Improve health care for people with rare diseases through access to diagnostic tests, new drugs and other treatments, improved primary care and specialised services;

- Promote research on rare diseases through advocacy for targeted research funds and development of national and international multidisciplinary research partnerships;
- Increase knowledge of the epidemiology and impact of rare diseases in Australia through research;
- Develop and disseminate information to educate patients, parents, carers and the general public, about rare diseases that is relevant in the Australian context;
- Develop an umbrella organisation to support people affected by any rare disease by linking existing organisations to facilitate the co-ordinated development of integrated peer support networks, contact among families and contact among rare diseases interest groups;
- Advocate to government in partnership with families, for people affected by rare diseases.

A rare disease symposium, entitled Awakening Australia to Rare Diseases: Global perspectives, was hosted by Western Australia on 18-20 April 2011[93]. Building on the work initiated by the Australian Paediatric Surveillance Unit and the National Rare Disease Taskforce, the symposium was an important step in the process of developing a rare disease strategy in Australia. Decisions taken included an endorsement to develop a National Plan, an agreement to form a single overarching advocacy group for rare diseases in Australia, an agreement on the need for national rare disease registries, and an agreement on the need to explore how service delivery could be improved.

In 2012, rare disease stakeholders from Western Australia joined ranks with international rare disease and orphan drug information portal Orphanet. Simultaneous with this action, key players from Western Australia's Department of Health and Office of Population Health Genomics began the process of developing a scoping paper to analyse the need for a national rare disease strategy in the country. In 2013 the paper was released[94], however the Australian Health Ministers Advisory Council did not collectively support the recommendation of the Scoping paper that Australia develop a National Rare Diseases Plan. Although Western Australia and Northern Territory confirmed their written support for a National Plan for Rare Diseases other states and territory chose not to espouse the plan. AHMAC requested more information on the status of genetic testing, disease coding and clinical pathways. Rare Voices Australia has planned for 2014, in each of the 5 states, a half day seminar giving opportunities for Patient Organisation leaders to provide their valued feedback while the other half day seminar will be designed and facilitated for a specific group being the Executive leaders, policy makers and advisors in health who will be individually invited to give their valued feedback on the need for a National Plan for Rare Diseases.

Meanwhile, in Western Australia, the Department of Health is committing to specific actions, including a trials centre for innovative treatments for rare diseases, national registries, screening policies and models, and actions around epidemiology. Western Australia health officials are encouraging other jurisdictions to participate in the Orphanet portal.

ii. New Zealand

The New Zealand Organisation for Rare Diseases (NZORD) and groups within its network are promoting earlier diagnosis, improved clinical care and disability support, and more effort to research health interventions and therapies. A proposal has been submitted to the National Health Committee for the development of a rare diseases action plan for New Zealand.

Orphan Drug Policy has been included as one of the TGA/Medsafe Joint Agency (ANZTPA) Harmonisation Activities[95]. The primary goal is to provide an appropriate mechanism to facilitate access to safe and effective orphan drugs. The secondary goal is to minimise the likelihood that the orphan drug process could be misused for products that are commercially viable.The business

[93] http://www.ojrd.com/content/7/1/50/abstract
[94] http://www.genomics.health.wa.gov.au/publications/docs/Scoping_Paper_National_RD_Plan_September_2013.pdf/
[95] http://www.anztpa.org/projects/harmonisation-pm-orphan.htm

process and implementation pathway for orphan drugs that is reflective of the approved policy decision is anticipated by May 2014.

e) Other countries

i. Russian Federation

Federal Law N° 323-FZ of 21 November 2011 "On the basis of public health protection in the Russian Federation" specifically mentions in Article 44 medical care to citizens suffering from rare diseases. Rare diseases are defined in this text as affecting no more than 10 cases per 100 000 population. An official list of diseases classified as rare, chronic and life threatening in Russia has been defined by the Ministry of Health in 2013 and includes 24 diseases. A national registry for patients with these conditions is foreseen by the legislation. The current law defines an orphan drug but there are no details about the requirements for obtaining orphan drug designation, financial or regulatory incentives for orphan drug development. The draft amendments are currently being discussed to provide more clarification on registration process and development requirements for orphan drug in Russia.

There is an active alliance of rare disease patient organisations, the National Association of Rare Diseases Patients, in place and which organises the annual Rare Disease Day.

ii. Ukraine

As per the Regulation Order of the Ministry of Health N°3 of 4 January 2013, "limited use" or orphan products should meet the following criteria:

- Intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating rare condition affecting no more than 5 in 10 000 persons, or intended for the same and without incentives, marketing of the product would not generate sufficient return to justify the expenses borne by the manufacturer with regard to the medicinal product;
- There are no other approved satisfactory methods of diagnosis, prevention or treatment of the condition in question or, if such method exists, that the medicinal product applied for will be of significant benefit to the patients.

If the applicant can prove that it is impossible to support the application for MA by comprehensive data on efficacy and safety because of the rarity of the intended indication, marketing authorisation may be issued under exceptional circumstances, i.e. subject to certain commitments to be accepted by the sponsor (e.g. post-approval studies allowing reassessment of the benefit-risk ratio).The official dossier review time will be reduced from 210 working days for normal applications to 90 days for designated orphan drugs.

iii. Kazakhstan

As per the Regulation Order of the Ministry of Health n°735 of 18 Nov 2009, a medicinal product may be considered an orphan drug if it is used "rarely or in less than 10 000 individuals" living in Kazakhstan. As such, the product can be included on the List of Orphan Drugs

- If scientific knowledge level at the time of filing application for state registration does not allow to obtain complete information, or
- If obtaining additional information would contradict generally accepted principles of medical ethics.

A positive decision on the registration of orphan drugs is contingent on commitments made by the applicant to:

1. Carry out a specific study program (which will be the basis for annual re-evaluation of the benefit-risk ratio);
2. Ensure the administration of the medicinal product under strict medical supervision;
3. Immediately inform the governmental body of any adverse effects, and measures taken.

During the period in which these commitments are being fulfilled, the MOH will re-evaluate the benefit-risk ratio on an annual basis. The instructions on the therapeutic indications and other information on the registered orphan drug must contain a note on the missing data.

Inclusion of a product on the List of Orphan Drugs will allow government to allocate funds for state procurement of the product.

2. Expert services in Europe

2.1. Centres of expertise in Member States

DG Health and Consumers established the High Level Group (HLG) on Health Services and Medical Care as a means of taking forward the recommendations made in the reflection process on patient mobility. One of the working groups of this High Level Group, in collaboration with the EC Rare Diseases Task Force (RDTF), focused on reference networks of centres of expertise for rare diseases. In the context of this working group, a number of criteria for national centres of expertise for rare diseases were defined in 2006[96] based on the experience of countries with designation processes already in place.

Based on this work, the EUCERD elaborated a set of recommendations which were adopted on 24 October 2011 as the EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States[97]. The homogeneity of quality criteria for centres of expertise in Member States will be a key concept and concern in the context of the implementation of the EU Cross-Border Healthcare Directive[98], in which rare diseases are specifically mentioned.

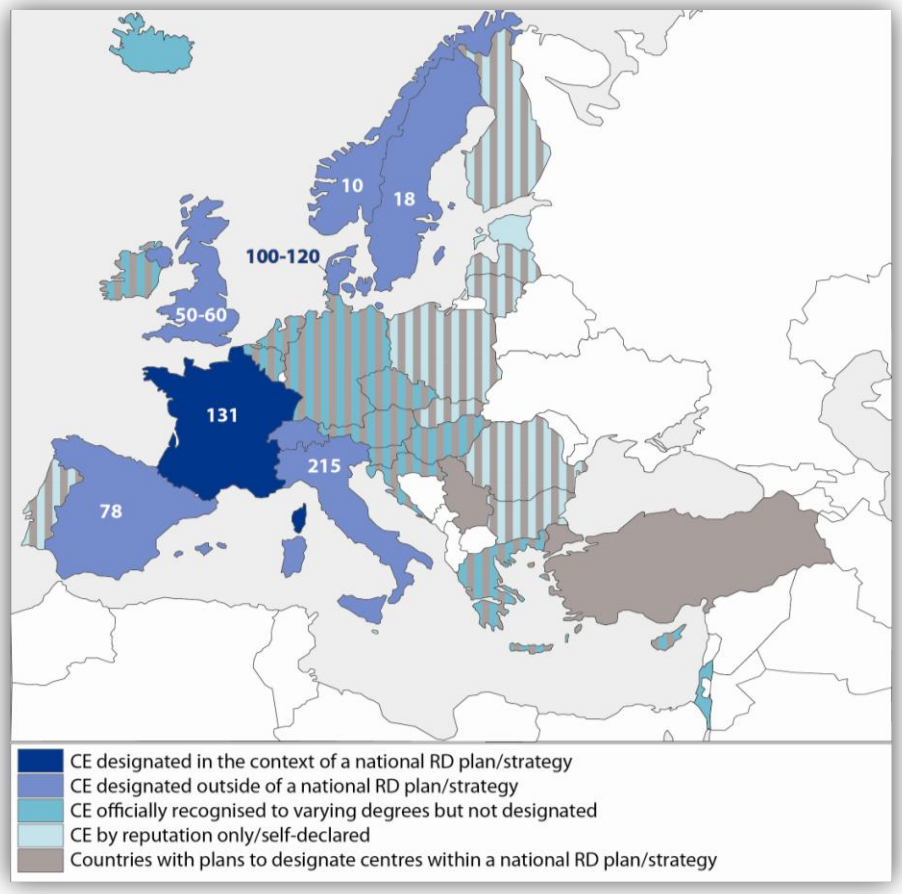

Figure 3: State of the art of centres of expertise at national level in Europe and number of designated centres where they exist (December 2013)

[96] http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf
[97] http://www.eucerd.eu/upload/file/EUCERDRecommendationCE.pdf
[98] http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf

France has have designated centres of expertise for rare diseases in the context of a national plan/strategy for rare diseases. A few countries also currently have officially designated centres of expertise for rare diseases (i.e. selected and financed by health authorities) outside of a national plan/strategy for rare diseases: Denmark, Norway, Sweden, Spain, Switzerland, and the United Kingdom[99]. Italy has regionally designated centres of expertise for rare diseases. It should be highlighted that the designation criteria and processes vary from country to country, sometimes even from region to region within a country, even if the designation criteria are often in line with the recommendations of the EUCERD issued in 2011.

A number of countries have non-designated centres of expertise for rare diseases which are acknowledged by authorities to varying degrees: Austria, Belgium, Croatia, Cyprus, Czech Republic, Germany, Greece, Hungary, Ireland, Israel, Iceland, the Netherlands and Slovenia[100].

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

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

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

2.2. European Reference Networks (ERNs)

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

A number of pilot ERNs for rare diseases were 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). The EUCERD Scientific Secretariat carried out a *Preliminary Analysis of the Outcomes and Experiences of pilot European Reference Networks for Rare Diseases*[101] in late 2010 which yielded a number of initial conclusions.

This document is one element which has helped contribute to the reflection on criteria for ERNs for rare diseases over the past few years of the Cross-Border Healthcare Expert Group. Their work will be carried out in the context of the implementation of the European Cross-Border Health Care Directive, in which ERNs for rare diseases are explicitly mentioned in Article 12[102]: *"The Commission shall support Member States in the development of European reference networks between healthcare providers and centres of expertise in the Member States, in particular in the area of rare diseases."* The same article of the Directive states that European reference networks shall have at least three of the following objectives:

a) to help realise the potential of European cooperation regarding highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and health technologies;

[99] Further details concerning the designation processes in these countries can be found in the relevant country section in Parts V &VI of this report.
[100] These countries also often have self-declared centres of expertise/centres with a reputation for expertise. Further details concerning the exact situation in these countries can be found in the relevant country section in Parts V &VI of this report.
[101] http://www.eucerd.eu/upload/file/Reports/2011ERNAnalysis.pdf
[102] http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf

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

To prepare these acts, the Commission carried out extensive and exhaustive consultative processes including the creation of the aforementioned Cross-Border Healthcare Expert Group which assisted the Commission on this task. In the case of the implementing acts the Commission was assisted by the Committee on Cross-Border Healthcare composed of Member States representatives. A public consultation was launched in late 2012 on the criteria for the European Reference Networks and healthcare providers wishing to join the network under the framework of article 12 of the Directive on cross-border healthcare, along with a conceptual paper and questionnaire[103]: the results were published in July 2013[104]. Visits to Member States, workshops and meetings with experts, medical societies, patients' organisations and stakeholders also took place.

In 2012, to further contribute to this process, the EUCERD elaborated recommendations on European Reference Networks for rare diseases[105], which were adopted in January 2013. The 21 recommendations on European Reference Networks build upon the previous recommendations of the EUCERD on centres of expertise and work of the HLG/RDTF, and will serve both to inform the Commission services and Expert Group working on criteria for the creation and designation of ERNs in the context of the Cross-Border Healthcare Directive on the specificities of RD, as well as the Member States who are developing their healthcare pathways at both the national and EU levels in the field of rare diseases in the context of national plans/strategies for rare diseases which the Council has urged all Member States to elaborate by 2013.

The focus at the European Commission from 2012 was the implementation of the Directive, led by the Committee on Cross-Border Healthcare, a legal forum where all 27 Member States met discuss general issues concerning the transposition of the directive. The delegated[106] and implementing[107] acts concerning the establishment of ERNs were adopted in 2014 and entered into force in May 2014. They define the criteria as provided in the Directive, establish the methodology of the whole process of deciding which European Reference Networks to support (including the process of selection and designation of the healthcare providers to be considered members of the European Reference Networks) and establish several categories of criteria for the adequate management, monitoring and evaluation of the networks.

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

[103] http://ec.europa.eu/health/cross_border_care/consultations/cons_implementation_ern_en.htm
[104] http://ec.europa.eu/health/cross_border_care/consultations/cons_implementation_ern_en.htm
[105] http://www.eucerd.eu/?post_type=document&p=2207
[106] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2014_147_R_0006
[107] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2014_147_R_0007

and whether identified laboratories meet quality standards. To fulfill this need, Orphanet[108] 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, 36 countries in 2011 and 37 countries in 2012 and 2013, with resources from the European Commission. In collaboration with the EuroGentest[109] Network of Excellence (financed by DG Research and Innovation), information on quality management has been added to the Orphanet database over the past five years. Information on genetic testing in Orphanet can be searched by disease name or by gene (symbol or name in English) as well as by laboratory or by professional. The information provided on laboratories includes data on quality management. Information is freely accessible online and access to all data can be granted upon request.

The data presented Orphanet database concerns tests available in the clinical setting and thus does not reflect the research capacity of a country. Countries regulate to varying extents the number of tests available in the clinical setting, for quality and/or reimbursement reasons.

At the beginning of 2014[110], the 1275 laboratories registered in Orphanet provided tests for 2362 genes and 3153 diseases. According to an analysis of Orphanet data in January 2014[111], the test offer differs greatly from one large country to another (Figure 4): Germany (1880 genes), Spain (1635 genes), France (1472 genes), Italy (1101 genes), United Kingdom (738 genes).

The test offer within medium and small-sized countries in Europe now ranges from 10 to 1113 genes[112]. This situation explains the large cross-border flow of specimens, highlighting the need to provide access to services in other countries when necessary, especially for very rare diseases. According to available data, only testing for cystic fibrosis is provided in the most number of European countries (30 out of 34 in the Orphanet database).

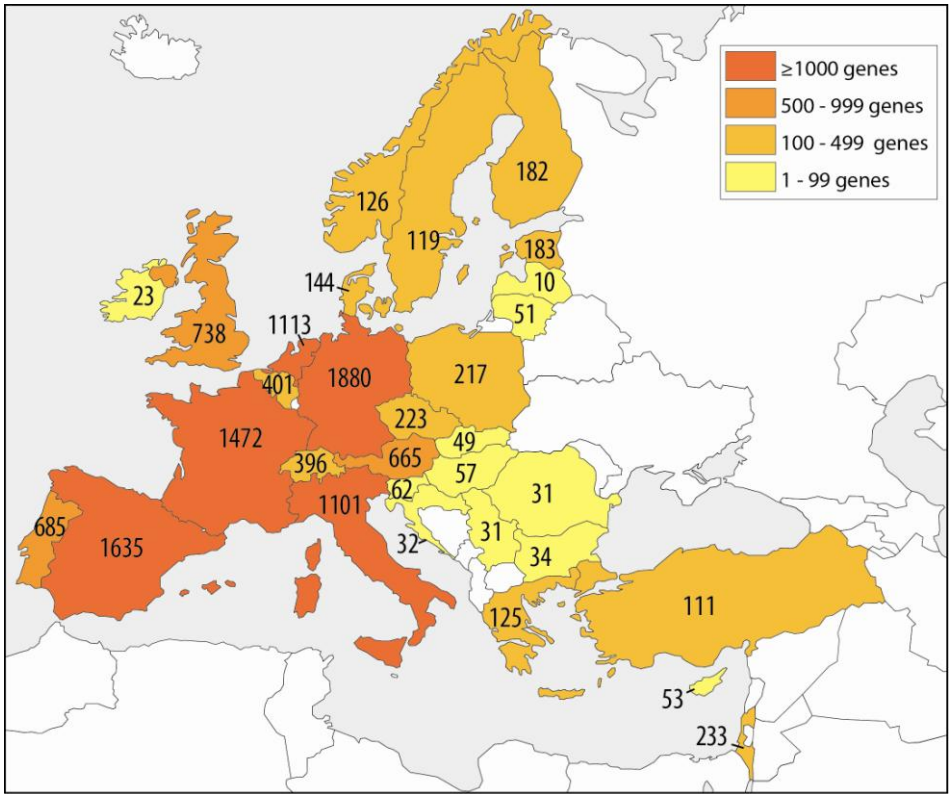

Figure 4: Number of genes tested in laboratories located in each European country amongst the 2362 genes tested in Europe (Orphanet data extraction, January 2014)

[108] www.orpha.net
[109] http://www.eurogentest.org/
[110] Figure from Orphanet data, January 2014.
[111] Figures from Orphanet data, January 2014.
[112] Figure from Orphanet data, January 2014..

An analysis of Orphanet database[113] showed that 871 rare diseases are tested in laboratories located in one country only in Europe (28% of diseases for which there is a test for the gene), and 2896 rare diseases are tested in 10 or less countries in Europe, with 2285 rare diseases tested in 5 or less countries in Europe. In terms of genes, 447 genes are tested in laboratories located in one country only in Europe, with 2125 genes tested in 10 or less countries in Europe and 1521 genes tested in 5 or less countries in Europe.

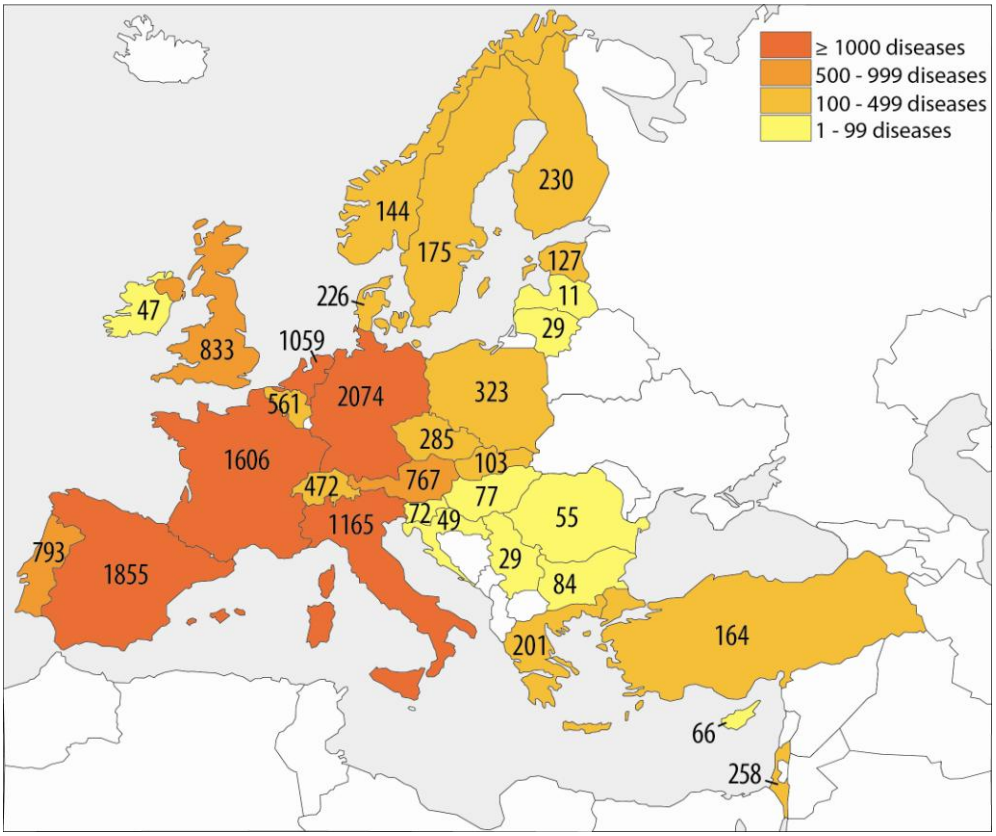

Figure 5: Number of rare diseases tested in laboratories located in each European country (Orphanet data extraction, January 2014)

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 tests, an analysis[114] of the 1 275 laboratories registered in Orphanet shows that 193 laboratories in 17 countries are accredited for at least some part of their diagnostic activities.

An article[115] was published in the *European Journal of Human Genetics* by the EuroGentest network in 2012 presenting results of a survey of molecular genetic testing laboratories and their quality assurance practices in Europe, demonstrating that *"although accreditation of laboratories and their participation in External Quality Assurance are accepted as effective and important tools to improve the accuracy and reliability of genetic testing, they are very rarely mandatory and implemented only patchily".*

In November 2012, the EC's Joint Research Centre in collaboration with EuroGentest and the EUCERD organised an expert workshop on the genetic testing offer in Europe. The conclusions and suggested points for future action were published in the final report[116], covering areas such as the organisation of genetic services, quality assurance, next generation sequencing and direct-to-consumer testing.

[113] Data extracted from Orphanet database in January 2014.
[114] Data extracted from Orphanet database in December 2013.
[115] Berwouts et al., European Journal of Human Genetics, 2012 Nov;20(11):1118-26. http://www.ncbi.nlm.nih.gov/pubmed/22739339
[116] http://ihcp.jrc.ec.europa.eu/our_activities/public-health/jrc-publishes-a-report-entitled-genetic-testing-offer-in-europe/at_multi_download/file?name=finalreportWSgenetic%20testing.pdf

3. Research and development

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

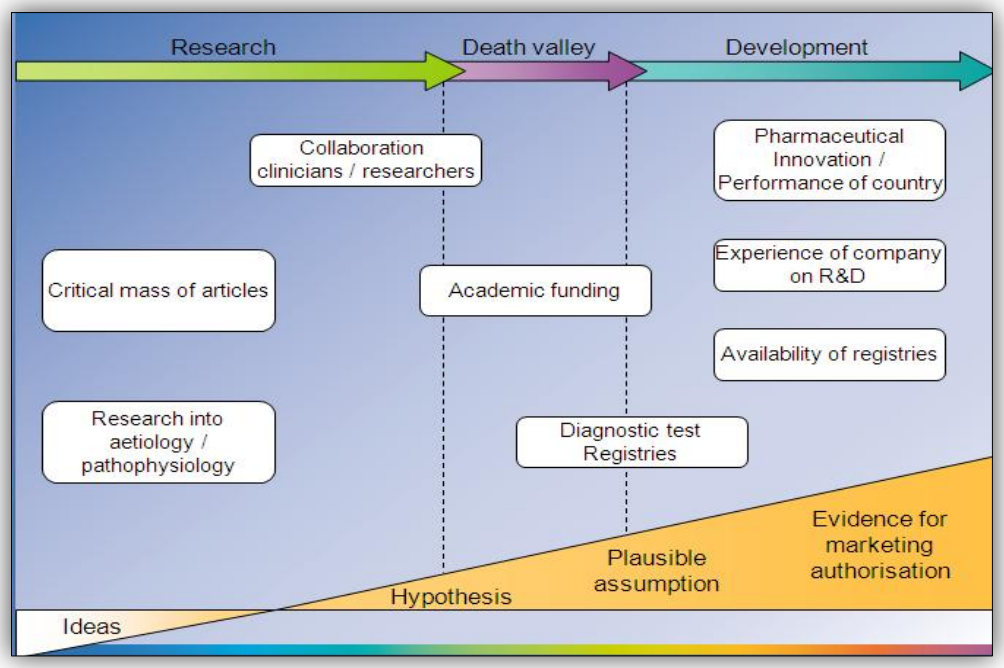

Figure 6: Schema representing the bottlenecks between research and development of therapies for rare diseases[117]

The field of rare diseases, however, provides a range of opportunities to drive forward research and R&D in general (section 3.3.) 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

[117] Graphic courtesy of Ségolène Aymé.
Death valley – This part of the research and development process is the 'translation gap' where there is no obvious funding body. This is the grey zone between basic research which is supported by academic funding and development which is supported by Industry funding : it is a moment when it is too early for Industry to invest, and too late for the acquisition of knowledge.
Performance of a country – Performance of a country measured by indicators of innovation performance as described in H.E. Heemstra et al, Drug Discovery Today, 2008 Aug;13(15-16):670-6. Epub 2008 Jun 24.

specific codes in the International Classification of Diseases (ICD10) (see section 3.4.). 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.

Report on Rare Disease Research, Its Determinants in Europe and the Way Forward (2011)

The RareDiseasePlatform project[118] (RDPlatform), a three-year (2008-2011) support action project of the European Union's Seventh Framework Programme (HEALTH-F2-2008-201230), has produced an inventory of publicly funded research projects in the field of RD and orphan medicinal products, accessible through the research tab of the Orphanet website[119]. The RDPlatform project analysed the data collected by Orphanet and carried out a review of the relevant literature, to establish a state of the art of the research activities in the field of rare diseases in order to propose areas for action in the future. The report published as a result, "*Report on Rare Disease Research, Its Determinants in Europe and the Way Forward*[120]", was published in January 2011. This report sheds light on where research and development (R&D) in the field of rare diseases has been - and where it needs to go next. The report presents a compilation of data gathered within the RDPlatform project. As such it offers readers an inventory of publicly-funded research initiatives on the national and international levels in the field of rare diseases and orphan medicinal products. The data, accessible on pan-European rare disease and orphan drug informational portal Orphanet, encompasses ongoing research projects, clinical trials, and registries. Other areas covered in the report include testing, therapeutic development, and R&D determinants (such as prevalence and medical area). The rare disease ontologies, data repositories and bioinformatics tools are given special emphasis in the report.

[118] http://www.rdplatform.org/
[119] http://www.orpha.net
[120] http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

3.1. Research funding

3.1.1. At Member State level

a) National rare disease research programmes

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

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

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

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

The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis, few medicinal products and difficult access to care. That is why rare diseases are a prime example of a research area that strongly profits from coordination on a European scale. ERA-Net E-Rare was launched in 2006 and its second phase in 2010 (E-Rare-2, 2010 - 2014, FP7). The major goals of E-Rare are to foster systematic exchange of information and build a transnational research programme on rare diseases. The E-Rare Consortium gathers seventeen research-funding organisations from 13 European and Associated countries (Austria, Belgium, France, Greece, Germany, Hungary, Italy, Israel, Portugal, Romania, Spain, the Netherlands and Turkey) as well as and Poland and Latvia, as observers.

To continue and expand its activities in accelerating the development of new diagnostics and therapeutics for patients suffering from rare diseases in 2012 E-Rare joined the International Rare Diseases Research Consortium (IRDiRC). As a member of IRDiRC E-Rare strongly promotes transnational funding activities and facilitates the participation of a wide range of different funding organisations which might not have a strong RD research funding priority giving them the opportunity to participate in the shaping of the rare diseases research landscape and policies.

Since 2007 E-Rare has become one of the major contributors to transnational rare diseases research funding. The EC supports the coordination costs among the funding agencies. However, each national funding agency participating in the call funds the research carried out in their own countries once the projects have been selected.

The E-Rare Consortium has launched 6 joint transnational calls (2007, 2009, 2011, 2012, 2013 and 2014) for collaborative multidisciplinary research projects open for any rare disease (except rare cancers and rare infectious diseases), with a wide range of possible topics and approaches. A total of 640 multinational applications involving more than 2600 research groups from European and associated countries were submitted to the first 5 calls. Importantly, the 4th Joint Transnational Call (2012) was dedicated specifically to provide young, independent investigators the opportunity of building transnational collaborations in the field of rare disease research. The 6th Joint Transnational Call (JTC2014) is dedicated to development of innovative therapeutic approaches for rare diseases.

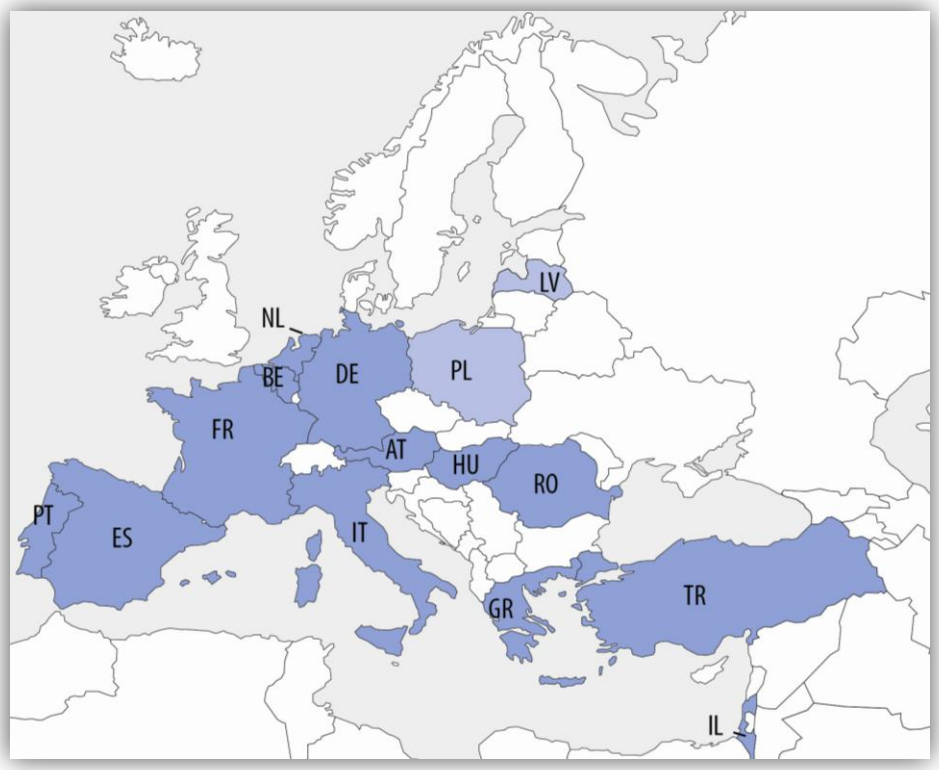

Figure 7: European countries with national research agencies participating in the E-Rare (2) ERANET for rare diseases (May 2014)

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

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

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

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

The Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7, 2007-2013[121]). 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. The Work Programme 2012 for FP7 Health included a major funding package for rare diseases research in the call for proposals FP7-HEALTH-2012-INNOVATION-1 opened on 20 July 2011. As the result of the call 26 new research projects related to rare diseases were launched with the EU contribution of €144 million.

The European Commission released on 10 July 2012 the content of a new call for proposals[122] based on the FP7 Health Work Programme 2013: for this call, one specific rare disease topic is included: *Development of imaging technologies for therapeutic interventions in rare diseases.* Altogether 7 projects were funded in this topic with the overall EU contribution of €40 million. The Call included also a topic for *New methodologies for clinical trials for small population groups* which resulted in funding of 3 projects related to rare diseases with the total EU contribution of €8 million.

For the period 2007–2013, close to 120 research projects related to rare diseases have been funded in FP7 Health Theme with an EU contribution of over €620 million. The projects launched in FP7 include also an ERA-Net on rare diseases funded from the 2010 Work Programme.

Horizon 2020[123] the new Framework Programme covering the period 2014-2020: calls related to the field of rare diseases were launched at the end of 2013 in the context of this financial instrument (Support for European Reference Networks: efficient network modelling and validation, New therapies for rare diseases, and Integrating and opening existing national and regional research infrastructures of European interest). Within Horizon 2020 €5 million has been ear-marked for the continuation of the activities of the ERA-Net on rare diseases, €60 million has been ear-marked for successful proposals concerning the area of new therapies for rare diseases which contribute to the objectives of, and follow the guidelines and policies of, the International Rare Diseases Research Consortium, IRDiRC, and grants towards research activities that will help towards integrating and opening existing national and regional research infrastructures of European interest, such as rare diseases.

Data on projects funded by the EC is available in Orphanet[124].

[121] http://cordis.europa.eu/fp7/home_en.html

[122] http://ec.europa.eu/research/participants/portal/page/cooperation;efp7_SESSION_ID=m0pTRn7GxnWW8LynmvWsxs9w6J1KJQC4ByLwcYvzJhm6GL0qNLQX!1982354445?callIdentifier=FP7-HEALTH-2013-INNOVATION-1#wlp_call_FP7

[123] http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-establact_en.pdf

[124] http://www.orpha.net/consor/cgi-bin/ResearchTrials.php?lng=EN

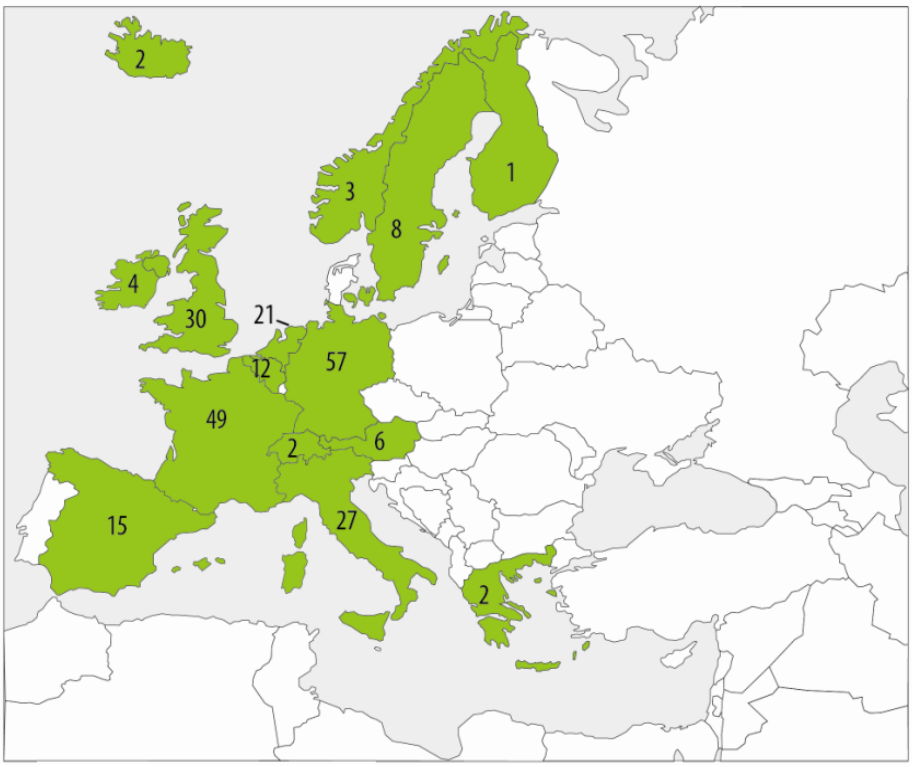

Figure 8: Number of FP7 rare disease related projects in which research groups in European countries have participated as leading partner (Orphanet data extraction, February 2014)

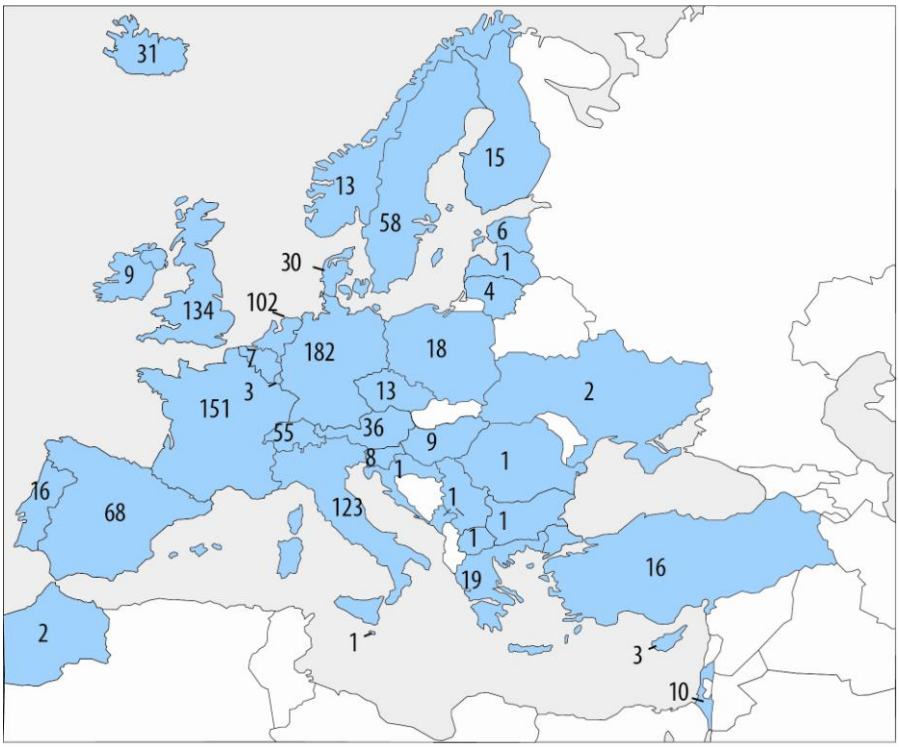

Figure 9: Number of FP7 rare disease related projects in which research groups in European countries are partipating partners (Orphanet data extraction, February 2014)[125]

[125] The projects in which a team is leading partner are not counted, unless there is/are more than one team in a country for the project, one leading and the other(s) participating.

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

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

The International Rare Disease Research Consortium (IRDiRC[126]) was launched in April 2011 to foster international collaboration in rare diseases research. The European Commission and the US National Institutes of Health initiated the discussions, and other stakeholders, including other funding agencies, were also invited to join the consortium. In October 2011 there was a meeting to identify principal research topics and regulatory challenges in this international context, as well as to establish the governance of the consortium.

IRDiRC teams 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 also requires harmonisation of policies related to research use, standardisation, and dissemination. A policy agenda is currently in development.

The IRDiRC is governed by an Executive Committee, three Scientific Committees and twelve working groups. The Executive Committee involves representatives of funding members and three patients' organisations, namely EURORDIS, NORD and the US Genetic Alliance. There are three Scientific Committees, for Diagnostics (including sequencing and characterisation), Therapies (including pre-clinical and clinical development) and Interdisciplinary aspects of rare diseases research (including ontologies, natural history, biobanking, registries etc). The Scientific Committees advise the Executive Committee on research priorities and progress made from a scientific viewpoint. Members of the Scientific Committees were appointed in 2012[127].

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

The funding agencies[128] now committed to the IRDiRC are from the following countries: Australia, Canada, China, Finland, Italy, France, Germany, Georgia, South Korea, the Netherlands, Spain, the United Kingdom, and the United States, in addition to the European Commission[129].

[126] http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html
[127] http://ec.europa.eu/research/health/medical-research/rare-diseases/governance_en.html
[128] The full list can be found here: http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members_en.html
[129] http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members_en.html

Figure 10: Countries with funding agencies committed to the IRDiRC (December 2013)

The EC announced its commitment to supporting the logistical organisation of IRDiRC activities through a dedicated support action topic in the FP7-HEALTH-2012-INNOVATION-1[130] call for proposals (Work Programme 2012). The project funded in this topic, SUPPORT-IRDiRC provides a Scientific Secretariat for the IRDiRC since its launch in October 2012 for a six-year period.

The Call FP7-HEALTH-2012-INNOVATION-1 resulted in the funding of a number of projects contributing directly to the IRDiRC objectives for a total of €40 million. Three large-scale integrating projects are being funded in the area of -Omics for rare diseases: EURenOmics will systematically apply –omics technologies for the molecular characterisation of rare kidney disorders in view of developing new diagnostics and treatments, NEUROMICS aims to use the most sophisticated -omics technologies to revolutionise diagnostics and develop pathomechanism-based treatments for large groups of rare neuromuscular and neurodegenerative diseases and RD-Connect will create an integrated platform connecting registries, biobanks and clinical bioinformatics for rare disease research into a central resource for researchers worldwide. Also 10 new research projects were funded for preclinical and clinical development of orphan drugs with the major involvement of industry and small and medium sized enterprises. The kick-off meetings of these projects were held in Barcelona on 25-27 January 2013.

The first IRDiRC conference[131] was held on 16-17 April 2013 in Dublin, Ireland, bringing together more than 400 participants representing Europe, North America, Australia and Asia. April 2013 also saw the publication of the IRDiRC's policies and guidelines document[132]. This document outlines the principles that the IRDiRC members agree to follow as well as the recommendations from the Scientific Committees. The general policies of the IRDiRC emphasise the collaboration in rare diseases research, the involvement of patients and their representatives in all relevant aspects of research, as well as the sharing of data and resources. Policies and guidelines are also defined for the following topics: ontologies, diagnostics, biomarkers, patient registries, biobanks, natural history, therapeutics, models, publication and intellectual property, and communication on IRDiRC.

[130] http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-1 and http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-2

[131] http://www.irdirc.org/wp-content/uploads/2013/06/IRDiRC_conference_report_April2013.pdf

[132] http://www.irdirc.org/wp-content/uploads/2013/06/IRDiRC_policies_24MayApr2013.pdf and http://www.irdirc.org/wp-content/uploads/2013/06/IRDiRC_Policies_Longversion_24May2013.pdf

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.

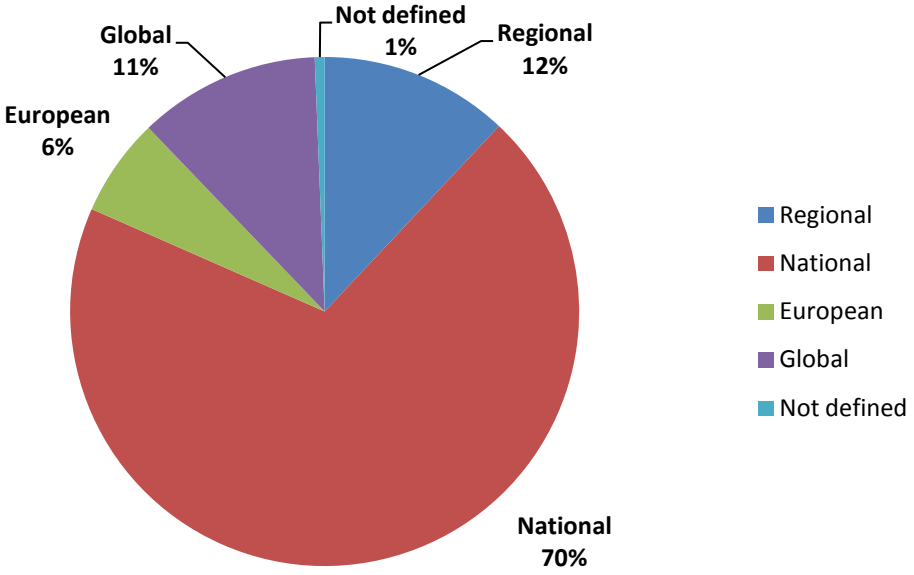

Figure 11: Geographical coverage of rare disease registries in Europe registered in the Orphanet database (January 2014)

According to the data in the Orphanet database, there are 641 disease registries in Europe[133] (40 European, 74 Global, 446 national, 77 regional, 4 undefined).

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

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

The Directorate for Health and Consumers and Joint Research Centre (JRC) have agreed on the active involvement of JRC in the development of public health initiatives in the field of rare diseases and an administrative agreement between the Directorate for Health and Consumers and JRC was signed in December 2013. For this reason, the JRC is currently developing a European Platform on Rare Diseases Registration. The main objectives for this platform are to provide a central access point for information on rare diseases patients' registries for all stakeholders, to support new and existing registries in view of their interoperability, to provide IT tools to maintain data collection and to host activities of the surveillance networks. The European Platform on Rare Diseases Registration platform will work to coordinate the activities of two surveillance networks: EUROCAT (European surveillance of congenital anomalies) and SCPE (Surveillance of Cerebral Palsy in Europe).

[133] Data extracted from Orphanet, January 2014, covering EU countries and surrounding countries participating to the Orphanet consortium. More information can be found in the *Orphanet Report Series – Rare Disease Registries in Europe* http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

3.3. State of the art of rare disease research activities in Europe

So far the Orphanet database contains 5 707 ongoing research projects for an estimated 2 129 rare diseases[134] taking place in EU countries and surrounding countries participating in the Orphanet consortium.

In addition, an analysis[135] of the Orphanet database also shows that there are 2 257 ongoing clinical trials registered in the database for 30 countries, covering 595 diseases.

Figure 12: Number of research projects and clinical trials by stage/type of research taking place in the EU countries and surrounding countries participating in the Orphanet consortium (Orphanet data extraction, March 2014) [136]

Category	Type of project/study	Number of projects
Basic research	Gene search	513
	Mutations search	595
	Gene expression profile	281
	Genotype-phenotype correlation	393
	In vitro functional study	1048
	Animal model creation/ study	509
	Human physiopathology study	748
Pre clinical research	Pre-clinical gene therapy	179
	Pre-clinical cell therapy	90
	Pre-clinical drug development	0
	Pre-clinical vaccine development	31
	Medical device/instrumentation development	25
Clinical research	Observational clinical study	452
	Clinical trials	2257
	Epidemiological study	224
Diagnostics & biomarkers	Diagnostic tool / protocol development	295
	Biomarker development	158
Other	Health sociology study	79
	Health economics study	15
	Public health / health services study	72
Total number of projects and studies		**7964**

[134] Data extracted from Orphanet concerning EU countries and surrounding countries participating in the Orphanet consortium, February 2014.
[135] Extraction from Orphanet in March 2014. This number includes trials taking place in different countries for the same study.
[136] Data extracted from Orphanet concerning EU countries and surrounding countries participating in the Orphanet consortium, February 2014.

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 the low number of projects in Figure 11. The category "clinical research" includes non-therapeutical clinical research, epidemiological research and clinical trials. "Diagnostics 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 of pharmaceuticals, Orphan designations act as a proxy when considering potential products in development. Around 977 substances and 1457 designations are registered in the Orphanet database covering around 539 rare diseases[137]. In Europe there are 783 active substances and 991 designations covering 399 diseases in Orphanet and in the USA there are 403 active substances and 467 positive designations covering 318 diseases. According to an analysis[138] carried out by Orphanet, there are 164 medicinal products (with European Market Authorisation) to potentially treat 183 diseases. Of these, 68 orphan medicinal products (with European Market Authorisation and European Orphan Designation) target 78 diseases. In comparison, in the United States 367 medicinal products with US Marketing Authorisation and US Orphan Designation represent 379 indications for rare diseases (however, the prevalence threshold to define rarity is different in Europe and the USA): 20 medicinal products are present in both lists.

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. This work is currently supported by the Joint Action EUCERD: Working for Rare Diseases (N° 2011 22 01). The Orphanet nomenclature of rare diseases is a stable one, directly exploitable by information systems and available on request as an open-source service via www.orphadata.org.

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. After having been open for comments in 2012, the ICD-11 draft can be browsed online at http://apps.who.int/classifications/icd11/browse/f/en. This includes 5681 rare diseases.

[137] Analysis carried out by Orphanet in March 2014.
[138] Analysis carried out by Orphanet in March 2014.

In addition to this effort to update ICD, the Orphanet inventory of diseases is cross-referenced with other nomenclatures, namely SnoMed-CT, MeSH and MedDRA. The list of rare diseases, the classifications and the cross-referencing with other terminologies is available on www.orphadata.org.

France has decided to use Orphacodes in addition to the exisiting coding sytem for rare diseases in the health care system and as of 2012 hospital records concerning rare diseases require an Orphacode in addition to an ICD code. Germany is in the process of introducing the use of Orphacodes alongside ICD10 codes in the German health care system. Other countries are also considering the use of Orphacodes in their health information systems.

4. Orphan medicinal products and other therapies for rare diseases

The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000)[139] was adopted in December 1999 and came into force in the European Union in 2000. The Regulation addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides incentives for products receiving an orphan designation (e.g. protocol assistance, market exclusivity, centralised procedure). The incentives contained in the legislation aim to assist sponsors receiving orphan medicinal product designations in the development of medicinal products with the ultimate goal of providing medicinal products for rare diseases to patients.

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

4.1. Orphan designated products at European level

Since its implementation, the Regulation on Orphan Medicinal Products has yielded more than 1 234 positive opinions for orphan product designation, adopted from 1 789 applications reviewed since 2000. To date, the distribution of the prevalence of conditions for which the designations have been adopted shows that the most frequently designated conditions have been those that affect between 1 and 3 in 10 000 patients, that is between approximately 50 000 and 150 000 people (receiving 50% of all orphan designations). Indeed, 48% 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.

[139] This section reproduces information from http://ec.europa.eu/health/rare_diseases/orphan_drugs/strategy/index_en.htm

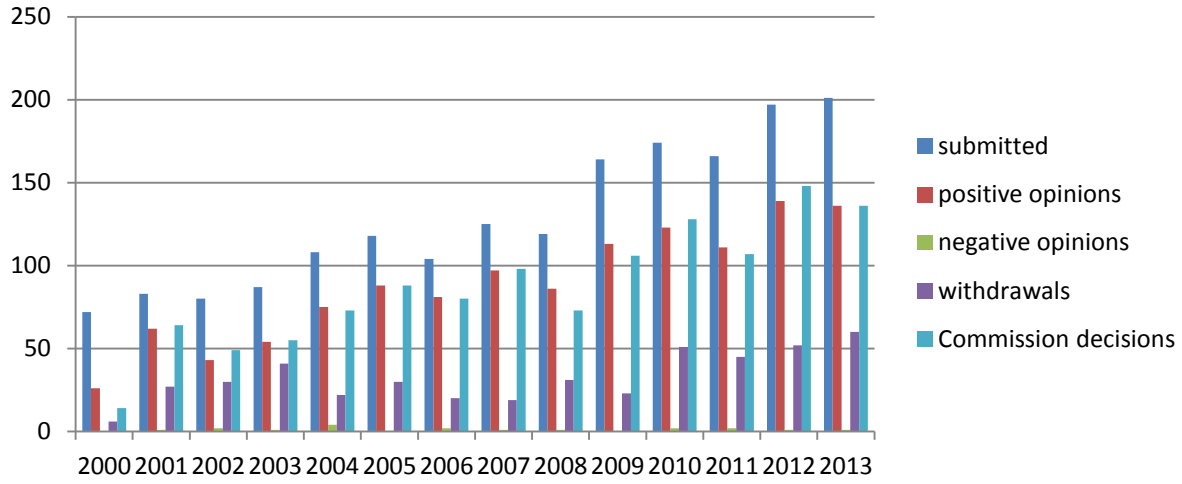

Figure 13 : Status of orphan designation applications (January 2014)[140]

The number of applications has increased steadily each year during the first decade of the Regulation with 201 applications received in 2013. Eighty-five designated products had received marketing authorisation by the end of 2013[141], of which oncology is by far the most common therapeutic area (40%). The average time span between designation and authorisation is 4.8 years.

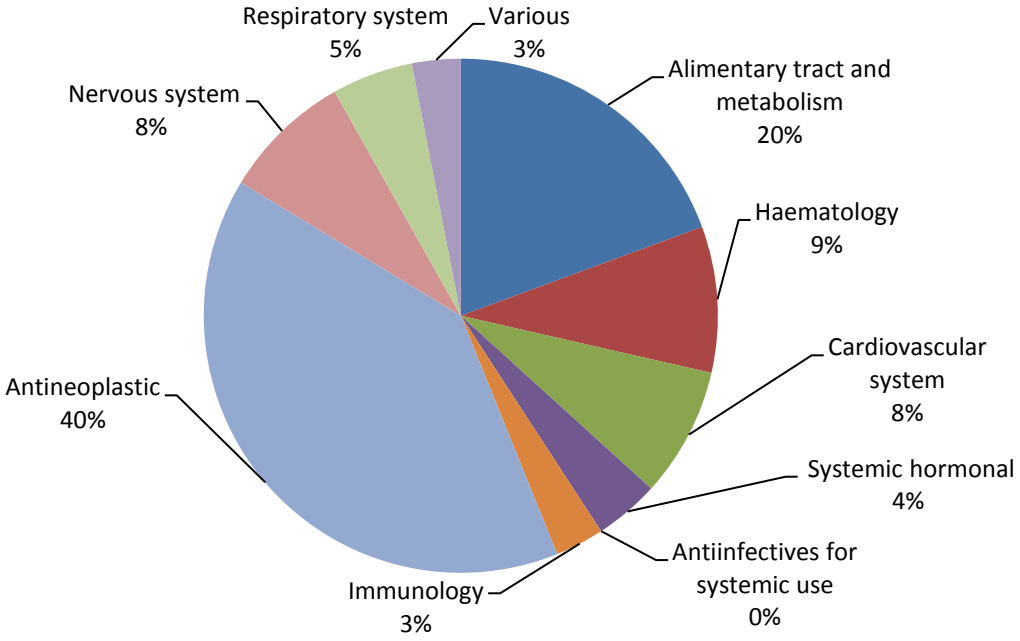

Figure 14: Distribution of orphan designation positive opinions in 2013 by therapeutic area[142]

In 2013 alone, the COMP adopted 136 positive opinions on orphan designations with around 100 diseases covered by these deignations. The European Commission granted 136 orphan designations in 2013[143]. Seven

[140] Figures and data courtesy of the European Medicines Agency, January 2014.
[141] This figure includes withdrawals and extension of indications/variation.
[142] Courtesy of the European Medicines Agency, January 2014.
[143] Data provided by EMA :
http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2014/01/WC500159429.pdf

orphan medicinal products received marketing authorisation in 2013 covering 8 conditions (due to variations). This information can be accessed via the European Community Register of Medicinal Products[144].

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): as of 2013, the COMP had given more than 80 positive opinions for advanced therapy products out of a total of 1 234 positive opinions for orphan medicinal product designation.

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

4.2. Availability of orphan medicinal products at Member State level

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

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

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

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

One or the main factors limiting access to new orphan medicinal products in the European Union is no longer market authorisation, but the Health Technology Assessment (HTA) in individual Member States. This results in notable differences in terms of access for patients in one country to another: this issue is not addressed in the Cross-Border Healthcare Directive. However, there are two initiatives in this field which aim to ultimately improve access to orphan medicinal products:

a) The Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow
b) The Mechanism of coordinated access to orphan medicinal products (MoCA-OMP)

[144] http://ec.europa.eu/health/documents/community-register/html/index_en.htm

Firstly, before exploring these two initiatives, it should be highlighted that as part of the European Medicine Information Network (EMINet) project, a report was published in 2011 on an *Initial Investigation to Assess the Feasibility of a Coordinated System to Access Orphan Medicines*[145]. This report, commissioned by the European Commission DG Enterprise and Industry, presents a country-by-country survey of accessibility to orphan medicines, with an emphasis on product distribution through Centres of Expertise and derogatory procedures for accessing products in situations of restricted availability (typically Compassionate Use-type programmes). Taking Pompe disease and pulmonary arterial hypertension as examples, the EMINet report surveys both the availability of treatments across Europe and the distribution of centres of expertise for the diseases. The EMINet findings, combined with the EUCERD Recommendation on Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow (September 2012), contribute to the debate on efficient and equitable distribution of orphan medicinal products. Both reports seek to further the understanding of product access and availability for rare disease treatments across Europe. This feeds in to the reflection on a coordinated system for accessing orphan medicinal products.

a) EUCERD Recommendation on Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow (September 2012)

In 2012 the EUCERD issued a recommendation on improving the assessment of the Clinical Added Value of Orphan Medicinal Products (CAVOMP), encouraging the creation of an Information Flow[146]. It has been acknowledged over recent years that, while the EU Regulation on Orphan Medicinal Products EC 141/2000 has stimulated research and development of orphan medicinal products in the EU, equitable and timely access to approved orphan medicinal products for rare diseases patients remains an issue. Large disparities in access exist between and even within the European Member State countries.

To address this issue, several policy documents have called for an increased cooperation between EU-level authorities and Member States, notably in order to improve access to Orphan Medicinal Products for people living with rare diseases:

- The EU Regulation on Orphan Medicinal Products (16 December 1999)
- Final Conclusions and Recommendations of the EU High Level Pharmaceutical Forum[147]
- The Commission Communication on "Rare Diseases: Europe's Challenges" (11 November 2008)
- The Council Recommendation on a European Action in the Field of Rare Diseases (8 June 2009).

The EUCERD was asked to make recommendations to the European Commission on potential ways to facilitate scientific information exchange on orphan medicinal products, in order to support the Member States in their processes of making informed decisions on the scientific assessment of the clinical effectiveness of an orphan medicinal product.

This EUCERD recommendation highlights the fact that the lifecycle of an orphan medicinal product is a continuum of evidence generation, which is needed by assessors and decision makers, as well as being necessary to improve the good use of medicines and thereby optimising the use of limited resources.

The EUCERD recommendation encourages the creation of an Information Flow between individual Member States and between Member States and the EU bodies, which would bridge existing knowledge gaps, especially at the time of marketing authorisation. This information flow and sharing fits into existing regulatory, clinical, Health Technology Assessment (HTA), pricing and reimbursement processes, while avoiding additional burdens.

The CAVOMP information flow recommended by the EUCERD includes the four following time points:

- Timepoint 1: Early dialogue
- Timepoint 2: Information exchange: compilation Report and evidence definition / Evidence Generation Plan (EGP)
- Timepoint 3: Follow-up of the EGP
- Timepoint 4: Assessment of relative effectiveness

[145] http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access_orphans_initialinvest_052011_en.pdf
[146] http://www.eucerd.eu/?post_type=document&p=1446
[147] http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum_final_conclusions_en.pdf

The recommendation capitalises on existing mechanisms, procedures and regulatory frameworks, and does not bring new obstacles to the assessment process: each element within the Information Flow would be maintained by the corresponding institution responsible for that activity during each particular point in time.

The EUCERD Recommendation on *Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow* will ultimately accelerate access to approved orphan medicinal products, by providing the most robust set of information possible, while encouraging pricing and reimbursement decisions based on the value of the orphan medicinal products and promoting good medical practices throughout the EU. The Recommendation has been submitted to the European Commission.

b) Mechanism of coordinated access to orphan medicinal products (MoCA-OMP)

In addition, the Working Group "Mechanism of coordinated access to orphan medicinal products (MoCA OMP)[148]", one of the groups of the Platform on Access to Medicines in Europe (part of the ongoing Process of Corporate Social Responsibility initiated by Commissioner Tajani), has developed a definition of "coordinated real life access". The term "coordinated real life access" refers to when:

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

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

Results of most working groups under the platform "Access to medicines in Europe" were endorsed by the Steering Group members[149] in April 2013. In terms of the Mechanism of Coordinated Access to Orphan Medicinal Products working group, agreement was reached on a final report[150] which includes "Key conclusions and recommendations"[151], and an indicative set of criteria, such as available alternatives or response rate against which value could be assessed[152], so as to ultimately facilitate access for patients.

On another note, the budgetary impact of orphan medicinal products is progressively coming under the spotlight: budgetary considerations are tightly linked to availability issues. Increasingly Member States are monitoring and publishing data on the budgetary impact of orphan medicinal products. Schey et al[153], estimate that although the number of approved orphan medicinal products has increased following European legislation, the growth in cost of these drugs as a proportion of total pharmaceutical expenditure, is likely to plateau over the next decade as orphan growth rates converge with those in the pharmaceutical market at large. Based on this forecast, it is suggested that the European orphan medicinal product legislation is not leading to a disproportionate impact on pharmaceutical expenditure.

148 http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/platform_access/index_en.htm#h2-2

149 http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/platform_access/index_en.htm

150 http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/orphans_conlusions_en.pdf

151 http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/orphans_conlusions_en.pdf

152 http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/orphans_framework_en.pdf

153 Estimating the budget impact of orphan medicines in Europe: 2010 – 2020, Orphanet Journal of Rare Diseases, September 2011, Schey et al., http://www.ojrd.com/content/6/1/62

5. Patient organisations

According to the Council Recommendation (8 June 2009), the WHO has defined the empowerment of patients as a "pre-requisite for health" and encourages a "proactive partnership and patient self-care strategy to improve health outcomes and quality of life among the chronically ill"[154]. In this sense, the role of independent patient groups is crucial both in terms of direct support to individuals living with the disease and in terms of the collective work they carry out to improve conditions for the community of rare disease patients as a whole and for the next generations. The Council also recommends that Member States *"consult patients and patients' representatives on the policies in the field of rare diseases and facilitate patient access to updated information on rare diseases"* as well as *"promote the activities performed by patient organisations, such as awareness-raising, capacity-building and training, exchange of information and best practices, networking and outreach to very isolated patients".*

5.1. EURORDIS

EURORDIS[155] 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-Téléthon), the European Commission, corporate foundations and the health industry. EURORDIS represents over 600 rare disease organisations in 58 countries (of which 26 are EU Member States), covering more than 4 000 different rare diseases. It is therefore the voice of the 30 million patients affected by rare diseases throughout Europe.

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

EURORDIS is actively involved in the work carried out by the European Medicines Agency (EMA) and the European Commission in the field of health research and healthcare. EURORDIS has 7 representatives and 2 observers on EMA scientific committees and a Working Party: the Committee for Orphan Medicinal Products (COMP), the Committee for Advanced Therapies (CAT), the Paediatric Committee (PDCO), the Patients' and Consumers' Working Party (PCWP). From July 2010 until July 2013, EURORDIS was represented by 4 patients' representatives and their alternates at the European Union Committee of Experts on Rare Diseases (EUCERD). The EUCERD has now been replaced by the Commission Expert Group on Rare Diseases. EURORDIS has 1 representative and their alternate as well as 2 Observers. The 3 other patients' representatives and their alternates in the Expert Group represent the European Network of National Alliances of rare disease patients' organisations, the European Network of European Federations of rare diseases and EGAN - European Genetic Alliances' Network. They are all members of EURORDIS.

[154] http://www.euro.who.int/Document/E88086.pdf
[155] www.EURORDIS.org

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 under development or already in place. Many also have a place on official committees treating issues directly related to the needs of rare disease patients.

An increasing number of National Alliances of rare disease patient organisations have been created in Europe. The Member States where National Alliances have been established include: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovak Republic, Spain, Sweden and the United Kingdom. In addition, Alliances have been established in Switzerland in 2010 and in Russia in 2011.

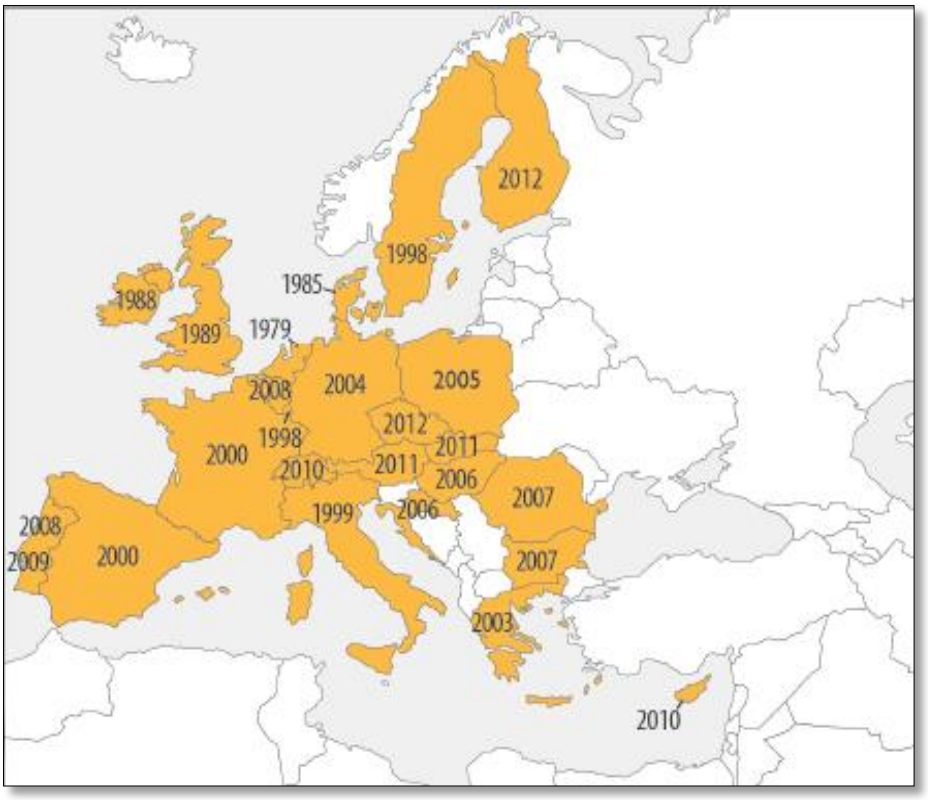

Figure 15: Countries in Europe with a national alliance for rare disease patient organisations and year founded

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

EURORDIS and the National Alliances also work together to help translate European directives or recommendations into national policies such as adopting a national plan for rare diseases and implementing the EU Directive on Patients' Rights in Cross-Border Healthcare.

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

In 2014, 2 565 disease-specific patient organisations were registered in the Orphanet database[156]. Of these, 2 146 were national disease-specific patient organisations, 276 were regional disease-specific organisations, 73 were European disease-specific patient organisations, and 69 were international disease-specific patient organisations.

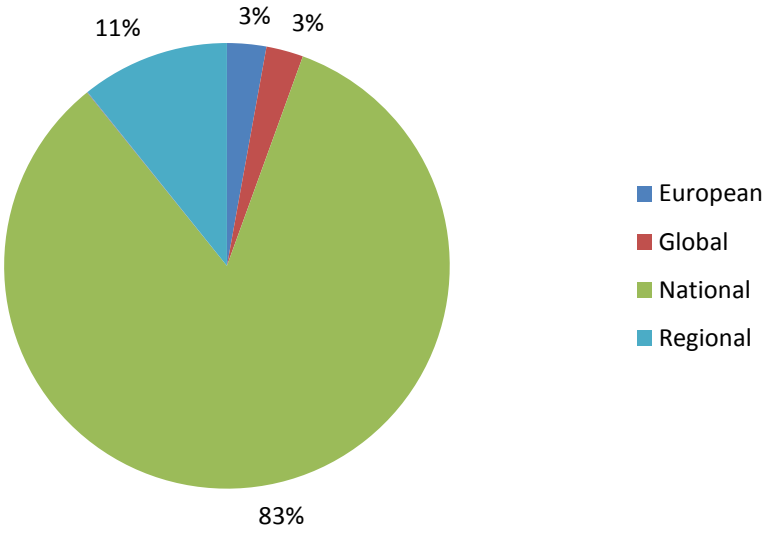

Figure 16: Geographical coverage of disease-specific patient organisations in the Orphanet database (March 2014)

In parallel to the Council of National Alliances, EURORDIS has created the Council of European Federations and Networks (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 to help raise awareness for patients, families and carers living with rare diseases. Following the success of the first year, the participants decided Rare Disease Day should be observed on the last day of February each year. The campaign has progressively become an international event, with organisations in the USA joining in 2009. Participation has steadily grown around the world. Events were held in 73 countries in 2013 and in 84 countries in 2014.

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

[156] Data extracted from the Orphanet database in March 2014 concerning countries in the Orphanet consortium.

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

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

EURORDIS coordinates the campaign at the international level and, where possible, the National Alliances coordinate events at the national level. Together they decide on a common annual theme and common actions. EURORDIS provides a communication material tool kit and operate the Rare Disease Day website (www.rarediseaseday.org) and social media channels.

6. Information services

6.1. Orphanet

Orphanet[157] 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 inventory of diseases, the encyclopaedia and the collection of data on expert services in European countries (since 2000 with DG Health and Consumers grants and since 2004 with DG Research funding). Orphanet data is collected in each European Member State and is expert validated.

In 2013, around 20 million pages were viewed, thus on average around 54,000 pages viewed per day. This figure has increased by 61% in comparison to 2012 (12.2 million page views in 2012). The users come from 211 countries. The top ten countries visiting the site are: France, Italy, United States, Germany, Spain, Mexico, Brazil, Canada, Belgium and Switzerland[158].

To resolve the issue of information dispersion Orphanet provides direct online access to all stakeholders to: an inventory of rare diseases and an encyclopaedia in 6 languages (English, French, Spanish, German, Italian and Portuguese). Each European country will soon have an access point to Orphanet in their national language(s).

Each disease in Orphanet has a unique identifier and is placed in a poly-hierarchy classification system. All the classifications of diseases can easily be displayed on the website. Orphanet has also developed an encyclopaedia published in an electronic, open-access journal, the Orphanet Journal of Rare Diseases[159]. 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 37 countries. To promote quality services, data on quality management of clinical laboratories are available on the website. Distinct logos indicate which laboratories are certified, accredited and/or participate in external quality assessment. This information is gathered and validated in partnership with EuroGentest. To facilitate collaboration between researchers and between researchers and Industry, Orphanet lists all ongoing national and European-level funded research projects by type of research and by disease. The licensing opportunities are displayed, as well as the patient registries, biobanks and highly specialised platforms and know-how, which may be of interest in R&D. To help patients establish contact with other patients, Orphanet provides information on existing patient organisations. In addition to these services, Orphanet provides an inventory of orphan medicinal products and other products for rare diseases in Europe. To support policy-makers, Orphanet regularly publishes reports in a collection entitled “Orphanet Report Series”: reports in the series include lists

[157] www.orpha.net
[158] Information from Orphanet 2013 Activity Report http://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2013.pdf
[159] www.orjd.com

of rare diseases with their prevalence[160], lists of orphan drugs in Europe[161], lists of rare disease registries in Europe[162] and lists of collaborative research projects and clinical networks in the field of rare diseases funded by the European Commission[163].

The European Commission proposed to fund Orphanet as a Joint Action between the European Commission and the Member States from April 2011, with a budget of €7.2 million.

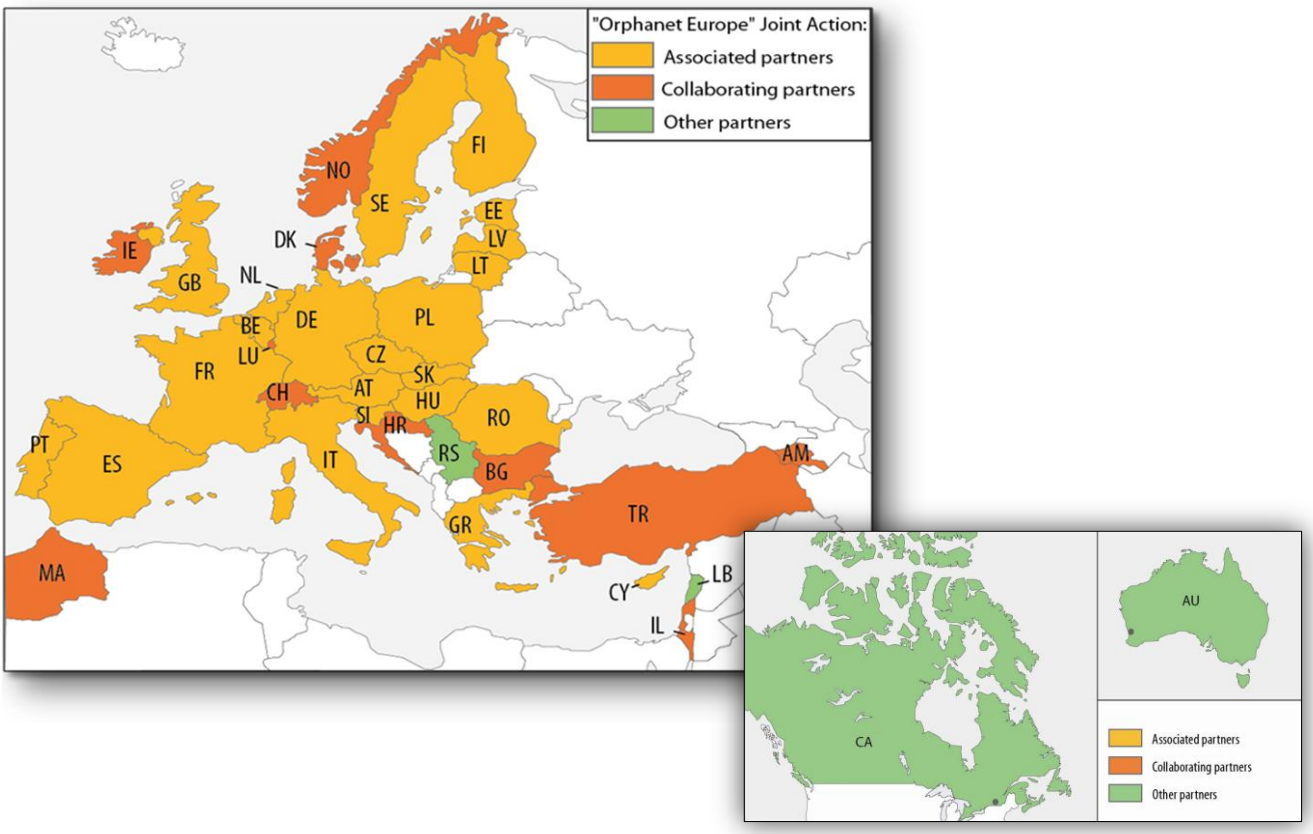

Figure 17: Countries participating in the Orphanet Joint Action (2011-2013)

The Orphanet network has recently expanded at the International level: Canada joined Orphanet in 2011, Australia in 2012, and negotiations have started with Argentina, Brazil, Chile, China, Japan and Russia.

The main achievements[164] of 2013 were:

- The Orphanet rare diseases ontology (ORDO) produced in collaboration with the EBI is now available on Bioportal (http://purl.bioontology.org/ontology/OntoOrpha). It represents a powerful research tool.
- The international website and the database have been translated into Dutch and since June 2013 all the information is accessible to users in Dutch.
- The encyclopaedia of rare diseases has been expanded and updated. As of 31 December 2013, some abstracts are available in Finnish, Polish, Greek and Slovak in addition to English, French, German, Italian, Spanish, Portuguese and Dutch. Emergency guidelines are available in Polish in addition to English, French, German, Italian, Spanish and Portuguese.

[160] http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
[161] http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf
[162] http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf
[163] http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf
[164] http://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2013.pdf

- A new collection of texts in the Orphanet Encyclopedia has been established. It is devoted to the disabilities associated with each rare disease and is addressed to the professionals in the field of disability as well as to the patients and their families.
- The directory of expert centres, medical laboratories, clinical trials, research projects, networks, registries and patient organisations has been expanded and updated.
- A new Orphanet Report Series was created about the European infrastructures useful to rare diseases.
- The list of rare diseases (in English and French) has been published as an Orphanet Report Series for more effective communication but also for easy retrieval of the Orpha codes by clinicians and coders.
- Most of the Orphanet Report Series have been updated (List of Rare Diseases, Prevalence of Rare Diseases, Lists of Orphan Drugs, Orphanet Activity Reports, and Satisfaction Surveys).
- An Orphanet mobile application was released for iPhone, iPad and Android, including the list of rare diseases, textual information and list of expert centres.
- The Orphanet Activity report 2012 has been translated into French, Italian and Spanish.
- The Orphanet Standard Operating Procedures, according to which Orphanet national teams agree to work, have been posted on the website.
- The Orphanet nomenclature has been included in several national health information systems; working groups and collaborations were set up in France, Germany, Belgium and Latvia. Collaborations are planned with Greece and Hungary.
- Germany has aligned the Orpha codes with its national extension and plans to add the missing codes in the next two years (up to 2016). DIMDI is developing a file for implementation in existing IT-systems which makes coding easier for coders and standardises coding results, if coded in both systems.
- The Orphanet online registration tool was launched in order to allow health professionals, patient organisations and researchers to submit or update their information related to rare diseases in Orphanet.

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

The dataset encompasses:

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

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

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

Orphadata provides a guide for users that defines and describes the elements of the dataset. Orphadata is intended to contribute to accelerating R&D and to facilitate global adoption of the Orphanet nomenclature. Since January 2012, Orphadata products were downloaded more than 57 000 times, with an average of 4 800 downloads per month.

6.2. Official information services/centres at Member State level

Apart from the information on national expert services provided by Orphanet, a number of Member States have established official information services or information centres specifically concerning rare diseases at Member State level. Official rare disease information services are those designated and/or funded by national authorities. The countries having established these services/centres are: Austria, Bulgaria, Croatia, Denmark France, Italy, the Netherlands, Romania and Sweden. Norway's centres of expertise also play the role of official information centres for rare diseases. Countries are also establishing/have established National Contact Points in the context of the implementation of the Cross-Border Healthcare Directive[165].

In addition, Rarelink[166] is a web resource providing information on rare diseases which has developed through collaborations between the former Center for Små Handicapgrupper (Denmark, discontinued in 2010), the Department for Rare Disorders in the Directorate for Health and Social Affairs (Norway), and the Swedish National Centre for Rare Diseases (Sweden), with the recent collaboration of Harvinaiset (Finland). These government bodies have for several years made a joint effort at disseminating knowledge regarding rare disorders. A key element of this effort has been the publication of information on the internet. Rarelink is available in Norwegian, Swedish, Danish, Finnish and Icelandic.

6.3. Official rare disease helplines at Member State level

A few European countries have official rare disease-specific helplines aimed at providing information to patients, families and professionals alike. Official rare disease helplines are those designated/accredited and/or funded by national authorities. These countries are: Bulgaria, Croatia, France, Italy, the Netherlands, Norway, Portugal, Romania, Sweden and Spain. Denmark ran such a service until 2012. The United Kingdom also has a well recognised helpline providing information orientated to patients with rare diseases. Some additional countries have non-official helplines, notably those run by national alliances of rare disease patient organisations, and the remaining countries often maintain non rare-disease specific helplines to help orientate users of national health systems, with patient organisations often also providing support by telephone.

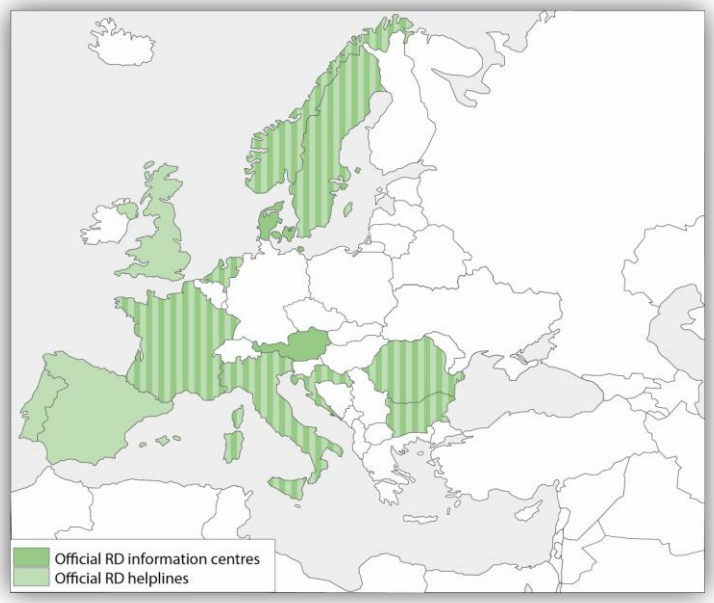

Figure 18: Countries in Europe with official information centres and helplines for rare diseases (December 2013)

[165] http://ec.europa.eu/health/cross_border_care/docs/cbhc_ncp_en.pdf
[166] www.rarelink.org

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 15 000 subscribed readers, twice a month. OrphaNews Europe was launched on the 15 June 2005 and over 100 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 pulication of OrphaNews Europe is supported by the AFM (Association Française contre les Myopathies) and the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01 from March 2012. National editions of the newsletter are available when national funding is available: this is the case in France (since 2003) and in Italy (since 2011).

CONTRIBUTIONS AND SOURCES[167]

A full list of the over one hundred contributors to the State of the Art report and its sources can be found here:
http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivities_ContributionsSources.pdf

This report was compiled by Charlotte Rodwell
(Scientific Secretariat of the EUCERD Joint Action, INSERM US14, France)

METHODOLOGY AND STRUCTURE

1. SOURCES

The main sources of data for the update of the present report were those collected through the systematic surveillance of international literature and the systematic query of key stakeholders carried out in order to produce the OrphaNews Europe newsletter, various reports published by the European Commission (including past reports of the workshops of the EUCERD) and other specialised reports on topics concerning the field of rare diseases and orphan medicinal products. The principal information sources and the collection of data are described in detail here below.

- **European Commission websites and documents**
  Information and documentation from the European Commission was used in order to establish this report, principally accessed through the rare disease information web pages of the Directorate General Public Health[168] and Directorate General Research CORDIS website[169] as well as the site of the European Medicines Agency[170], in particular the pages of the COMP[171] (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**
  Data from the OrphaNews Europe[172] newsletter for the 2012 period was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France[173] (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

- **EUCERD Publications**
  Parts III, IV and V of this report present an update of the information previously published in the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*[174] (July 2010), *2011*

[167] The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.
[168] http://ec.europa.eu/health/rare_diseases/policy/index_en.htm
[169] http://cordis.europa.eu/home_fr.html
[170] www.ema.europa.eu
[171] 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
[172] http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews
[173] http://www.orpha.net/actor/cgi-bin/OAhome.php
[174] http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf

Report on the State of the Art of Rare Disease Activities in Europe of the eucerd[175]*, 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD*[176], and the *2013 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Disease*[177]*s* The methodology for the production of these previous reports is outlined in their respective introductions. In addition, reports from previous workshops of the EUCERD, including the EUCERD Joint Action have been used.

- **Reports of the EUCERD meetings**
  The reports of 2013 meetings of the EUCERD were used in order to identify upcoming initiatives and incentives in the field of rare diseases, and to report on the events held to mark Rare Disease Day 2013.

- **Reports on orphan medicinal products**
  The information provided for each Member State concerning the state of affairs in the field of orphan medicinal products has been elaborated, when referenced, from the basis of the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*[178] 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)*[179]. This report notably provided information for the Member State sections on Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The Office of Health Economics Briefing Document *"Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries (No. 52 October 2009)"* also provided information on orphan medicinal product availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V was added during the revision of the 2012 edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*[180] by Donald Macarthur: this report is referenced in footnotes when used.

- **EURORDIS website and websites of national alliances of patient organisation**
  The site of EURORDIS, the European Organisation for Rare Diseases[181] was used to provide information on EURORDIS activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national patient alliances were also consulted for information. In addition to this the Rare Disease Day 2012 site[182], maintained by EURORDIS, also provided information on events at Member State level[183] concerning Rare Disease Day.

- **Orphanet**
  The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare

[175] http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf ; http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf ; and http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf
[176] http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf ; http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesII.pdf ; and http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf
[177] http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf
[178] http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf
[179] *Politiques relatives aux maladies orphelines et aux médicaments orphelins* https://kce.fgov.be/sites/default/files/page_documents/d20091027332.pdf
[180] http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf
[181] http://www.EURORDIS.org/secteur.php3
[182] http://www.rarediseaseday.org/
[183] http://www.rarediseaseday.org/country/finder

disease research projects, registries, clinical trials, patient organisations and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links[184] to other web-based information services and help-lines which were used to collect information at country-level. The Orphanet Country Coordinators also provided valuable input into the elaboration of information at country level, notably via contributions to OrphaNetWork News. The national Orphanet websites were also consulted to gather national events and initiatives.

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

2. METHODOLOGY

The present report provides an updated compilation of information from the previous reports of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the European Union Committee of Experts on Rare Diseases, 2011 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases, 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases* and *2013 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Disease*) which have covered activities up to the end of 2012. The present edition takes into account advances and activities in the field of rare diseases and orphan medicinal products at EU and MS level in 2013.

Once this information from the previous report was updated using the sources cited above, a draft of each country section (Part V) was sent in March 2014 to EC Expert Group on Rare Diseases Member States representatives with a guidance document providing an explanation of the type of information to include if available for each category. The Member State representatives were asked to contact a range of identified key stakeholders in their country for input. The stakeholders identified for each country included: the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, partners of the E-Rare consortium, Member State representatives on the COMP, representatives of national competent authorities, coordinators of national plans for rare diseases and other rare diseases experts identified at national level. The Member State representatives integrated the stakeholder feedback into their report before returning it to the Scientific Secretariat for homogenisation and extraction of developments in 2013 to be included in Part II. Final drafts of Parts II, V, VI concerning their country were sent to the EC Expert Group on Rare Diseases Member State representatives for final validation, to the best of their knowledge, in May 2014.

Part III and IV of the report on activities at European Union level was for input, to the best of their ability, to colleagues at the European Commission and the European Medicines Agency (EMA) respectively: this process was carried out in April 2014 by the Scientific Secretariat of the EUCERD Joint Action. The European Commission and its agencies are not responsible, however, for the completeness and the accuracy of the information presented in this report. The new activities in 2013 were extracted and added to Part II.

Part I was the final volume of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe is the result of an analysis of the information collected for Parts II, III, IV and V. Part I was drafted by the Scientific Secretariat of the EUCERD Joint Action and then sent to all EC Expert Group on Rare Diseases Member State representatives for their input concerning their country's activities before publication in June 2014.

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

3. REPORT STRUCTURE

The report is structured into three main parts: Part I consists of an overview of the activities in the field of rare diseases in Europe at EU and MS level; Part II is an extraction of the developments at EU and MS level in 2013 based on Parts III, IV and V; Part III concerns activities of the European Commission; Part IV concerns European Medicines Agency activities and other European activities/events at European level apart from the activities of the European Commission; Part V concerns activities at EU MS level, as well as five other non-EU European countries where information was available; Part V provides the content of Parts II and V in individual country-specific reports.

Each part is followed by a a link to a selected bibliography outlining the sources used to produce that part of the report, which includes a list of the European Commission documents referred to in the report and a list of web addresses by country listing national sources of information on rare diseases and links to documents concerning national plans or strategies for rare diseases when in place. Each part is also followed by a link to the list of contributors to the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous edition of the report. A list of frequently used acronyms has also been included in each part to ease reading.

Part I provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts III, IV and V, which serve to provide more detailed background information at EU and MS level. The overview is structured into a number of topics: political framework, expert services in Europe, research and development, orphan medicinal products and therapies for rare diseases, patient organisations and information services.

Part II is a new section of the report, providing information extracted from Parts III, IV and V, relative only to the new activities and initiatives reported for the year 2013.

Part III of the report focuses on activities in the field of rare diseases at EC level is split into four sub-sections:

1. EC activities related to rare diseases in the field of public health;
2. EC activities related to rare diseases in the field of research;
3. EC activities in the field of orphan medicinal products and therapies for rare diseases.

The sub-section concerning the EC activities actions in the area of Public Health is divided into three parts: an overview of DG Health and Consumers' activities in the field of public health, activities in the field of rare diseases funded by DG Health and Consumers, and activities of DG Health and Consumers indirectly related to rare diseases. The sub-section concerning the EC activities in the field related to research in the field of rare diseases presents information concerning DG Research and Innovation's 5th, 6th and 7th framework programmes for research, technological development and demonstration activities and Horizon 2020 related to rare diseases, as well as information concerning the International Rare Disease Research Consortium (IRDiRC).

Part IV of the report contains information on the activities in the field of rare diseases of the EMA and other rare disease activities at the European level, including selected transversal EU activities and conferences at European level:

- European Medicine Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases, EMA Committee for Orphan Medicinal Products' activities, EMA Committee on Human Medicinal Products' activities, European legislation and activities in the field of clinical trials, European legislation and activities in the field of advanced therapies, European legislation and activities in the field of medicinal products for paediatric use, other EMA activities and initiatives relevant to rare diseases and orphan medicinal products, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan medicinal products.

- The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-

Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2013.

Part V concerns the rare disease activities in the field of rare diseases in each of the 28 Member States plus Iceland, Norway, and Switzerland in addition to Serbia and Turkey as candidates for EU membership, as well as Israel. These sections are organised in alphabetical order by country.

The information on each country is clearly divided into a number of categories:

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise[185]
- Registries
- Neonatal screening policy
- Genetic testing[186]
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Guidelines
- Training and education initiatives
- National rare disease events in 2013[187]
- Hosted rare disease events in 2013[188]
- Research activities (National research activities, Participation in European research projects[189], Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability[190], Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products), Other therapies for rare diseases
- Orphan devices
- Specialised social services

The categories for which information is provided depend wholly on the information available following data collection from the described sources and contact with stakeholders. If no detail has been given for a topic, the mention “no specific activity/information reported” has been added.

Part VI concerns the rare disease activities in the field of rare diseases in each of the 28 Member States plus Iceland, Norway and Switzerland in addition to Serbia and Turkey as candidates for EU membership, as well as Israel. This section is the same as Parts II and V, except that the information is presented as a separate document for each country to facilitate dissemination at country level.

Each section has two parts: firstly the state of the art up until the end of 2013, and secondly the state of the art of activities in 2013 only so as to easily identify new actions and activities.

[185] The term “official centre of expertise” used in this report means officially designated via a (ministerial) procedure.
[186] This section contains data extracted in January 2014 from www.orpha.net of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term ‘estimated’ is used as the concept of a single disease is a variable one).
[187] As announced in OrphaNews Europe.
[188] As announced in OrphaNews Europe.
[189] Number of projects (Framework Programme 7 funded, including E-Rare) in which research teams from the country are participating as extracted from www.orpha.net in March 2014.
[190] Contacts were asked to provide information on availability of orphan medicinal products (i.e. which drugs are launched on the market/sold at national level). As this information is often hard to identify, some countries instead provided information on which drugs are accessible (i.e. reimbursed, on a positive drug list etc.). It is explicitly explained in each case which of these concepts is being referred to.

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