

2013 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE



PART III: EUROPEAN COMMISSION ACTIVITIES IN THE FIELD OF RARE DISEASES

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

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ACRONYMS

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

GENERAL INTRODUCTION

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

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2012. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of 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 2012

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

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

1. METHODOLOGY AND SOURCES

The main sources of data for the update of the present report were those collected through the systematic surveillance of international literature and the systematic query of key stakeholders carried out in order to produce the OrphaNews Europe newsletter, various reports published by the European Commission (including past reports of the workshops of the 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 Health¹ and Directorate General Research CORDIS website² as well as the site of the European Medicines Agency³, in particular the pages of the COMP⁴ (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**

Data from the OrphaNews Europe⁵ 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

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

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

³ www.ema.europa.eu

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30

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

analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France⁶ (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

- **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*⁷ (July 2010), *2011 EUCERD Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases*⁸ and the *2012 EUCERD Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases*⁹. 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 2012 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 2011.

- **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*¹⁰ 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*)¹¹. 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 to the 2012 edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*¹² by Donald Macarthur: this report is referenced in footnotes when used.

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

⁷ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

⁸ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesI.pdf> ;
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf> ; and
<http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

⁹ <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesI.pdf> ;
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesII.pdf> ; and
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf>

¹⁰ http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

¹¹ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*

http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646

¹² <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

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

The site of EURORDIS, the European Organisation for Rare Diseases¹³ 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 site¹⁴, maintained by EURORDIS, also provided information on events at Member State level¹⁵ concerning Rare Disease Day.

- **Orphanet**

The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials, patient organisations and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links¹⁶ 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. REPORT PREPARATION, REVISION AND VALIDATION

The present report provides an updated compilation of information from the previous reports of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the European Union Committee of Experts on Rare Diseases, 2011 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases and 2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases*) which have covered activities up to the end of 2011. 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 2012.

Once this information from the previous report was updated using the sources cited above, a draft of each country section (Part V) was sent in February 2013 to EUCERD Member States representatives with a guidance document providing an explanation of the type of information to include if available for each category. The Member State representatives were asked to contact a range of identified key stakeholders in their country for input. The stakeholders identified for each country included: representatives at the EUCERD in the respective countries and their alternates, the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, partners of the E-Rare consortium, Member State representatives on the COMP, representatives of national competent authorities, coordinators of national plans for rare diseases and other rare diseases experts identified at national level. The Member State representatives integrated the stakeholder feedback into their report before returning it to the Scientific Secretariat for homogenisation and extraction of developments in 2012 to be included in Part II. Final validation of Parts II, V, VI concerning their country were sent to the EUCERD Member State representatives for final validation, to the best of their knowledge, in May 2013.

Part III and IV of the report on activities at European Union level was sent for validation, to the best of their ability, by the representatives at the EUCERD of the European Commission Directorate Generals for Health and Consumers, Research and Innovation, Enterprise and Industry, and the European Medicines Agency (EMA) respectively: this process was carried out in March/April 2013 by the Scientific Secretariat of the EUCERD. The

¹³ <http://www.EURORDIS.org/secteur.php3>

¹⁴ <http://www.rarediseaseday.org/>

¹⁵ <http://www.rarediseaseday.org/country/finder>

¹⁶ http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN

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 2012 were extracted and added to Part II.

Part I was the final volume of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe is the result of an analysis of the information collected for Parts II, III, IV and V. Part I was drafted by the Scientific Secretariat of the EUCERD and then sent to all EUCERD members and their alternates for their input before publication in May 2013.

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 2012 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 selected bibliography outlining the sources used to produce that part of the report, which includes a list of the European Commission documents referred to in the report and a list of web addresses by country listing national sources of information on rare diseases and links to documents concerning national plans or strategies for rare diseases when in place. Each part is also followed by a list of contributors the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous report. A list of frequently used acronyms has also been included in each part to ease reading.

Part I provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe 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 2012.

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 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 2012.

Part V concerns the rare disease activities in the field of rare diseases in each of the 27 Member States plus Iceland, Norway and Switzerland in addition to Croatia 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 expertise¹⁷
- Registries
- Neonatal screening policy
- Genetic testing¹⁸
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Good practice guidelines
- Training and education initiatives
- National rare disease events in 2012¹⁹
- Hosted rare disease events in 2012²⁰
- Research activities (National research activities, Participation in European research projects²¹, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability²², 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 27 Member States plus Iceland, Norway and Switzerland in addition to Croatia and Turkey as candidates for EU membership, as well as

¹⁷ The term "official centre of expertise" used in this report means officially designated via a (ministerial) procedure.

¹⁸ This section contains data extracted in December 2012 from the Orphanet database of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term 'estimated' is used as the concept of a single disease is a variable one).

¹⁹ As announced in OrphaNews Europe.

²⁰ As announced in OrphaNews Europe.

²¹ Past and ongoing participation in DG Research and Innovation financed projects. Some countries have added information on additional European projects.

²² 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.

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 2012, and secondly the state of the art of activities in 2012 only so as to easily identify new actions and activities.

INTRODUCTION^{23,24}

Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (not more than 5 people affected per 10 000 people in the European Union, as defined by the European Regulation on Orphan Medicinal product) that special combined efforts are needed to address them so as to prevent significant morbidity, perinatal or early mortality, or a considerable reduction in an individual's quality of life or socio-economic potential. 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 products²⁵. 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.

European cooperation aims to bring together the scarce resources for rare diseases fragmented across EU Member States. European action aims to help patients and professionals collaborate across Member States so as to share and coordinate expertise and information. This will be achieved through (for example) networks linking centres of expertise in different countries, and by making use of new information and communication technologies ("E-Health"). The European Commission (EC) aims to develop successful existing actions, such as the previous health programme on rare diseases, the Research and Technological Development Framework Programmes, and the specific regulatory framework already in place to provide incentives for the development of 'orphan' medicinal products for these conditions.

The European Commission has a coordinated approach to the field of rare diseases and orphan medicinal products in the areas of research, public health, regulatory aspects of pharmaceuticals and access to treatment. Three Directorates General of the European Commission are implicated in initiatives and/or incentives at European Union level in the field of rare diseases and orphan medicinal products: the Directorate General Enterprise and Industry, the Directorate General Health and Consumers, and the Directorate General Research and Innovation.

A retrospective of the actions of these three Directorates General in the field of rare diseases and orphan medicinal products up to the end of 2012 is provided below by theme: public health, research and orphan medicinal products and therapies for rare diseases.

²³ http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

²⁴ Disclaimer: the European Commission is not responsible for the completeness and correctness of the information included in this report.

²⁵ http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

1. EUROPEAN COMMISSION ACTIVITIES RELATED TO RARE DISEASES IN THE FIELD OF PUBLIC HEALTH

1.1. Overview of European Commission Directorate General for Health and Consumers' activities in the field of rare diseases

The Community action programme on rare diseases, including genetic diseases, was adopted by the European Commission for the period 1 January 1999 to 31 December 2007. The aim of the programme was to contribute, in co-ordination with other Community measures, to ensuring a high level of health protection in relation to rare diseases. As a first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases. This programme was not an initiative proposing actions but a mechanism for funding, for the first time, EU initiatives in the field of rare diseases.

Rare diseases are now one of the priorities in the second programme of Community action in the field of health (2008-2013)²⁶. According to the Work Plans for the implementation of the Public Health Programme, the two main lines of action are the exchange of information via existing European information networks on rare diseases, and the development of strategies and mechanisms for information exchange and co-ordination at EU level to encourage continuity of work and trans-national co-operation.

Furthermore, regarding rare diseases projects, DG Health and Consumers prioritises networks, which centralise information on as many rare diseases as possible - not just a specific group or a single disease - to improve information, monitoring and surveillance.

On 11 November 2008, the European Commission adopted the Communication on Rare Diseases: Europe's challenge²⁷ setting out an overall Community strategy to support Member States in diagnosing, treating and caring for the 36 million EU citizens with rare diseases. This Communication on European Action in the Field of Rare Diseases was drafted by the European Commission in close collaboration with the Rare Diseases Task Force between June and October 2007. The 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 document opened for public consultation²⁸ in mid-November 2007: interested parties were invited to comment on and respond to 14 key questions about rare diseases and explore relevant issues. Almost 600 contributions were received from 15 MS during the three-month consultation period, outdistancing the previous contender for most responses by over 400 comments (the average number of responses to a consultation is 60). This reaction was taken as a sign of proof of the pertinence of the Communication on Rare Diseases and the desire across Europe to see its provisions implemented in the near future. The comments received were consulted and the document was adapted accordingly. Following this, the Communication was subject to an impact assessment that studied the political and financial consequences, amongst other considerations, between March and June 2008. It then went for an inter-service consultation from July 2008 through October 2008 involving DG Enterprise, DG Research and Innovation, DG Information and Society, DG Budget, DG Employment, DG Relex, DG Market and the legal service of the European Commission. Finally, on 11 November 2008, the Communication on rare diseases was adopted via oral procedure, by the college of Commissioners, along with a proposal for a European Council Recommendation on a European action in the field of rare diseases.

The Council adopted on 8 June 2009 the proposal for a Council Recommendation on an action in the field of rare diseases. 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,

²⁶ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>

²⁷ http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

²⁸ http://ec.europa.eu/health/ph_threats/non_com/docs/raredis_comm_draft.pdf

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.

1.1.1. European Commission Rare Diseases Task Force (2004 – 2009)

In January 2004, the European Commission created the Rare Diseases Task Force (RDTF). Established via Commission Decision 2004/192/EC of 25 February 2004 on the programme of Community action in the field of public health (2003 to 2008), the RDTF was charged with:

- advising and assisting the European Commission Public Health Directorate in promoting the optimal prevention, diagnosis and treatment of rare diseases in Europe, in recognition of the unique added value to be gained for rare diseases through European co-ordination;
- providing a forum for discussion and exchange of views and experience on all issues related to rare diseases.

Its members included current and former project leaders of European research projects related to rare diseases, member state experts and representatives from relevant international organisations (European Medicines Agency, World Health Organization, Organisation for Economic Co-operation and Development).

In the first 4 years of its mandate, the RDTF created three working groups (WG) reflecting topics it considered to be priorities in the field of rare diseases.²⁹

The WG on Standards of Care created in June 2005 worked on the concept of Centres of Expertise (CE) and European Reference Networks (ERN) in the field of Rare Diseases. Its work fed into a more general reflection on CE and ERN undertaken by the EC's High Level Group on Health Services and Medical Care. The group also considered discussions on genetic testing, genetic screening, and orphan medicinal products: reports were produced on European Centres of Reference (2005³⁰, 2006³¹), Assessing treatable rare diseases and the proportion of patients eligible for treatment (2007)³², Assessing the European Added-Value of ERN (2008)³³.

The WG on Coding and Classification, in collaboration with the World Health Organization on the International Classification of Diseases (ICD), contributed to the revision of the existing ICD-10 in view of the adoption in 2015 of the new ICD-11 considering all other existing methods of classification to ensure transparency, with meetings held in 2006, 2007 and 2008.

The WG on Public Health Indicators considered a selection of rare diseases with high priority for epidemiological surveillance. The WG determined the definition of rare diseases which can be identified in mortality certificates and will work on a feasibility study for using mortality data as public health indicators. The first meeting was in January 2006 with a report on the subject in March 2008³⁴. A report was also produced following a 2008 workshop on Patient Registries and Databases³⁵.

OrphaNews Europe was created as the bi-monthly electronic newsletter of the Rare Diseases Task Force (and now continues to be published as the newsletter of the European Union Committee of Experts on Rare Diseases). Every two weeks it publishes news and comments of interest to the rare diseases community: patients, healthcare professionals, researchers, industry professionals and health policy makers.

The final meeting of the RDTF was held on 23 October 2009. The RDTF has been replaced by the European Union Committee of Experts on Rare Diseases (EUCERD). The Joint Action to support the RDTF's Scientific Secretariat for the remainder of its duration (ending 31 December 2011) supported the activities of the EUCERD until the beginning of the EUCERD Joint Action in March 2012. The previous RDTF working groups have been discontinued.

1.1.2. Council Recommendation on an action in the field of rare diseases (8 June 2009)

On 8 June 2009, the Council approved a Council Recommendation on an action in the field of rare diseases³⁶. In early 2009, the European Parliament and the European Social and Economic Committee issued opinions on the Proposal for a Council Recommendation, overwhelmingly supporting the contents of the crucial document. The amendments issued during this process were incorporated into the final text adopted on 8 June 2009 by the European Council of Ministers - a body that serves to define the general political guidelines of the European

²⁹ http://www.eucerd.eu/PP_2.html (Subsection "Working groups")

³⁰ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>

³¹ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

³² <http://www.eucerd.eu/upload/file/Publication/RDTFOD2007.pdf>

³³ <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

³⁴ <http://www.eucerd.eu/upload/file/Publication/RDTFHI2008.pdf>

³⁵ <http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf>

³⁶ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

Union and is the main decision-making agent. Every Council meeting is attended by one minister from each EU country. For the meeting on the rare disease Recommendation, it was typically the ministers of health who attended.

Some countries already have national rare disease plans in place. France was the first country to implement a national plan specifically for rare diseases; Bulgaria, Portugal, Greece, Spain, the Czech Republic and Romania have since followed suit. Other MS are in the midst of defining strategies for rare disease research, diagnostics, treatments, and care. And many other countries are gathering momentum and expertise to launch the process.

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 medicinal products, 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.

For an adequate follow-up of both documents (the Commission Communication and the Council Recommendation) the European Commission shall produce, by the end of 2013 and in order to allow proposals in any possible future programme of Community action in the field of health, 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 their families.

1.1.3. European Union Committee of Experts on Rare Diseases (EUCERD) (2010)

The European Commission Decision C(2009)9181 of 30 November 2009 formally established a European Union Committee of Experts on Rare Diseases. This new structure, evoked in Point 7 of the Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's Challenges, adopted on 11 November 2008, recommends that the European Commission be assisted by a European Union Advisory Committee on Rare Diseases:

"The preparation and implementation of Community activities in the field of rare diseases require close cooperation with the specialised bodies in Member States and with the interested parties. Therefore, a framework is required for the purpose of regular consultations with those bodies, with the managers of projects supported by the European Commission in the fields of research and public health action and with other relevant stakeholders acting in the field."

Thus, *"the Committee acting in the public interest shall assist the Commission in formulating and implementing the Community's activities in the field of rare diseases, and shall foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved"*.

Specifically, the European Union Committee of Experts on Rare Diseases is 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 submit 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 European Union Committee of Experts on Rare Diseases replaces the European Commission's Rare Diseases Task Force (RDTF) established via Commission Decision 2004/192/EC of 25 February 2004 on the programme of Community action in the field of public health (2003 to 2008).

The new Committee consists of 51 members, including one representative from the ministries or government agencies responsible for rare diseases to be designated by the government of each Member State; four patient organisation representatives; four pharmaceutical industry representatives; nine representatives of ongoing and/or past Community projects in the field of rare diseases financed by the programmes of Community action in the field of health, including three members of the pilot European Reference Networks on rare diseases; six representatives of ongoing and/or past rare diseases projects financed by the Community Framework Programmes for Research and Technological Development; and one representative of the European Centre for Disease Prevention and Control. A call for expressions of interest was published at the end of 2009 for designating the representatives of patient organisations, industry, rare diseases research projects under Framework Programmes for Research and Technological Development, and rare diseases projects under Health Programmes representatives of the new Committee. Via the Commission Decision 2010/C 204/02 of 27 July 2010 the appointment of the members of the European Union Committee of Experts on Rare Diseases were adopted. The Committee met for the first time on 9-10 December 2010 in Luxembourg and elected Ségolène Aymé (Orphanet) as its Chair, with Kate Bushby (Treat-NMD), Yann Le Cam (EURORDIS) and Helena Kääriäinen (MS representative for Finland) as its three Vice-Chairs, with a two-year term of office. Observers from non EU countries were issued invitations to the EUCERD's meetings in 2011. Until the 29 February 2012 the EUCERD was supported by the Joint Action for the support of the former RDTF/EUCERD Scientific Secretariat: from March 2012 until February 2015, the activities of the EUCERD are supported by a dedicated Joint Action³⁷.

Meetings and workshops

In 2012 a number of workshops were held with the support of the EUCERD Joint Action: Workshop on National Planning for Rare Diseases (10-11 September 2012, Rome)³⁸, Workshop on European Reference Networks (ERNs)³⁹ (25 & 26 September 2012, Newcastle), Workshop on cross-referencing of terminologies⁴⁰ (27-28 September 2012, Paris), Workshop on rare diseases registration⁴¹ (13 November 2012, Luxembourg), Workshop on Specialised Social Services for RD⁴² (6-7 December 2012, Zalau, Romania). An additional workshop was organised with the collaboration of the EC's Joint Research Centre in Ispra and Eurogentest on 19-20 November 2012 on the Genetic Testing offer in Europe⁴³.

The EUCERD held three meetings in 2012 in Luxembourg on 26-27 January⁴⁴, 20-21 June⁴⁵, and 14-15 November⁴⁶. A range of topics were discussed over the year including European Reference Networks, the

³⁷ See section on Joint Actions 1.2.1.

³⁸ http://www.europlanproject.eu/newsite_986987/events6.html

³⁹ http://www.eucerd.eu/?page_id=2019

⁴⁰ http://www.eucerd.eu/?page_id=1799

⁴¹ http://www.eucerd.eu/?page_id=2023

⁴² http://www.eucerd.eu/?page_id=2191

⁴³ 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

⁴⁴ http://www.eucerd.eu/?post_type=document&p=1152

Clinical Added Value of Orphan Medicinal Products, 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.

Recommendations on CAVOMP Information Flow

In 2012 the EUCERD issued a recommendation on improving the assessment of the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow⁴⁷. It has been acknowledged over recent years that, while the EU Regulation on Orphan Medicinal Products has stimulated research and development of orphan medicinal products in the EU, equitable and timely access to authorised 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 in order to improve access to Orphan Medicinal Products for people living with rare diseases:

- Final Conclusions and Recommendations of the EU High Level Pharmaceutical Forum⁴⁸
- 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: Compilation Report and evidence definition / Evidence Generation Plan (EGP)
- Timepoint 3: Follow-up of the EGP
- Timepoint 4: Assessment of relative effectiveness

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 OMP and promoting good medical practices throughout the EU.

The Recommendation has been submitted to the European Commission.

Report on State of the Art of Rare Disease activities in Europe

Each year the Scientific Secretariat of the European Union of Experts on Rare Diseases (EUCERD) elaborates a comprehensive report covering the state of the art of rare diseases activities at European and Member State level.

The *2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases* aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2011.

⁴⁵ http://www.eucerd.eu/?post_type=document&p=1135

⁴⁶ http://www.eucerd.eu/?post_type=document&p=2156

⁴⁷ http://www.eucerd.eu/?post_type=document&p=1446

⁴⁸ http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum_final_conclusions_en.pdf

The report is a comprehensive resource for the rare disease community and has been met with praise at both the EU and MS levels for providing valuable insight into understanding the current resources and activities in the field of rare diseases across Europe that will help determine future strategies to meet the needs of rare disease patients and their families in Europe and further afield.

The 2012 edition of the report is split into five parts this year:

- Part I: Overview of rare disease activities in Europe⁴⁹
- Part II: Key developments in the field of rare diseases in 2011⁵⁰
- Part III: European Commission activities in the field of rare diseases⁵¹
- Part IV: European Medicines Agency activities and other European activities in the field of rare diseases⁵²
- Part V: Activities in EU Member States and other European countries in the field of rare diseases⁵³

Part I is a general overview, geared to a more general public, whilst Parts II, III, IV and V provide a more detailed report of the situation for stakeholders who wish to learn more about the situation at European or national level. In addition, an individual document for each country covered by the report, containing the extracted data from the report, have been produced for the first time this year in order to encourage the dissemination of this information at national level.

The 2012 edition of the report been elaborated with the collaboration of the members of the EUCERD in concertation with a wide range of stakeholders at national level. This report is a deliverable of the EUCERD Joint Action (EJA) : Working for Rare Diseases (N° 2011 22 01). All parts of the report are free to download from www.eucerd.eu.

For the first time, the Scientific Secretariat of the EUCERD has produced individual reports for each European country containing an extraction of the data published in the *2012 EUCERD Report on the State of the Art of Rare Disease Activities in Europe* related to activities in that specific country. These country editions of the report provide both an overview of national activities up to the end of 2011, as well as a specific focus on the latest activities and developments in 2011. The reports are intended for use and dissemination at the national level, as an up-to-date source of information and support tool for stakeholders wishing to raise awareness of the field of rare diseases. These reports are now available on the EUCERD website in the pages dedicated to other resources at the national level.

OrphaNews Europe

*OrphaNews Europe*⁵⁴ is the official newsletter of the EUCERD and was previously the official newsletter of the RDTF. Twice a month, the newsletter delivers political and scientific news concerning the field of rare diseases and orphan medicinal products. The newsletter has over 14'000 registered readers from all over the world and representing all stakeholder groups. In 2010, a reader satisfaction survey⁵⁵ was carried out with over 1000 responses from around 50 different countries. The overwhelming majority of readers were either 'satisfied' or 'very satisfied' with the newsletter. A new search engine feature, powered by Google Custom Search, was added to the archives in 2011, and a tool for the translation of the newsletter into other languages was developed. Italy identified national funding for these translations and the first edition of *OrphaNews* in Italian⁵⁶ was launched in December 2011. The Newsletter is published in French as well since 2003.

1.1.4. European Commission work plans implementing the second programme of Community action in the field of health (2008-2013)

The European Commission on 23 February adopted a Work Plan for 2009⁵⁷ implementing the second programme of Community action in the field of health (2008-2013). Amongst the rare disease initiatives earmarked for funding are two calls for tenders that contribute to the implementation of the Commission Communication on Rare Diseases: Europe's challenges: 1) evaluation of population newborn screening practices in Member States; and 2) repertorying rare disease information, diagnosis and treatment using

⁴⁹ http://www.eucerd.eu/?post_type=document&p=1378

⁵⁰ http://www.eucerd.eu/?post_type=document&p=1381

⁵¹ http://www.eucerd.eu/?post_type=document&p=1384

⁵² http://www.eucerd.eu/?post_type=document&p=1387

⁵³ http://www.eucerd.eu/?post_type=document&p=1390

⁵⁴ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

⁵⁵ http://www.orpha.net/orphacom/cahiers/docs/GB/Orphanews_survey2010.pdf

⁵⁶ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=ItaliaNews>

⁵⁷ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:053:0041:0073:EN:PDF>

existing European initiatives (in particular Orphanet). To support rare disease pilot reference networks and networks of information, there is a call for proposals for new projects as well as a call for operating grants that enable existing networks to continue.

The European Commission on 18 December 2009 adopted the Work Plan for 2010⁵⁸ implementing the second programme of Community action in the field of health (2008-2013) which continued support to rare disease projects and networks. Amongst the rare disease initiatives earmarked for funding were two proposals for Joint Actions that contribute to the implementation of some relevant aspects of the Commission Communication on Rare Diseases: Europe's challenges: 1) a technical action to support the development of the Orphanet database on rare diseases and orphan medicinal products which is run by a large consortium of European partners and which is the most important rare diseases database in the world: in order to implement the establishment of a dynamic EU inventory of rare diseases it will be necessary to further develop the database, and 2) a technical action to support the European Surveillance on Congenital Anomalies (EUROCAT) network which is run by a large consortium of European partners in order to create a sustainable prevalence data system for 95 congenital anomaly subgroups which are to be updated annually. In order to improve procedures to access orphan medicinal products a call for tender concerning the creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines was also launched.

Following its adoption on 22 February, the Work Plan for 2011⁵⁹ implementing the second programme of Community action in the field of health (2008-2013) was published in the Official Journal of the European Union. The 2011 Work Plan placed more emphasis and resources on "... a focused cooperation with the Member States". The Plan's Smart Growth priority, part of the European Commission strategy for reinvigorating Europe in the next 10 years, specifically included rare diseases within its scope. Meanwhile, cancer and rare diseases were priorities under the "Diseases" theme – one of five main areas of focus of the 2011 Work Plan. A Call for Proposals for projects, operating grants, conferences and joint actions have been issued by the Executive Agency for Health and Consumers following the publication of the Work Plan⁶⁰. According to the announcement, "...This call for proposals is seeking for very specific projects in seven different areas, where only one project per call will be funded; exception will be made for the rare disease networks". Grants included in the call included a Joint Action to *Support to the implementation of national plans/strategies on rare diseases and related measures to implement Council Recommendation and Commission Communication on rare diseases* (i.e. a Joint Action to support the work of the EUCERD) and project grants to support European rare diseases information networks.

The 2012 Work Plan⁶¹ of the Health Programme adopted on 1 December 2011 was published in the Official Journal of the European Union on 8 December 2011. It set the annual priorities for implementation of the EU Health Programme. Based on this decision, the Executive Agency for Health and Consumers (EAHC) launched the calls for proposals for joint actions, operating grants, projects and conference grants. Of note to the rare disease community was the Support for European rare diseases information networks project call.

The annual work plan 2013⁶² for the health programme was adopted on 28 November 2012. €2 million has been foreseen in the work plan to establish a sustainable platform to coordinate and maintain registries and networks on rare diseases, and financing is foreseen for a paediatric oncology pilot network in the context of the implementation of the Cross-Border Healthcare Directive.

Under the provisions of the Commission Implementing Decisions on the awarding of grants for proposals corresponding to the years 2008, 2009, 2010 and 2011 under the Second Health Programme (2008-2013), the Commission has funded activities to a total of €21'434'895 in the area of rare diseases during this period. An additional funding of €4.5 million was planned for 2012.

Mid-Term Evaluation of the EU Health Strategy 2008-2013 final report encompasses rare diseases in its scope

The final report of the *Mid-Term Evaluation of the EU Health Strategy 2008-2013* was made available online in 2011⁶³. Prepared by the Public Health Evaluation and Impact Assessment Consortium, the evaluation was commissioned by DG Sanco in order to guide the implementation of the Strategy going forward, and to take stock of the actions implemented to date. Rare diseases fall within the scope of the EU Health Strategy and the

⁵⁸ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:340:0001:0046:EN:PDF>

⁵⁹ http://ec.europa.eu/health/programme/docs/wp2011_en

⁶⁰ http://ec.europa.eu/health/programme/how_does_it_work/call_for_proposals/index_en.htm

⁶¹ http://ec.europa.eu/health/programme/docs/wp2012_en.pdf

⁶² http://ec.europa.eu/health/programme/docs/wp2013_en.pdf

⁶³ http://ec.europa.eu/health/strategy/docs/midtermevaluation_euhealthstrategy_2011_report_en.pdf

number of Member States (MS) that have adopted an action plan on rare diseases, on the basis of the Council Recommendation of 8 June 2009 on an Action in the Field of Rare Diseases, is listed as a proposed implementation indicator that can serve to measure future progress of MS against the EU Health Strategy. The report cites the issue of the *Communication on a European Action in the Field of Rare Diseases* as an action that demonstrates progress made in relation to stated EU Health Strategy actions. A table in the report that lists the numbers of EC action areas in relation to the EU Health Strategy does not distinguish rare diseases from chronic, common or communicable disorders and thus is of limited interest to the rare disease community. Globally, the report finds that *"In most MS, the influence of the EU Health Strategy on national health strategies is limited"...* and that...*"The EU Health Strategy's main value is that it acts as a guiding framework and, to some extent, as a catalyst for actions at the EU level"*.

1.1.5. Eurobarometer European Awareness of Rare Diseases Report (2011)

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

Seeking to gauge the awareness for rare conditions as well as the level of public support for European-level measures, the survey found that *"...approximately 2 out of every 3 respondents know that rare diseases affect a limited number of people and require very specific care. Almost 1 in every 5 personally knows of someone suffering from a rare disease"*. While there were *"significant differences"* in awareness between the Member States, some *"...95% of respondents believe there should be more European cooperation in this area and that rare disease patients should have the right to access appropriate care in another Member State"*. The survey, in the form of questionnaire, was undertaken in each of the 27 European Union Member States, with approximately 1000 citizens from each country participating, for a total of 26,574 interviews. The release of the report coincides with the formal adoption of the Cross Border Healthcare Directive – legislation of particular relevance to rare disease patients and their families. In a press release, John Dalli, European Commissioner for Health and Consumer Policy, stated: *"I am encouraged to see that EU citizens want more European co-operation on rare diseases. This is important, because the required medical expertise may not be available within national borders. ...I want to stress that the European Commission is engaged in added value action to help citizens access the care they need across the EU"*.

While the results of the Eurobarometer survey are clearly encouraging, rare disease stakeholders cannot rest on their laurels. The assessment found that detailed knowledge of rare diseases and available resources was scant, despite support for national and European-level action as well as improved research, access to care and awareness-raising. Nevertheless, the key finding of the survey is that *"...the European public almost unanimously supports a coordinated EU strategy for improving the treatment of people suffering from rare diseases. It is only within the context of other major national health issues that respondents are slightly less supportive although even here the majority of Europeans are still willing to make rare diseases a priority"*. The full Eurobarometer report⁶⁴ is available in English, French and German. Fact-sheets for each of the Member States are available in the country's EU language and also in English.

1.2. Activities in the field of rare diseases funded by DG Health and Consumers

EU actions in the field of rare diseases use the funding facilities provided by the annual Commission Decision concerning the adoption of a financing decision for the ongoing year in the framework of the second programme of Community action in the field of health (2008-2013) and on the selection, award and other criteria for financial contributions to the actions to this programme. This allows project grants, operating grants, grants for joint actions, conference grants and direct grants to be awarded to international organisations as well as to cover procurement and other actions. From 2008 onwards the Executive Agency for Health and Consumers (EAHC) is entrusted by the European Commission to help with the implementation of

⁶⁴ http://ec.europa.eu/health/rare_diseases/eurobarometers/index_en.htm

the selected actions in the Health Programme. Those actions intend to always have a special European dimension and should serve to implement the objectives defined in the Commission Communication and in the Council Recommendation.

1.2.1. Joint Actions

Joint actions are activities carried out by the European Union and one or more Member States or by the EU and the competent authorities of other countries participating in the Health Programme together. Member States/other countries participating in the Health Programme which wish to participate in joint actions must declare this intention to the Commission. With the exception of NGOs operating at EU level, only organisations established in Member States/other countries participating in the Health Programme which have made this declaration can apply for participation in joint actions.

Joint action to support the RDTF/EUCERD scientific secretariat and revision of the International Classification of Diseases in the field of rare diseases (2009-2011)

A Joint Action⁶⁵ to support the RDTF's Scientific Secretariat started in January 2009 for a three year period, to help promote action on the prevention of rare diseases and to provide analysis and technical assistance in support of the development or implementation of a policy in the area of rare diseases and orphan medicinal products. This joint action also aimed to contribute to the revision of the International Classification of Diseases in the field of rare diseases.

The specific aims of the project included:

- provision of scientific support for the activities of the RDTF by identifying existing documentable indicators that are relevant to rare diseases and collecting data on a yearly basis;
- dissemination of political and scientific information to all stakeholders through ad-hoc reports and an electronic newsletter (OrphaNews Europe), including information on national and EU incentives;
- liaison between EU agencies and services and major stakeholders to enhance collaboration and maximise input and outcomes;
- provision of assistance to the RDTF on other scientific issues that may be identified in the course of the project.

The traceability of rare diseases in health information systems was also be improved thanks to this Joint Action by: assigning International Classification of Diseases codes (ICD10) to rare diseases; proposing changes to improve the classification in view to the future adoption of the ICD11 through the technical platform developed by the WHO and with the assistance of an international expert group; and cross-referencing with other classification systems such as MedDRA and SNOMED-CT. To date the following chapters of the ICD have been produced with the support of this joint action and have been made available for revision by the community of experts: nutritional diseases, diseases of the nervous system, respiratory diseases, haematological diseases, endocrine diseases, endocrine diseases, metabolic diseases, immunological diseases, and developmental anomalies. The revision of the ICD alpha and beta draft will continue in the EUCERD Joint Action: Working for Rare Diseases (2012-2015).

Workshops have been organised within the scope of the project around three work themes: indicators for rare diseases, initiatives and incentives for rare diseases and the coding and classification of rare diseases. These workshops included:

- RDTF workshop on Initiatives and Incentives in the field of rare diseases (Paris, 9 November 2009)
- RDTF workshop on Indicators for Rare Diseases (Paris, 10 November 2009)
- EUCERD technical workshop on the coding and classification of rare diseases –Manchester, 27 January 2010)
- EUCERD workshop on Indicators for Rare Diseases (Paris, 24 November 2010)
- EUCERD technical workshop on the coding and classification of rare diseases –Manchester, 7 December 2010)
- EUCERD workshop on National Centres of Expertise for Rare Diseases and European Reference Networks (Luxembourg, 8-9 December 2010)

⁶⁵ More information can be found on www.eucerd.eu section "Activities".

- EUCERD Workshop on National Centres of Expertise for Rare Diseases and Networking Between Centres of Expertise (Luxembourg 21-22 March 2011)
- EUCERD Workshop on Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States (Luxembourg, 8 September 2011)
- EUCERD/EMA Workshop “Towards a Public-Private Partnership for Registries in the Field of Rare Diseases” (London, 4 October 2011)
- EUCERD/EuroBioMed Rare2011 event “Sharing Data to Improve Health Care Management for Rare Diseases” (Montpellier, 4 November 2011).

The following reports of the RDTF and EUCERD have been published with the support of this joint action:

- RDTF Workshop on Initiatives and Incentives 9th November 2009: Summary Report⁶⁶
- EUCERD Report: 2009 Report on Initiatives and Incentives in the Field of Rare Diseases of the EUCERD - July 2010⁶⁷
- RDTF Report: Health indicators for rare diseases I - Conceptual framework and development of indicators from existing sources - April 2010⁶⁸
- EUCERD Workshop Report: Centres of expertise and European Reference Networks for Rare Diseases (8-9/12/10)⁶⁹
- EUCERD Workshop Report: National centres of expertise for rare diseases and networking between centres of expertise for rare diseases (21-22/03/2011)⁷⁰
- EUCERD Report: Preliminary analysis of the experiences and outcomes of pilot European Reference Networks for rare diseases - May 2011⁷¹
- RDTF Report: Patient Registries for Rare Diseases - April 2009, Update June 2011⁷²
- EUCERD Report: 2011 Report on the State of the Art of Rare Diseases Activities in Europe - Part I: Overview of Rare Disease Activities in Europe and Key Developments in 2010 - July 2011⁷³
- EUCERD Report: 2011 Report on the State of the Art of Rare Diseases Activities in Europe - Part II: European Commission and other European Activities - July 2011⁷⁴
- EUCERD Report: 2011 Report on the State of the Art of Rare Diseases Activities in Europe - Part III: Activities in EU Member States and other European Countries - July 2011⁷⁵
- EUCERD Report: Health indicators for rare diseases II - Conceptual framework for monitoring quality of care (September 2011)⁷⁶
- EUCERD/EMA Workshop Report: Towards a public-private partnership for registries in the field of rare diseases (4 October 2011)⁷⁷
- EUCERD Recommendations on Centres of Expertise for Rare Diseases in Member States (24 October 2011)⁷⁸

Joint Action to support the European Surveillance on Congenital Anomalies (EUROCAT) network (2010-2013)

EUROCAT⁷⁹, the European network of population-based registries for the epidemiologic surveillance of congenital anomalies, was conceived in 1974, at a workshop convened by the European Economic Community's Committee on Medicinal and Public Health Research to improve "the methodology of population studies throughout the Community". Congenital anomalies were chosen as first topic for concerted action. EUROCAT was established in 1979 by the EC Directorate General XII (Science, Research and Development) as a prototype

⁶⁶ <http://www.orpha.net/nestasso/EUCERD/upload/file/RDTFSummaryII.pdf>

⁶⁷ <http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

⁶⁸ <http://www.orpha.net/nestasso/EUCERD/upload/file/RDTFIndicators2010.pdf>

⁶⁹ <http://www.orpha.net/nestasso/EUCERD/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf>

⁷⁰ <http://www.orpha.net/nestasso/EUCERD/upload/file/EUCERDReport220311.pdf>

⁷¹ <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

⁷² <http://www.orpha.net/nestasso/EUCERD/upload/file/RDTFRegistriesrev2011.pdf>

⁷³ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf>

⁷⁴ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf>

⁷⁵ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

⁷⁶ <http://www.orpha.net/nestasso/EUCERD/upload/file/EUCERDIndicators2011.pdf>

⁷⁷ <http://www.orpha.net/nestasso/EUCERD/upload/file/EUCERDWorkshopRegistries2011.pdf>

⁷⁸ <http://www.orpha.net/nestasso/EUCERD/upload/file/EUCERDRecommendationCE.pdf>

⁷⁹ <http://www.eurocat-network.eu/>

for European surveillance aiming to assess the feasibility of pooling data across national boundaries, in terms of standardization of definitions, diagnosis and terminology and confidentiality. Funding was transferred in 1991 to Directorate General V (Employment, Industrial Relations and Social Affairs, Health and Safety), to function as a service for the surveillance of congenital anomalies in Europe. EUROCAT was maintained by registry subscriptions between 1998 and 2000, before European funding was re-established under the Programme of Community Action on Rare Diseases of Directorate General Health in November 2000. EUROCAT has been funded under EC DG Health Public Health Programme since March 2004 and will be funded as a Joint Action between the European Commission and the Member States from April 2011.

EUROCAT surveys over 1.7 million births per year in Europe, with 43 registries present in 23 countries representing coverage of 29% of the European birth population. Contributing registries are high quality, multiple source registries, ascertaining terminations of pregnancy as well as birth. EUROCAT is a WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies.

The aims of the project are to: to provide essential epidemiologic information on congenital anomalies in Europe; to facilitate the early warning of new teratogenic exposures; to evaluate the effectiveness of primary prevention; to assess the impact of developments in prenatal screening, act as an information and resource center for the population, health professionals and managers regarding clusters or exposures or risk factors of concern; to provide a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children; and to act as a catalyst for the setting up of registries throughout Europe collecting comparable, standardised data.

As part of the Joint Action outcomes, EUROCAT systematically monitors the rates of birth defects over time. The *EUROCAT Statistical Monitoring Report 2009*⁸⁰ described trends in Europe for the ten year period 2000-2009.

Two major surveys are been conducted by EUROCAT: one on the 'Prevention on Congenital Anomalies by Folic Acid and Folates' has been addressed to 33 respondents in 23 Member States and the results are being analysed. A second one on 'Public Health Action on Primary Prevention of Congenital Anomalies' was launched in 2012. In addition, data was placed on the EUROCAT website in 2012 concerning the prevalence of selected monogenic syndromes in Europe⁸¹ and presented at the ECRD 2012 conference.

Joint Action to support the Orphanet database (2011-2013)⁴

Orphanet⁸² is the reference portal for information on rare diseases and orphan medicinal products in Europe. Orphanet, and 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 Public Health grants and since 2004 with DG Research funding). Orphanet is accessed by 20,000 users each day from over 200 countries. 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); a search by sign and symptom function to facilitate diagnosis; expert clinics in Europe including national centres of expertise and European networks; medical laboratories and available tests; patient organisations; ongoing research including clinical trials and registries; an inventory of orphan medicinal products and other products intended for rare diseases; OrphaNews, a newsletter about scientific and political progress in the field of rare diseases; and the thematic studies and reports offered by the *Orphanet Report Series*⁸³. Reports in the series include a list of all rare diseases by alphabetical order, lists of rare diseases with their prevalence⁸⁴, lists of orphan medicinal products in Europe⁸⁵, lists of rare disease registries in Europe⁸⁶ and lists of collaborative research projects and clinical networks in the field of rare diseases funded by the European Commission⁸⁷.

This central role of Orphanet is fully recognised by the European Commission and the Council as a key element for improving the diagnosis and care in the field of rare diseases in order to provide and disseminate accurate information in a format adapted to the needs of professionals and of affected persons:

⁸⁰ <http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf>

⁸¹ www.eurocat-network.eu/accessprevalencedata/prevalencetables

⁸² www.orpha.net

⁸³ http://www.orpha.net/consor/cgi-bin/Education_Home.php?Ing=EN

⁸⁴ http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

⁸⁵ http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_medicinal_products_in_europe.pdf

⁸⁶ <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

⁸⁷ <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

- Point 4.3 of the Commission Communication states that the Commission should contribute establishment of an EU dynamic inventory of rare diseases will contribute to tackle some of the main causes of neglecting the issue of rare diseases including the ignorance of which diseases are rare. The Commission will ensure that this information continues to be available at European level, building in particular on the Orphanet database, supported through Community programmes.
- Point II.4 of the Council Recommendation states that Member States should contribute actively to the development of the EU easily accessible and dynamic inventory of rare diseases based on the Orphanet network and other existing networks as referred to in the Commission Communication on rare diseases.
- Article 13.a of the Directive on Cross Border Health Care states that it should be possible to make health professionals aware of the tools available to them at Union level and to assist them in the correct diagnosis of rare diseases, in particular using the Orphanet database and European reference networks.

In this context, the Commission proposed in 2010 to fund Orphanet as a Joint Action between the European Commission and the Member States from April 2011.

The Kick-Off Meeting of the Orphanet Joint Action, gathering all national country coordinators and Member State health representatives took place on 7 and 8 June 2011 in Paris. The meeting had a rich agenda, which included reviewing the contents and operating procedures of Orphanet, brain-storming to identify priority actions on the national and European levels, and establishing governance. The overriding aim of the Joint Action is to improve and adapt the presence of Orphanet in each participating country. Objectives thus include improving the existing services –including the inventory of rare diseases and the classification being elaborated via a collaboration with World Health Organization expert groups; concentrating on expanding and updating the core encyclopaedia of rare diseases; and annotation with signs and symptoms. Developing new tools and services are also objectives of the Joint Action, including building a Orphanet ontology and developing several new services. Priority initiatives that are natural to the Joint Action include expanding the language availability of the Orphanet database and related documents. Dutch will be added soon to the six official existing European languages of the site (English, French, German, Italian Portuguese, and Spanish). The Orphanet Emergency Guidelines were also amongst the documents considered a priority for translation into national languages. Capitalising on the newly developed Orphadata tools, it is now possible to customise the popular Orphanet Report Series to feature national data. Orphanet country sites are developed under the Joint Action, allowing each country to feature its own special mix of news, publications and events related to rare diseases and orphan medicinal products in its own language. As of 31 December 2012, 37 national websites are online including 14 new sites compared to 2011: Armenia, Australia, Belgium, Canada, Croatia, Cyprus, Denmark, Hungary, Latvia, Lebanon, Luxembourg, Morocco, Norway and Romania.

Putting in place appropriate governance is one the biggest changes the Joint Action ushers in. All the country coordinators are members of the management board, in charge of the implementation of the decisions of the Steering Committee. The Steering Committee is composed of representatives of Health Authorities from the participating countries, in charge of supervising national activities and formulating future strategies. The Orphanet Joint Action now also has an external International Advisory Board which reports to the Steering Committee and reviews all the Joint Action activities.

Within the framework of the Joint Action, Orphanet seeks to become more cost-effective, more user-friendly and to achieve sustainability.

Key developments in 2012 include⁸⁸:

- A new Orphanet homepage was launched in the summer of 2012. This new version is intended to meet the needs of site users who asked for a less cluttered, more user-friendly homepage.
- All the countries which constitute the Orphanet consortium have a national website which is either published entirely in their national language or with a layout published in English and the mandatory texts in the national language.
- The consortium has expanded toward Australia: Western Australia joined Orphanet in 2012. Negotiations were initiated with Argentina, Brazil, China, Chile, Japan and Russia.
- So as to better identify patients in the healthcare system and to improve knowledge of their healthcare pathways, as of 1 December 2012, the Orpha number has been implemented in the French information systems for all hospitalised patients.

⁸⁸ <http://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2012.pdf>

- The servers hosting Orphanet have moved from Paris to the largest civil data centre in France which is based in Montpellier, the CINES.
- A “suggest and update” button is available at the bottom of the disease pages to allow the experts and/or the users to suggest modifications and comments to the texts available online.
- Diseases are now cross-referenced with UMLS, MeSH, MedDRA and SNOMED CT.
- Genes are now cross-referenced with Ensembl, Reactome and IUPHAR.
- The Orphanet ontology of rare diseases is now available on Bioportal.
- The encyclopaedia of rare diseases has been expanded and updated. As of 31 December 2012, some abstracts are available in Finnish and Polish in addition to English, French, German, Italian, Spanish, and Portuguese.
- The directory of expert centres, medical laboratories, clinical trials, research projects, networks, registries and patient organisations has been expanded and updated.
- A survey of the centres of expertise listed in Orphanet has been organised to check whether they match the quality criteria defined by the European Union Committee of Experts on Rare Diseases (EUCERD).
- The list of rare diseases (in English and French) has been published as an Orphanet Report Series for more effective communication.
- 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).
- The Orphanet Activity report 2011 has been translated into French, Italian, Spanish and Polish.

Orphadata is a new website, launched in the context of the Joint Action to make Orphanet data available for re-use in research. Since January 2012, Orphadata products were downloaded more than 57,000 times, with an average of 4 800 times a month.

EUCERD Joint Action: Working for rare diseases (2012-2015)

A new joint action between the European Commission and the EU Member States to support the EUCERD was approved in 2011 and started in March 2012. The Joint Action had its kick-off meeting in mid-March 2012 and will run through February 2015. Coordinated by Pr. Kate Bushby (Vice-Chair of the EUCERD, Joint Coordinator of TREAT-NMD, Newcastle University, UK) several work packages for the EUCERD Joint Action will support identified priority areas of the EUCERD’s work. Specifically, this Joint Action will address the following priority areas of the Council Recommendation:

- Enhancing the visibility and recognition of RD;
- Contributing to the development and dissemination of knowledge on RD, from specialised research, through to the support of the healthcare professionals and the empowerment of patients;
- Contributing to improvements in access to quality services and care, from diagnosis, through to care and social support and innovative therapies.

This Joint Action comprises five main areas of work:

- The implementation of plans and strategies for rare diseases at national level;
- The standardisation of rare disease nomenclature at international level;
- Mapping the provision of specialised social services and integration of rare diseases into mainstream social policies and services;
- The leveraging of the value of EU networking for improving the quality of care for rare diseases;
- The integration of rd initiatives across thematic areas and across member states.

The Joint Action will also support the production of *OrphaNews Europe* and the annual *EUCERD Report on the State of the Art of Rare Disease Activities in Europe*. Over the next three years of the EUCERD Joint Action, committee members, along with invited experts, will convene regularly to move forward these initiatives. The activities and outcomes of the EUCERD Joint Action are available on the EUCERD website⁸⁹ which has been re-looked during the first year of the Joint Action.

In 2012 a number of workshops were held with the support of the EUCERD Joint Action: Workshop on National Planning for Rare Diseases (10-11 September 2012, Rome), Workshop on European Reference

⁸⁹ http://www.eucerd.eu/?page_id=54

Networks (ERNs) (25 & 26 September 2012, Newcastle), Workshop on cross-referencing of terminologies (27-28 September 2012, Paris), Workshop on rare diseases registration (13 November 2012, Luxembourg), Workshop on Specialised Social Services for RD (6-7 December 2012, Zalău, Romania).

1.2.2. Project grants

EU projects creating networks of action in the field of rare diseases

Various projects were supported in the framework of the Programme for Community Action on Rare Diseases⁹⁰ for 1 January 1999 to 31 December 2003, the EU Public Health Programme 2003-2008⁹¹ and the Second EU Public Health Programme 2008-2013⁹² in order to improve the exchange of information via existing European information networks on rare diseases, to promote better classification, to develop strategies and mechanisms for exchanging information between people affected by a rare disease, volunteers and professionals, to define relevant health indicators and develop comparable epidemiological data at EU level, and to support an exchange of best practise and develop measures for patient groups and also aid the development of European Reference Networks of Centres of Expertise and the identification of rare diseases.

Amongst the projects which have been selected for funding by DG Health and Consumers are⁹³: European Surveillance on Congenital Anomalies (EUROCAT) network, the EU ENERCA project, the EU SCN project, the EU Rare Forms of Dementia project, the EU MUSCLENET project, the EU CAUSE project, the European Information Network on Paediatric Rheumatic Diseases project, the EU EDDNAL project, The EU project Establishing European Neurofibromatosis Lay Group Network, EU Information Network for Immunodeficiencies Project, EU TEAM project - Transfer of expertise on rare metabolic diseases in adults, European Myasthenia Gravis Network, European Autism Information System, ORPHANET, European Register on Cushing's Syndrome (ERCUSYN), European Haemophilia Safety Surveillance System, PRES Network for Autoinflammatory Diseases in childhood (EuroFever), the European network for central hypoventilation syndromes: Optimising health care to patients (EU-CHS), Public Health Genetics (PHGEN) project, European Registry and network for Intoxication type Metabolic Diseases (E-IMD) project and EU rare diseases registry for Wolfram syndrome, Alstrom syndrome and Bart Biedl syndrome (EURO-WABB) project, the European Platform for Rare Disease Registries (EPIRARE) project, the European Haemophilia Network (EUHANET), the Information Network on Rare Cancers (RARECARENet) project, European registry of patients with McArdle disease and very rare muscle glycogenolytic disorders (MGD) with exercise intolerance as the major symptom (EUROMAC), the Inherited NeuRoMetabolic Diseases Information Network (InNerMeD-INetwork), the EU rare diseases registry for Niemann-Pick Disease type A, B and C (NPDR), the European Surgical Registry for Rare Endocrine Tumours (EUROCRINE), and the European network and registry for homocystinurias and methylation defects (E-HOD).

Pilot European Reference Networks for Rare Diseases (ERN)⁹⁴

DG Health and Consumers established the High Level Group 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 RDTF, focused on reference networks of centres of expertise for rare diseases⁹⁵.

Some principles were developed regarding European Reference Networks (ERNs) for rare diseases by this group, including their role in tackling rare diseases and other conditions requiring specialised care, patient volumes and some criteria that such centres should fulfil. The aim was to give both, health professionals and patients, access to high level, shared expertise in a given field. 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.

The suggested conditions for designation as a centre of expertise participating in an ERN include:

- Appropriate capacities for diagnosing, following-up and managing patients, with evidence of good outcomes, where applicable;

⁹⁰ http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf

⁹¹ <http://www.orpha.net/testor/cgi-bin/OTmain.php?PHPSESSID=43c50b5eec72a9b89f68faad7a33b30d&UserCell=workingGroup>

⁹² <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:301:0003:0013:EN:PDF>

⁹³ http://ec.europa.eu/health/rare_diseases/projects/index_en.htm

⁹⁴ Information taken from http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm#fragment1

⁹⁵ http://ec.europa.eu/health/archive/ph_overview/co_operation/mobility/docs/highlevel_2005_013_en.pdf

- Sufficient activity and capacity to provide relevant services at a sustained level of quality;
- Capacity to provide expert advice, diagnosis or confirmation of diagnosis, to produce and adhere to good practice guidelines and to implement outcome measures and quality control;
- Demonstration of a multi-disciplinary approach;
- High level of expertise and experience, as documented through publications, grants or honorific positions, teaching and training activities, etc.;
- Strong contribution to research;
- Involvement in epidemiological surveillance, such as registries;
- Close links and collaboration with other expert centres at national and international level, and capacity to network;
- Close links and collaboration with patient associations, where they exist.

Although centres of expertise participating in an ERN should fulfill most of the above criteria, the comparative relevance of those various criteria will depend on the particular disease or group of diseases covered. Another important principle is to respect national governments' primary responsibility for organising, financing and delivering healthcare. As national authorities are best placed to oversee and keep regular contact with the expert centres located on their territory, they should play an active role in the process. The working group also noted this list could be revised with the outputs coming from the implementation and development of the ERN pilot projects financed by DG Sanco.

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

The EUCERD Scientific Secretariat carried out a *Preliminary Analysis of the Outcomes and Experiences of pilot European Reference Networks for Rare Diseases* in late 2010 which was presented and discussed at a EUCERD workshop on 8-9 December 2010. The report has been approved by the EUCERD and is available online⁹⁶ and the outcomes have served in the elaboration of the EUCERD Recommendations on European Reference Networks for Rare Diseases which aim to help the elaboration of the criteria for ERNs underway at European level in the scope of the implementation of the Cross-Border Healthcare Directive.

EU Projects supporting cooperation between rare diseases organisations

Projects were supported in the framework of the Programme of Community Action on Rare Diseases⁹⁷ from 1 January 1999 to 31 December 2003 and the EU Public Health Programme 2003-2008⁹⁸ in order to strengthen collaboration at European level among patient organisations, develop partnerships among all alliances and develop European recommendations and national action plans⁹⁹.

Another significant priority EU action is to increase the visibility and operational capacity of organisations and networks active in the field of rare diseases. In this context, the EU has supported several projects managed by EURORDIS, the European Organisation for Rare Diseases. EURORDIS is a patient-driven alliance of patient organisations and individuals active in the field of rare diseases¹⁰⁰.

The Rare Disease Patient Solidarity project (RAPSODY¹⁰¹) ran from 2006 to 2008 and was aimed at improving access to, and quality of, fundamental services for patients, families and patient organisations, as well as health professionals. The project included the creation of the Network of Rare Disease Help Lines, with

⁹⁶ <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

⁹⁷ http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf

⁹⁸ http://eur-lex.europa.eu/pri/en/oj/dat/2002/l_271/l_27120021009en00010011.pdf

⁹⁹ Projects financed to support this action include RAPSODY, PARACELUS, EU PARD, POLKA and OPERA.

¹⁰⁰ <http://www.EURORDIS.org/>

¹⁰¹ www.rapsodyonline.eu

the aim to increase the service provided by help lines by creating a common approach and sharing expertise, to provide support and training to these help lines, to improve the visibility of these services at national and European levels, to increase funding opportunities for the individual help lines and the network, and to ensure that the membership policy promotes excellence. Other aims of the project were to promote networks of respite care centre and therapeutic recreation programmes.

The POLKA¹⁰² project was launched in September 2008: it aimed to develop strategies and mechanisms for exchange of information amongst people affected by rare diseases as well as organise support for European Networks of Reference for rare diseases in an effort to establish guidelines for best practice on treatment, and to share knowledge on rare diseases, together with evaluation of performance. The POLKA project also supported the organisation of the 2010 European Conference on Rare Diseases which was held in Krakow, Poland (13-15 May 2010). EURORDIS organised the 2012 European Conference on Rare Diseases and Orphan Products in Brussels, Belgium (23-25 May 2012) through a separate grant.

Project for Rare Diseases National Plans Development – EUROPLAN (2008-2011)

The Council Recommendation on an action in the field of rare diseases¹⁰³ concentrates on supporting and strengthening the adoption before the end of 2013 of national plans and strategies aimed at addressing rare diseases. The Council recommends that Member States should establish and implement plans or strategies for rare diseases at the appropriate level or explore appropriate measures for rare diseases in other public health strategies, in order to aim to ensure that patients with rare diseases have access to high quality care, including diagnostics, treatments, habilitation for those living with the disease and, if possible, effective orphan medicinal products, and in particular:

- 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;
- Take action to integrate current and future initiatives at local, regional and national levels into their plans or strategies for a comprehensive approach;
- Define a limited number of priority actions within their plans or strategies, with objectives and follow-up mechanisms;
- Take note of the development of guidelines and recommendations for the elaboration of national action for rare diseases by relevant authorities at national level in the framework of the ongoing European Project for Rare Diseases National Plans Development (EUROPLAN) selected for funding over the period 2008-2011 in the first programme of Community action in the field of public health.

EUROPLAN was a three-year DG Sanco financed project running from April 2008 to March 2011 which involved representatives of the national health authorities of 21 EU MS, with the aim of promoting health care planning for rare diseases at national level by developing guidelines and recommendations for the elaboration of national action for rare diseases by relevant authorities at national level.

The National Centre for Rare Diseases (Istituto Superiore di Sanità, Italy) led the project which brought together 57 associated and collaborating partners from 34 countries, including clinicians, scientists, health authorities, and patient groups (including EURORDIS, the European Organisation for Rare Diseases), ensuring a broad representation of different EU MS contexts and experiences and patients' points of view. In addition, the project ensured an inclusive and wide engagement of stakeholders: ministries, regional and local authorities, health care planners, programme managers, health care professionals, researchers and patients. The elaboration of the Council Recommendation on a European action in the field of rare diseases will ensure that common policy guidelines are shared everywhere in Europe. The recommendations developed by EUROPLAN promoting national plans and best practices for rare diseases within EU MS will help link national efforts with a common strategy at European level. This "double-level" approach aims to ensure that progress is globally coherent and follows common orientations throughout Europe.

The project has notably helped to: elaborate recommendations as tools to facilitate the development of a national plan or strategy for rare diseases; elaborate indicators for monitoring national plans/strategies; discuss the recommendations with stakeholders; and disseminate the recommendations. The project has resulted in the publication of a joint report with the Scientific Secretariat of the EUCERD on initiatives and incentives in the field of rare diseases¹⁰⁴ at national and European level, a guidance document containing the

¹⁰² http://img.rarediseaseday.org/polka/polka_brochure_final.pdf

¹⁰³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

¹⁰⁴ <http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

EUROPLAN recommendations for the elaboration of the national plans or strategies for rare diseases¹⁰⁵, a report on indicators for monitoring the implementation and evaluating the impact of national plan or strategy for rare diseases¹⁰⁶, the organisation of 15 EUROPLAN National Conferences and a report on the results.

National conferences and workshops on the subject of national plans and strategies, supported by this project, took place throughout 2010 in 15 European countries and aimed both to raise awareness of the Council Recommendation and to move forward the process of developing a national strategy for rare diseases in each particular country. The conferences shared a similar structure in order to better analyse results, and a final report was published after each event¹⁰⁷. A final conference, presenting the outcomes of the project and these national conferences was held on 25 February 2011 in Rome, Italy.

Continuity of some of the EUROPLAN activities, especially those related to technical assistance to Member States experiencing particular difficulties in the preparation of their national plan or strategy on rare diseases is scheduled in the scope of the EUCERD Joint Action 2012-2015.

Quality of Life in patients with Rare Diseases in Europe (BURQOL-RD) project

There is a need for a better understanding of the costs that rare diseases represent for the health systems. The Quality of Life in patients with Rare Diseases in Europe (BURQOL-RD) project, which started in April 2010, was selected for this purpose. BURQOL-RD aims to generate a model to quantify the socio-economic burden and HRQOL of people with rare diseases and their caregivers. The model will be initially generated for 10 rare diseases in 8 different European countries and will be adaptable and sufficiently sensitive to capture the differences in the distinct Health and Social Care Systems in the EU Member States. It will consist of a patient and carer-oriented survey to collect data on the burden of disease (socioeconomic costs) i.e. medicinal products, medical tests, transport, hospitalisation, etc., on health-related quality of life (based on EQ-5D for adults and EQ-5D-Y for children between 6 and 17), on disability (using the Barthel Index) and on demographic data. Also a Caregivers survey collecting data on Health related quality of life (EQ-5D), over-burden of the caregiver (Zarit Scale), time utilisation and demographic data. The survey was launched in autumn 2011. The BURQOL-RD model will provide an integrated and harmonised means to assess the impact of new public health policies, interventions and treatments for rare diseases “in” and “among” EU Member States. Moreover, the associated dissemination activities undertaken by BURQOL-RD will also improve awareness of rare diseases and literacy among European citizens.

Building consensus and synergies for the EU Registration of Rare Diseases Patients (EPIRARE) Project

The general objective of this initiative which started in April 2011 is to build consensus and synergies to address regulatory, ethical and technical issues associated with the registration of rare diseases patients and to elaborate possible policy scenarios. Specific attention will be given to the scenario of the creation of an EU platform for the collection of data on rare disease patients and the communication of this data among qualified users, based on a feasibility study. To this aim, the project will define the options for the preparation of a legal basis, the possible scope to achieve the most effective synergies, the corresponding governance framework and the possible options for sustainability. The feasibility of registration of a minimum data set common to all rare diseases designed to inform policy-making, the conditions to admit research-driven disease or treatment-specific modules and the ways to ensure a long-lasting data flow will be assessed. The development of guiding reports, including the legal and organisational framework for the registration of rare disease patients is strategic for building up an evidence base for Community, public health policies, health service management, clinical research and the assessment of orphan medicinal products effectiveness and appropriateness of use. The successful establishment of a, EU registration of health data, for rare diseases, may represent an important example paving the way to the EU-wide registration of data regarding other health conditions.

EPIRARE launched in 2011 a survey of registry leaders to explore the functioning, resources, problems, needs and expectations of existing registries in European Member States and in other Countries. The final aim is to develop tools and services in support of existing registries and to favour the creation of new ones where needed. The survey is directed to both active and past rare disease registries. The preliminary results are available online¹⁰⁸. The final outcomes of the project are expected in 2013.

¹⁰⁵ http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf

¹⁰⁶ <http://www.europlanproject.eu/public/contenuti/files/EP-D6-Indicators.pdf>

¹⁰⁷ <http://www.EURORDIS.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN20%20National%20Conference%20Final%20Reports>

¹⁰⁸ <http://www.epirare.eu/quest4.html>

1.2.3. Call for Tenders

The aim of a call for tender is to purchase the provision of services, the execution of works, the supply of assets or to conclude building contracts. Two important calls for tenders have been launched in the field of rare diseases.

Call for Tender: Evaluation of population newborn screening practices for rare disorders in Member States of the European Union (2009-2011)

In July 2009 a call for tender was launched for an evaluation of the current situation of newborn screening (NBS) practices for rare disorders in the MS of the EU and was awarded to the Istituto Superiore di Sanità in Italy. The tender started on 30 December 2009 and ended on 29 July 2011.

There is a need to identify the current practices in the Member States, including: for which reasons the diseases to be screened are selected, how the decisions to expand the list of diseases are taken, what technologies are used and what organisation is in place to ensure comprehensive screening of all newborns and to evaluate the performance of the programmes.

This tender aimed to deliver: an extensive report on the practices of NBS for rare disorders implemented in all the Member States including number of centres, estimation of the number of infants screened and the number of disorders included in the NBS as well as reasons for the selection of these disorders; the identification of types of medical management and follow-up implemented in the Member States; the establishment of a network of experts analysing the information and formulating a final opinion containing recommendations on best practices and recommending a core panel of NBS conditions that could be included in all MS practices; and the development of a decision-making matrix that could be used by Member States programs to systematically expand (or contract) screening mandates.

Two meetings of the EU network of experts on new born screening were held in 2010 to examine the criteria for implementing newborn screening and to discuss the analysis of the data collected by a survey of EU Member States, candidate Countries, EEA/EFTA and potential candidate countries concerning new born screening in each country. A consensus conference was organised in June 2011 to finalise the report on NBS practices¹⁰⁹ and the expert opinion¹¹⁰ containing recommendations on best practices which were published in 2012. An executive report¹¹¹ to the EC was also issued. The EUCERD were presented with the results of the report in 2012 and the EC requested their opinion on areas in which EU-level collaboration could be envisaged in the future. The document was discussed by EUCERD members at their meetings in 2012 and an opinion will be formulated in 2013.

Call for Tender: Creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines (2010-2011)

A call for tender¹¹² was launched in 2010 for the creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines (CAVOD). This call was awarded to Ernst and Young for a duration of 9 months. The study was published in late 2011¹¹³: it aims to identify and assess possible options for creating a mechanism for the exchange of knowledge between Member States (MS) and European authorities on the scientific assessment of the relative effectiveness of orphan medicines. The European Union Committee of Experts on Rare Diseases (EUCERD) is considering carefully the data provided by the CAVOD report and will issue a recommendation to the EC and MS on improving informed decisions based on the clinical added value of orphan medicinal products information flow in 2012 suggesting how to best coordinate and exchange information health technology assessment for orphan medicinal products, capitalising on mechanisms already in place at the MS level and at EU-level structures, such as the European Medicines Agency and the EUnetHTA network. Following the outcomes of this tender the EUCERD has elaborated a recommendation for the EC and Member States on improving the assessment of the Clinical Added Value of Orphan Medicinal Products encourages the creation of an Information Flow¹¹⁴.

¹⁰⁹ http://ec.europa.eu/eahc/documents/news/Report_NBS_Current_Practices_20120108_FINAL.pdf

¹¹⁰ http://ec.europa.eu/eahc/documents/news/Expert_opinion_document_on_NBS_20120108_FINAL.pdf

¹¹¹ http://ec.europa.eu/eahc/documents/news/Executive_Report_to_EC_20120108_FINALE.pdf

¹¹² http://ec.europa.eu/eahc/documents/health/tenders/2010/EN/EAHC_2010_05_tenderSpecifications_EN.pdf

¹¹³ http://ec.europa.eu/eahc/documents/news/CAVOD_Final%20Report_vf_corrected_281011.pdf

¹¹⁴ http://www.eucerd.eu/?post_type=document&p=1446

1.2.4. Operational grants

Under the Health Programme, the European Union can offer support to finance some of the core operating costs for organisations that promote a health agenda in line with the EU Health Programme (2008-13). The purpose of an operating grant is to provide financial support towards the functioning of an organisation in its core activities, over a period that is equivalent to its accounting year, in order to carry out a set of activities.

Several Operating Grants have been awarded to EURORDIS (European Organisation for Rare Diseases). EURORDIS is fully recognised as the main partner of patients in the field of rare diseases and the line of the European Commission has been always to recognise this central role in all the political affairs concerning the implementation of rare diseases policy. As a consequence the Commission has privileged the funding of EURORDIS and does not finance, nor has plans to finance, individually every one patient organisations that exists in the EU. From the Health Programme EURORDIS has received funds from the side of the European Commission: the 2012 Operational Grant EURORDIS_FY2013, the 2011 Operational Grant EURORDIS_FY2012, the 2010 Operational Grant EURORDIS_FY2011, the 2009 Operational Grant EURORDIS_FY2010 and the 2008 OPERATING GRANT FOR RARE DISEASE ASSOCIATIONS (OPERA).

Other operating grants have been awarded to support the continuation of existing performing EU networks on information and registers in several areas.

1.3. Activities of the European Commission DG Health and Consumers indirectly related to rare diseases

Directive 2011/24/EU OF on the application of patients' rights in cross-border healthcare (2011)

Directive 2011/24/EU adopted in March 2011 clarifies patients' rights to access safe and good quality treatment across EU borders, and be reimbursed for it. The Directive will provide a firm basis for increased cooperation between national health authorities through several actions. Some provisions are addressing the issue of rare diseases.

In particular Article 12 foresees enhanced cooperation of Member States in the area of European reference networks (ERN). It foresees that Commission is going to adopt through legal means (delegated and implementing acts) the criteria and conditions which the ERN and the healthcare providers must fulfil.

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

The main added value of the ERN and therefore of the Centres of Excellence/Reference is to facilitate improvements in access to diagnosis and delivery of high-quality, accessible and cost-effective healthcare in the case of patients who have a medical condition requiring a particular concentration of expertise or resources, particularly in medical domains where expertise is rare.

It further clarifies that ERN could also be focal points for medical training and research, information dissemination and evaluation, especially for rare diseases. The Directive is not aiming to "create" new centres, but to identify already established centres of expertise and to encourage voluntary participation of healthcare providers in the future ERN.

Further more, Article 13 requires the Commission to support Member States in making health professionals more aware of diagnostic tools which may help rare disease patients, and in making patients more aware of the possibility of requesting a treatment abroad according and up to the entitlements they have in their Member State of affiliation. Article 8 also encourages Member States to seek the advice of experts when dealing with patients with rare diseases.

European Commission public consultation on criteria for European Reference Networks (2012)

The European Commission launched a public consultation¹¹⁵ 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 (Directive 2011/24/EU) at the end of 2012. A conceptual paper¹¹⁶ and a

¹¹⁵ http://ec.europa.eu/health/cross_border_care/consultations/cons_implementation_ern_en.htm

¹¹⁶ http://ec.europa.eu/health/cross_border_care/docs/cons_implementation_ern_concept_paper_en.pdf

questionnaire were prepared by Directorate General Health & Consumers for this consultation. European Reference Networks are of particular relevance in the field of rare diseases which are mentioned in the Directive as an example of a field of particular need for such networks. The Directive on the application of patients' rights in cross-border healthcare requires the European Commission to support Member States in the development of European Reference Networks between healthcare providers and centres of expertise. The main added value of the European Reference Networks and of the Centres of Expertise is to facilitate improvements in access to diagnosis and delivery of high-quality, accessible and cost-effective healthcare in the case of patients who have a medical condition requiring a particular concentration of expertise or resources, particularly in medical domains where expertise is rare (see Recital 54 of the Directive). European Reference Networks could also be focal points for medical training and research, information dissemination and evaluation, especially for rare diseases. Article 12 requires the Commission to adopt a list of criteria that the networks must fulfill, as well as the conditions and criteria which providers wishing to join networks must fulfill. The Commission is also required to develop and publish criteria for establishing and evaluating European Reference Networks: the Commission must also facilitate the exchange of information and expertise on the establishment of the networks and of their evaluation.

The following target groups were encouraged to give their views: patient organisations, health professionals' organisations and healthcare provider's organisations; healthcare providers and centres of excellence, academic and public health and healthcare specialised institutions; public authorities and government-appointed bodies responsible or involved in the definition of criteria and the establishment and evaluation of centres of reference/excellence and reference networks of centres providing highly specialised healthcare.

The aim of the consultation is to receive input and opinion of stakeholders based on evaluated experiences, regional or national models, technical and professional standards, existing criteria or recommendations, needs and feasibility and EU added value.

European Commission's Alzheimer and Dementias Communication (2009)

The European Commission adopted in late July 2009 a Communication¹¹⁷ on a European initiative for Alzheimer disease and other dementias along with a proposal for a Council Recommendation¹¹⁸ on measures to combat neurodegenerative diseases through joint programming of research activities. The Communication encompasses rare forms of dementia – which include frontotemporal dementia, Pick disease (lobar atrophy), Binswanger disease, and Lewy-Body dementia. The Communication makes reference to data from a project conducted by European Union patient platform Alzheimer Europe with the support of the European Commission that identified significant rare forms of dementia. The Communication encourages national and collaborative efforts in four key areas: prevention, the coordination of research across Europe, disseminating best practice for treatment and care, and the development of a common approach to ethical matters concerning the rights, autonomy, and dignity of people with dementia.

European Commission Communication on Action Against Cancer: European Partnership (2009)

The European Commission adopted on 24 June 2009 a Communication on Action Against Cancer¹¹⁹ and created a European Partnership on action against cancer (EPAAC). The significant problem of rare cancers (representing around 27% of new cancers diagnosed every year) needs particular coordination in this field. The Communication refers explicitly to the EU added-value that will represent cooperation on European Reference Networks, taking the example of rare diseases, which include many rare cancers. The EUCERD Joint Action is working on common areas for collaboration in the field of rare cancers with the future EPAAC Joint Action.

Directive regulating organ donations and transplantations (2010)

A directive¹²⁰ adopted on 7 July 2010 established common standards for safety and quality in the area of organ donation and transplantation – an issue pertinent to the scores of rare diseases that affect organs such as the heart, liver or kidneys. The new legislation seeks to level the playing field across Europe and offer protection to poor citizens vulnerable to illegal organ trafficking schemes. The European Parliament voted in mid-May 2010 to pass the directive, which is pending adoption by the Council of Ministers. The European Commission has also set forth a ten point action plan for organ transplantation and donation, which has been backed by the

¹¹⁷ http://ec.europa.eu/health/ph_information/dissemination/documents/com2009_380_en.pdf

¹¹⁸ http://ec.europa.eu/health/ph_information/dissemination/documents/rec2009_379_en.pdf

¹¹⁹ http://ec.europa.eu/health/ph_information/dissemination/diseases/docs/com_2009_291.en.pdf

¹²⁰ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:PDF>

Parliament. Under the new legislation, each MS must establish a national authority to monitor the safety and quality of both donations and transplantations. Recommendations have also been put forward for a database for organs and donors. Donation must be entirely voluntary and free from financial gain. Member States were expected to transpose the requirements of the Directive by 27 August 2012. There are presently some 60 000 Europeans awaiting organ transplantations - many with rare conditions.

Revision of the Directive of the European Parliament and Council of 27 October 1998 on *in vitro* diagnostic medical devices

The European Commission launched in June 2010 a public consultation on the revision of Directive 98/79 EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (the IVD Directive). Council Directive 90/385/EEC relating to active implantable medical devices, Directive 93/42/EEC concerning medical devices and Directive 98/79/EC on *in vitro* diagnostic medical devices harmonise safety and performance rules for medical devices in the EU. The IVD Directive, in particular, sets out the regulations governing the safety and efficacy of diagnostic tests marketed in Europe and creates a single market for *in vitro* diagnostic devices across the EU. The existing IVD Directive has been criticised for being inflexible and arbitrary in the way it classifies tests. The blanket exemption for tests produced in health institution laboratories is also criticised for being too broad and poorly defined. Due to both technological advances and identified emerging weaknesses identified in the regulatory framework, a public consultation was launched in 2008¹²¹ on the Recast of the Medical Devices Directives. Responses to this underlined a necessity for the revision of the IVD Directive, which has remained largely unchanged since its adoption in 1998, despite significant technological advancement in the sector.

In the context of the recast of the regulatory framework for medical devices and following the consultation mentioned above, the European Commission launched in 2010 a public consultation on technical aspects related to the revision of Directive 98/79/EC on *in vitro* diagnostic (IVD) medical devices. The summary of the responses to the public consultation launched in June 2010 on issues related to *in vitro* diagnostic medical devices were published online in February 2011¹²². Responses to this underlined a necessity for the revision of the IVD Directive, which has remained largely unchanged since its adoption in 1998, despite significant technological advancement in the sector.

The EU-funded Network of Excellence EuroGentest¹²³ has also produced a position paper on the revision of the IVD Directive, which has been adopted as EuroGentest policy. One central proposal of the EuroGentest document is that the exemption from CE-marking for in-house tests manufactured in public health service laboratories should be retained, but that it should be restricted to laboratories accredited to ISO 15189¹²⁴ or equivalent. This would provide a balance between test availability and patient safety. There have been calls for the abolition of the in-house exemption. If this were to occur, however, it would severely limit the scope of testing available - especially for rare diseases. The EuroGentest response¹²⁵ to the 2010 consultation robustly supports the retention of the exemption, while emphasising that patient safety should be ensured by restricting it to accredited laboratories.

In September 2012, the European Commission issued a Communication¹²⁶ and proposed two Regulations¹²⁷ designed to revise current European Union legislation on medical devices and *in vitro* diagnostic medical devices. The proposed Regulations are in response to the Conclusions of the Council adopted on 6 June 2011 on innovation in the medical device sector as well as the European Parliament Resolution (on defective silicone breast implants) adopted on 14 June 2012. The proposed Regulations seek to adapt current legislation “to the needs of tomorrow” by creating a “suitable, robust, transparent and sustainable regulatory framework” that will serve to encourage the development of innovative medical devices and *in vitro* diagnostic medical devices that are safe, and effective. The European Parliament and Council need to adopt the Regulations in order for them to become law. There are a number of rare diseases that include medical devices as part of their clinical management, particularly in paediatric populations.

¹²¹ http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/public_consultation_ivd_final_en.pdf

¹²² http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/ivd_pc_outcome_en.pdf

¹²³ <http://www.eurogentest.org/web/index.xhtml>

¹²⁴ <http://www.eurogentest.org/laboratories/qau/info/public/unit1/qmanagement/accreditation.xhtml>

¹²⁵ http://ec.europa.eu/health/medical-devices/files/ivd/50_ivd_en.pdf

¹²⁶ http://ec.europa.eu/health/medical-devices/files/revision_docs/com_2012_540_revision_en.pdf

¹²⁷ http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf and http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

EU Disability Strategy 2010-2020: A Renewed Commitment to a Barrier-Free Europe (2010)

In November 2010, the European Commission adopted a strategy that seeks to improve the situation of the estimated 80 million citizens living with a disability in Europe today. The 'EU Disability Strategy 2010-2020: A Renewed Commitment to a Barrier-Free Europe'¹²⁸ aims at removing the obstacles that prevent disabled people from participating fully in society on an equal basis with others. Specifically, the strategy aims to bring down barriers in areas such as accessibility, employment, health, education and social exclusion. The EU will support policies that improve disabled people's accessibility to the built environment, to services and to the latest technology, namely the Internet. For example, only 5% of public websites fully comply with web accessibility standards. Another important area is education. The EC has declared its support for the inclusion of children with disabilities in mainstream education, as well as lifelong learning and training opportunities for disabled adults. Bettering employment opportunities and ensuring disabled people are not socially excluded and do not fall in the poverty trap, are other important aspects the EU will try to address. People with rare diseases will benefit from these actions. In addition, the Commission is looking to carry out specific actions at the European level. For example, it wants to make sure that disability cards and parking permits can be used throughout the whole EU, and not just in individual member states. The EU Disability Strategy was presented at the Rare Disease Day 2011 European Symposium in Brussels, which focused on health inequalities.

Establishment of an eHealth network (2011)

In December 2011, the European Commission adopted a Decision¹²⁹ establishing an eHealth Network, as foreseen by the Directive on Patients' Rights in Cross-border Healthcare¹³⁰. For the first time, EU legislation includes provisions on eHealth with clear objectives to find modern, innovative solutions for providing better and safer healthcare for all Europeans. The Network will bring together the national authorities responsible for eHealth on a voluntary basis to work on common orientations for eHealth. The aim is to ensure EU wide interoperability of electronic health systems and wider use of eHealth. The eHealth Network is expected to translate the results of numerous research projects and pilot projects into real-life accessible services for European citizens. The utility of eHealth may be especially significant in the field of rare diseases, which is marked by scattered expertise and resources. eHealth will allow for remote diagnosis, remote monitoring of patients' conditions and secure sharing of patient records between healthcare professionals.

¹²⁸ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2010:0636:FIN:EN:PDF>

¹²⁹ http://ec.europa.eu/health/ehealth/docs/decision_ehealth_network_en.pdf

¹³⁰ http://ec.europa.eu/health/ehealth/policy/index_en.htm

2. EUROPEAN COMMISSION ACTIVITIES RELATED TO RESEARCH IN THE FIELD OF RARE DISEASES

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.

2.1. Fifth and Sixth Framework Programmes for research, technological development and demonstration activities (1998-2002, 2002-2006)

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. 47 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 focussing 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 the dialogue with all stakeholders, including patients.

A list of FP6 projects is provided on the Cordis website¹³¹ and the *Orphanet Report Series* lists EU-funded collaborative projects in the field of rare diseases¹³².

The FP6 ERA-Net for research programmes on rare diseases (E-Rare)¹³³ is a network of ten countries responsible for the development and management of national/regional research programmes on rare diseases. This project helps develop synergies among the national and/or regional research programmes of the participating countries, to establish a common research policy on rare diseases and to coordinate their national/regional research programmes, notably through the setting up of joint strategic activities and transnational calls for proposals.

¹³¹ <http://cordis.europa.eu/lifescihealth/major/rare-diseases-projects-1.htm>

¹³² <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

¹³³ <http://www.e-rare.eu/>

2.2. 7th Framework Programme for research, technological development and demonstration activities (2007-2013)

The Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7, 2007-2013¹³⁴) is composed of four main specific programmes – “Cooperation”, “Ideas”, “People” and “Capacities” – including cross-cutting issues such as support for SMEs, international cooperation, the contribution of research to EU policy, and societal considerations. 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.

Specifically, the focus for rare diseases collaborative research in FP7 is on pan-European studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions. This sector includes rare Mendelian phenotypes of common diseases. Supported projects should help identify and mobilise the critical mass of expertise in order (i) to shed light on the course and/or mechanisms of rare diseases, or (ii) to test diagnostic, preventive and/or therapeutic approaches, to alleviate the negative impact of the disease on the quality of life of the patients and their families, as appropriate depending on the level of knowledge concerning the specific (group of) disease(s) under study.

The European Commission has published several calls for proposals covering research on rare diseases in various areas of FP7 Health Theme. For the period 2007–2012, altogether 95 research projects related to rare diseases have been funded with an EU contribution of over €485 million. 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 proposals¹³⁵: this year, one specific rare disease topic is included: *Development of imaging technologies for therapeutic interventions in rare diseases*.

A list of FP7 projects is provided on the Cordis website¹³⁶ and the *Orphanet Report Series* lists EU-funded collaborative projects in the field of rare diseases¹³⁷.

The projects launched in FP7 include also an ERA-Net on rare diseases funded from the 2010 Work Programme. E-Rare-2¹³⁸ aims at coordinating national research programmes on rare diseases. Important aspects include exchanging information concerning research on rare diseases, and funding transnational collaborative research through joint transnational calls.

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

One project delivered a “*Report on Rare Disease Research, Its Determinants in Europe and the Way Forward*”¹³⁹. This report prepared in the context of the RareDiseasePlatform project (RDPlatform), a three-year support action project of the European Union’s Seventh Framework Programme (HEALTH-F2-2008-201230) that ran from May 2008 through April 2011 was published in 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 medicinal products informational portal Orphanet, encompasses ongoing research projects, clinical trials, and registries. Other areas covered in the report include testing, therapeutic development, and R&D determinants (such as prevalence and medical area). The rare disease ontologies, data repositories and bioinformatic tools are given special emphasis in the report.

¹³⁴ http://cordis.europa.eu/fp7/home_en.html

¹³⁵

http://ec.europa.eu/research/participants/portal/page/cooperation;efp7_SESSION_ID=m0pTRn7GxnWW8LynmvWxs9w6J1KJQC4ByLwcYvzJhm6GL0qNLQX11982354445?callIdentifier=FP7-HEALTH-2013-INNOVATION-1#wlp_call_FP7

¹³⁶ http://ec.europa.eu/research/health/medical-research/rare-diseases/projectsfp7_en.html

¹³⁷ <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

¹³⁸ <http://www.e-rare.eu/>

¹³⁹ http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

Breaking activities down by country, the RDPlatform report provides a snapshot of national, multi-national and EU project involvement for over 30 countries. The policy decisions that supported the research actions are outlined, including European-level policies. This information can be instructive to countries developing their own measures in the field of rare diseases and orphan medicinal products. The report also considers possible future actions to more efficiently build upon what has already been accomplished.

The *Report on Rare Disease Research, Its Determinants in Europe and the Way Forward* adds to a growing toolbox of resources designed to help move rare disease and orphan medicinal product research forward as productively as possible. Drafted by experts from the RDPlatform project, the report was reviewed by a large number of stakeholders and discussed at a workshop earlier this year. Together with the *Rare Diseases and Orphan Products* report produced late 2010 by the Institute of Medicine in the USA, the RDPlatform report will serve as a key document for the recently-formed International Rare Diseases Research Consortium (IRDiRC).

2.3. The International Rare Diseases Research Consortium (IRDiRC¹⁴⁰)

There is a recognised need for more international cooperation in research on rare diseases: to align taxonomy, diagnosis and treatment options, to optimise scattered and scarce resources (patients, experts, budgets), with a view to accelerate the development of new diagnostic and therapeutic options.

The European Commission (EC) and the USA's National Institutes of Health (NIH) held a joint workshop¹⁴¹ in Reykjavik, Iceland, on 27-28 October 2010, to discuss ways in which to foster transatlantic cooperation on research into rare diseases. This workshop was the first step of a process through which the EC and the NIH hope to establish an ambitious international research programme to speed up the development of diagnostic and therapeutic solutions for patients. This programme is intended to be open to other countries, in order to be truly international and not simply bilateral. Its principle was drafted a few months before this workshop when Dr Ruxandra Draghia-Akli (Director of the Health Directorate at the EC's DG Research and Innovation) and Dr Francis Collins (NIH Director) met to discuss the possibility of bilateral cooperation.

IRDiRC¹⁴² was officially established and launched during the second preparatory workshop held in Bethesda (USA) in April 2011. The group of funding agencies representatives agreed to have an Interim Executive Committee until the end of 2012. The group chose Dr. Ruxandra Draghia-Akli as the interim Chair.

In October 2011 in Montreal (Canada), the third preparatory workshop gathered around 100 participants representing public and private funding organizations, scientists, regulators, industry and patient groups. It focused on continuous efforts to develop common scientific and policy frameworks to guide the activities of the participating IRDiRC members.

Governance

IRDiRC is governed by the Executive Committee, three Scientific Committees and twelve working groups¹⁴³. Until April 2013, IRDiRC will be run by an Interim Executive Committee with representatives of all participating funding agencies. It is chaired by Dr Ruxandra Draghia-Akli, from the European Commission. To be considered as an IRDiRC funding member, the funding organisation should invest a minimum of \$10 million USD over 5 years in research projects/programmes contributing towards IRDiRC objectives. Letters of intent concerning IRDiRC membership must be signed by the authorising official committing the research funds. The Interim Executive Committee held two meetings in 2012, one in Brussels in January and another in Evry, France in September. Executive summaries of the meetings are available on the IRDiRC website.

The three Scientific Committees are for Diagnostics (including sequencing and characterisation), Therapies (including pre-clinical and clinical development) and Interdisciplinary aspects of rare diseases research (including ontologies, natural history, biobanking, registries etc). The Scientific Committees will advise the Executive Committee on research priorities and progress made from a scientific viewpoint. Members of the three IRDiRC Scientific Committees were appointed in 2012.

¹⁴⁰ http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html

¹⁴¹ http://ec.europa.eu/research/health/medical-research/rare-diseases/events-03_en.html

¹⁴² www.irdirc.org

¹⁴³ http://ec.europa.eu/research/health/medical-research/rare-diseases/governance_en.html

The IRDiRC Working Groups are composed of representatives of projects funded within the scope of the 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.

EC support for IRDiRC activities

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-1¹⁴⁴ 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. The Secretariat is located at the Rare Disease Platform in Paris, in the same structure housing the Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), pan-European rare disease and orphan drug information portal Orphanet, and the French Rare Disease Foundation. The contract for the SUPPORT-IRDiRC has been assigned to two partners: the INSERM (the French National Institute for Health and Medical Research) and the French Rare Disease Foundation. With this new resource, it is expected that the IRDiRC will have the means of achieving its ambitions.

The Call FP7-HEALTH-2012-INNOVATION-1 resulted in the funding of a number of projects contributing directly to the IRDiRC objectives. Three large-scale integrating projects were 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.

Committed Members of the IRDiRC

The funding agencies now committed to the IRDiRC are from the following countries: Australia, Canada, Italy, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States, in addition to the European Commission¹⁴⁵.

2.4. Access to scientific information

Access to scientific data is especially crucial in the field of rare diseases, an area suffering from a lack of knowledge and resources, fragmentation, and duplication of effort. In August 2008, the European Commission launched the Open Access Pilot in the Seventh Framework Programme (FP7) with the aim of providing improved Internet access to EU-funded research results, particularly peer-reviewed articles published in the scientific literature. Under the pilot scheme, articles produced via research funded under FP7 become freely accessible following a specific embargo period. Pushing the momentum to improve access to published scientific research results further, two key documents were adopted by the European Commission on 17 July 2012. The first, a Communication, entitled Towards better access to scientific information: Boosting the benefits of public investments in research¹⁴⁶ delineates actions that the European Commission intends to take “to improve access to scientific information and to boost the benefits of public investment in research”. Policies to be implemented under Horizon 2020, the next Framework Programme for Research and Innovation (2014-2020), are described. The second document, accompanying the Communication, is a Commission Recommendation on access to and preservation of scientific information¹⁴⁷. This document recommends that EU Member States (MS):

¹⁴⁴ <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>

¹⁴⁵ http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members_en.html

¹⁴⁶ http://ec.europa.eu/research/science-society/document_library/pdf_06/era-communication-towards-better-access-to-scientific-information_en.pdf

¹⁴⁷ http://ec.europa.eu/research/science-society/document_library/pdf_06/recommendation-access-and-preservation-scientific-information_en.pdf

- Define clear policies for the dissemination of and open access to scientific publications resulting from publicly funded research ;
- Ensure that research funding institutions responsible for managing public research funding and academic institutions receiving public funding implement the policies ;
- Define clear policies for the dissemination of and open access to research data resulting from publicly funded research ;
- Reinforce the preservation of scientific information ;
- Further develop e-infrastructures underpinning the system for disseminating scientific information
- Ensure synergies among national e-infrastructures at European and global level ;
- Participate in multi-stakeholder dialogues at national, European and/or international level on how to foster open access to and preservation of scientific information ;
- Designate by the end of the year a national point of reference ;
- Inform the Commission 18 months from the publication of this Recommendation in the Official Journal of the European Union, and every two years thereafter, of action taken in response to the different elements of this Recommendation, in accordance with formalities to be defined and agreed.

Together with the Communication and Recommendation, the Commission also adopted a Communication on A reinforced European Research Area partnership for excellence and growth¹⁴⁸ in which it sets out the key priorities for completing the European Research Area, one of which is the optimal circulation, access to and transfer of scientific knowledge. In January 2013 the European Economic and Social Committee gave a favourable opinion on the Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions – Towards better access to scientific information: Boosting the benefits of public investments in research - COM(2012) 401 final¹⁴⁹.

The Open Access Infrastructure for Research in Europe (OpenAIRE¹⁵⁰) launched in December 2010 at the University of Ghent in Belgium, provides a network of open repositories offering free electronic access to the scientific papers stemming from projects supported through the Seventh Framework Programme (FP7) in diverse fields – including cooperative research in the Health Theme and grants from the European Research Council. A European Commission press release¹⁵¹ describes the launch as “... an important step towards full and open access to scientific papers that could, for example, allow patients with rare illnesses to have access to the latest medical research results, or provide scientists with real-time updates about developments in their field”. The new structure is part of a larger bid to develop research infrastructures and e-infrastructures that can help boost Europe's competitiveness. According to the press release, only 15%-20% of some 2.5 million research articles published annually are available via open access journals or repositories. OpenAIRE originates from a European Commission pilot initiative that was launched in August 2008. FP7-funded projects “are requested to deposit peer-reviewed papers in online repositories and to provide open access within 6 or 12 months after publication depending on the thematic area”. Increasing access is particularly good news for the fields of rare disease and orphan medicinal product research, which depend on networking and collaboration to identify and bring together scattered resources and avoid duplication. It is hoped that the OpenAIRE infrastructure will particularly help those countries lacking research resources for their rare disease patients.

2.5. DG Research consultation on public-private partnership initiatives in health research

Public-private collaboration is considered crucial in the field of rare disease and orphan drug research, an area that suffers from a lack of resources and funding. Under the 7th Framework programme for research, technological development and demonstration activities (2007-2013) (FP7) the European Union (EU) entered

¹⁴⁸ http://ec.europa.eu/research/science-society/document_library/pdf_06/era-communication-partnership-excellence-growth_en.pdf

¹⁴⁹ <http://www.eesc.europa.eu/?i=portal.en.int-opinions.24976>

¹⁵⁰ www.openaire.eu

¹⁵¹ <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/10/1644&format=HTML&aged=1&language=EN&guiLanguage=fr>

into a Public Private Partnership (PPP) with the pharmaceutical industry, represented by its umbrella organisation European Federation of Pharmaceutical Industries and Associations (EFPIA). The Innovative Medicines Initiative (IMI) was established by Council regulation 73/2008 of 20.12.2007. Both partners contribute € 1 billion each to implement IMI. With this funding IMI is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients – including rare disease medicinal products. Based on the success of IMI the European Commission is now exploring whether under Horizon 2020 a renewed PPP should be launched. The Commission proposal for Horizon 2020 foresees that the priority "societal challenges" is also implemented through PPPs. Selection of PPPs will be based on a set of clearly defined criteria, including the added value of action at the EU level, the scale of impact on industrial competitiveness, sustainable growth and socio-economic issues, and the long-term commitment from all partners based on a shared vision and clearly defined objectives. As part of this process a public consultation was conducted in 2012¹⁵². The consultation seeks key views relating to the launch of a PPP in the life sciences research area under Horizon 2020 and what areas should be addressed.

2.6. Biobanks for Europe: A challenge for governance

A new report issued in 2012¹⁵³, produced by DG Research with the participation of an interdisciplinary group of experts, looks at the regulatory and ethical challenges of international biobank research. In order to link individual biobanks together as part of a pan-European infrastructure supporting medical research and health care, an adequate governance framework needs to be put in place. The development of a biobank infrastructure is seen as critical in the field of rare diseases where difficulties accessing specific rare samples can hinder research. This expert report offers a set of recommendations for the effective governance of a pan-European biobank network.

2.7. Reform of the EU Data Protection Directive

In January 2012, the European Commission proposed a comprehensive reform of the European Union's 1995 Data Protection Directive, seeking to update and modernise the legislation in view of the major technological advances made in recent years. The overhaul also aims to increase harmony between the 27 EU Member States which have implemented the current Data Protection Directive 95/46/EC differently, resulting in divergences in enforcement. The proposed Regulation will decrease the fragmentation by establishing a single set of rules valid across the EU. Specific provision on processing of personal data for health purposes and on historical, statistical and scientific research purposes will increase legal certainty and clarity on applicable rules for data protection in health research. The Commission's proposal for the Regulation is currently being discussed in the European Parliament and the Council.

¹⁵² http://ec.europa.eu/research/consultations/life_science_h2020/consultation_en.htm

¹⁵³ http://bookshop.europa.eu/en/biobanks-for-europe-pbKINA25302/downloads/KI-NA-25302-EN-C/KINA25302ENC_002.pdf;pgid=y8dIS7GUWMdsR0EAIMEUUsWb00006naClSsM;sid=vk4G5ut1qt0G-LsRpY6YQYlQuZ0ANeymuJ0=?FileName=KINA25302ENC_002.pdf&SKU=KINA25302ENC_PDF&CatalogueNumber=KI-NA-25302-EN-C

3. EUROPEAN COMMISSION ACTIVITIES RELATED TO RARE DISEASES IN THE FIELD OF ORPHAN MEDICINAL PRODUCTS AND THERAPIES FOR RARE DISEASES

3.1. EU activities under Regulation (EC) No 141/2000 on orphan medicinal products

Orphan Medicinal Product Regulation (16 December 1999)

The regulation on orphan medicinal products (Regulation (EC) No 141/2000)¹⁵⁴ 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 placing on the market of medicinal products for the diagnosis, prevention or treatment of rare conditions, as without such incentives, it is unlikely that medicinal 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 for incentives for products receiving an orphan designation. The incentives contained in the legislation aim to assist sponsors receiving orphan designations in the development of medicinal products with the ultimate goal of providing medicinal products for patients suffering from rare diseases.

Orphan designation is based on a number of criteria that the sponsor must establish. There are two alternative grounds for application: the first alternative for applications is based on the low prevalence of the condition in the EU. To receive designation under this first alternative, a medicinal product must target a life-threatening or chronically debilitating condition that affects not more than five in 10,000 persons in the EU at the time when the application is made. In addition, in the case that other satisfactory methods of diagnosis, prevention or treatment of the condition exist in the EU, the sponsor has to establish that the medicinal product will be of significant benefit to those affected by the condition.¹⁵⁵

The second alternative is to apply based on insufficient return: In these cases the sponsor must establish that without incentives it is unlikely that the return obtained once the medicinal product is on the market will generate sufficient return to justify the necessary investment. Under this alternative, the condition must be life-threatening, seriously debilitating or serious and chronic. Also under this alternative, the requirement of establishing significant benefit applies, if other satisfactory methods already exist for the condition. The concept of significant benefit is further defined in Commission Regulation (EC) No 847/2000 and further presented in Commission Communication 2003/C 178/02).

Normally the criterion of significant benefit is assessed at a very early stage in the development process of the medicinal product, therefore at the time of designation the arguments are based on justified assumptions that will have to be confirmed at the time of marketing authorisation, when, amongst other things, also efficacy and safety data are available.

The economic and regulatory incentives laid down in this regulation aim to assist sponsors in the development of medicinal products for rare diseases and include: the direct access to the centralised procedure for marketing authorisation, protocol assistance in the form of scientific advice from the European Medicines Agency (EMA) and the possibility to be granted fee reductions by the EMA, a period of market exclusivity of 10 years once the orphan product is authorised.

The regulation on orphan medicinal products also set up the Committee for Orphan Medicinal Products¹⁵⁶ (COMP) at the European Medicines Agency (EMA) to assist the Commission. According to the regulation the tasks of the Committee are: - to examine applications for the designation of medicinal products which are submitted to it in accordance with the regulation; - to advise the Commission on the establishment of a policy

¹⁵⁴ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF>

¹⁵⁵ For more detailed information on the regulation and its implementing rules, see under http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm

¹⁵⁶ This section reproduces information from <http://www.ema.europa.eu/htms/general/contacts/COMP/COMP.html>

on orphan medicinal products; to assist the Commission in liaising internationally on matters relating to orphan medicinal products for the EU; and – to assist the Commission in drawing up detailed guidelines.

The Commission adopts decisions on designation based on an opinion from the COMP. In 2012, the Commission granted 150 orphan designations. In addition, the Commission authorised nine orphan medicinal products in 2012. These newly authorised medicines aim at treating severe diseases such as lipoprotein lipase deficiency, short Bowel Syndrome, acute myeloid leukaemia or anaplastic large cell lymphoma¹⁵⁷.

The full list of orphan designations granted by the European Commission as well as of the orphan medicinal products which it has authorised is available in the Community register of orphan medicinal products held by the European Commission¹⁵⁸. The EMA maintains a searchable list of opinions on orphan designations¹⁵⁹.

It should be noted that, as of 1 February 2009, designated orphan medicinal products are eligible for reductions for all fees payable under Community rules pursuant to amended Regulation (EEC) 2309/93. Covered in the reductions, applicable to orphan products designated in accordance with Regulation (EC) 141/2000, are the fees for pre-authorisation activities (protocol assistance such as scientific advice), as well as for products using the centralised procedure: the application for marketing authorisation, inspections, and post-authorisation activities. The fee revisions reflect a policy of enhanced support for micro- small- and medium-sized enterprises (SMEs). An EMA press release stated: *“In the revised policy for 2009, the fee reduction for new applications for marketing authorisation to SMEs is increased to 100%. The fee reduction for post authorisation activities including annual fees to SMEs in the first year after granting a marketing authorisation is also increased to 100%. The 100% fee reduction for protocol assistance and 100% fee reduction for pre-authorisation inspections are maintained for all applicants. The 50% fee reduction for new applications for marketing authorisation submitted by applicants that are not SMEs is also maintained”*¹⁶⁰. The EMA revised the fee reduction policy in April 2011 to ensure adequate incentives are still offered with the EU contribution received for 2011. The revised policy was adopted with an aim to ensuring that incentives for Small and Medium-sized Enterprises (SMEs) developing orphan medicinal products are maintained at the same level as previous years. In order to keep this objective the fee reductions for bigger pharmaceutical companies have been decreased. The main changes introduced for 2011 are the following: 75% fee reduction for protocol assistance and follow-up procedures for non-SMEs. SMEs continue to benefit from a 100% reduction, as required by Article 7(3) of Regulation (EC) No 2049/2005. 10% fee reduction for initial marketing authorisation applications for non-SMEs. SMEs continue to benefit from a 100% reduction. SMEs will continue to avail in 2013 the free services of protocol assistance (scientific advice); fee waiver for initial market-authorisation applications, pre-authorisation inspections, post-authorisation applications and annual fee waiver in the first year from marketing authorisation. However, Non-SMEs developing orphan medicinal products will have fewer benefits in 2013 in some categories. Fee reductions for non-SME will now include a 40% reduction for non-paediatric protocol assistance (previously 75%) and no fee reductions for initial market-authorisation applications (previously 10%) and pre-authorisation inspections (previously 100%). Protocol assistance for paediatric-related medicines will continue to be free for non-SME.

3.2. European legislation and activities in the field of clinical trials

Regulation of Clinical Trials¹⁶¹

Clinical trials are investigations in humans intended to discover or verify the effects of one or more investigational medicinal products ("IMPs").

Requirements for the conduct of clinical trials in the EU are provided for in the “Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations

¹⁵⁷ Data provided by representatives of DG Health and Consumers.

¹⁵⁸ <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>

¹⁵⁹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d12b

¹⁶⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/09/WC500003876.pdf

¹⁶¹ This section reproduces information from http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index_en.htm (March 2010)

and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use” (known more commonly as the “Clinical Trials Directive”¹⁶²). In its Communication of 10 December 2008 to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on “Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector”, the Commission announced that an assessment would be made of the application of the Clinical Trials Directive. This assessment would consider, in particular, various options for improving the functioning of the Clinical Trials Directive with a view to making legislative proposals, if appropriate, while taking the global dimension of clinical trials into account.

The Clinical Trials Directive was reinforced by the “Commission Directive 2005/28/EC¹⁶³ of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products”: this Directive is better known as the “Good Clinical Practice Directive”.

Clinical trials submitted in any marketing authorisation application in the EU are required to be conducted in accordance with the Clinical Trials Directive. If the clinical trials are conducted outside the EU, but submitted in an application for marketing authorisation in the EU, they have to follow the principles which are equivalent to the provisions of the Clinical Trials Directive (cf. Annex I, point 8 of the “Directive 2001/83/EC¹⁶⁴ of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use”, known as the Community Code for medicinal products¹⁶⁵).

Revision of the EC Clinical Trials Directive

The Clinical Trials Directive, implemented in 2004, was developed in order to harmonise European regulatory systems pertaining to the clinical research environment, improve the protection of study participants, optimise safety information, and ensure quality and data credibility across Europe. However, the directive has been criticised by some scientists who accused the measure of hindering academic research, resulting in fewer new trials initiated with fewer patients enrolled. An increased workload for ethics committees was cited amongst the causes for slowing trial initiation¹⁶⁶. The Directive was particularly criticised over three principle points: the divergent application of the Clinical Trials Directive in the Member States; the increased administrative burden for clinical trials in view of regulatory requirements which do not take into account practical necessities and constraints; and the fact that clinical trial regulation does not sufficiently take into account the increasingly global scale of clinical trials.

A one-year project financed by the Seventh Framework Programme to measure and analyse the impact of the directive on clinical research in respect to different stakeholders, the Impact on Clinical Research of European Legislation (ICREL) project involved a longitudinal, retrospective, observational and comparative survey conducted with different stakeholders from each European country – competent authorities, ethics committees, and sponsors (public and private) - in order to assess how the Clinical Trials Directive has impacted the number, size, nature, costs, resources, workload and performance relating to clinical trials. The results of this project have been compiled into a report¹⁶⁷ that was published online in mid-June 2009. The ICREL data suggests that large pharmaceutical companies seem less affected by the new legislation than small- and medium-sized enterprises (SME) and non-commercial sponsors. An increase in workload was identified amongst all the stakeholders. There was also an increase in fees to competent authorities and to ethics committees. The cost of insurance dramatically increased for commercial sponsors, though not for non-commercial sponsors. Furthermore, an increase in clinical trial costs as a result of the Clinical Trials Directive was of particular concern to SMEs, non-commercial sponsors and the sponsors of orphan medicinal product trials. The survey detected a significant increase from 2003 to 2007 in the number of biotechnology product and orphan medicinal product trials, considered to reflect more the new orphan medicinal product regulation as well as scientific and technological progress rather than the implementation of the Clinical Trials Directive. The report concludes with a discussion of the findings and a series of conclusions and recommendations.

¹⁶² <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

¹⁶³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>

¹⁶⁴ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0067:EN:PDF>

¹⁶⁵ http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm

¹⁶⁶ <http://www.orpha.net/actor/EuropaNews/2006/060409.html#EUPol>

¹⁶⁷ http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

A European Commission public consultation was held in from 9 October 2009 to 8 January 2010¹⁶⁸ to assess the impact of the Directive and the replies were published soon after¹⁶⁹. In February 2011, a concept paper was submitted by the Directorate General for Health and Consumers for public consultation: this consultation did not repeat that of 2009/2010, but aimed to investigate the more technical aspects. This concept paper presented: a 'preliminary appraisal' of which option appears to be the most suitable one to address some of the key concerns of the Clinical Trials Directive, on the basis of the current state of the impact assessment; and the main figures that are being used to evaluate the impacts of the different policy options. The summary of responses to the Public consultation on the concept paper on the Revision of the 'Clinical Trials Directive' 2001/20/EC were published online in July 2011¹⁷⁰.

On 17 July 2012, the Commission adopted a "Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC"¹⁷¹. The adoption was announced in a press release supported 'questions and answers' document¹⁷² and was accompanied by an impact assessment report¹⁷³. The proposal has been submitted to the European Parliament and the Council.

3.3. European legislation and activities in the field of advanced therapies

Regulation on Advanced Therapy Medicinal Products (13 October 2007)¹⁷⁴

Amongst emerging new technologies, therapies and medicines are regenerative medicine, more personalised treatments, as well as the development of nanomedicines. The Commission monitors scientific progress and new technological developments with a view to reviewing the regulatory framework so as to make safe, novel treatments available to patients as early as possible.

Advanced therapy medicinal products are new medical products based on genes (gene therapy), cells (cell therapy) and tissues (tissue engineering). These advanced therapies herald revolutionary treatments of a number of diseases or injuries, such as skin in burn victims, Alzheimer, cancer or muscular dystrophy. They have a huge potential for patients and industry.

The lack of an EU-wide regulatory framework in the past led to divergent national approaches which hindered patients' access to products, hampered the growth of this emerging industry, and ultimately affected the EU competitiveness in a key biotechnology area.

On 13 October 2007, the European Parliament and Council adopted the Regulation on Advanced Therapy Medicinal Products (Regulation (EC) 1394/2007¹⁷⁵) designed to ensure the free movement of advanced therapy products within Europe, to facilitate access to the EU market and to foster the competitiveness of European companies in the field, while guaranteeing the highest level of health protection for patients.

The main elements of the Regulation are:

- A centralised marketing authorisation procedure, to benefit from the pooling of expertise at European level and direct access to the EU market.
- A new and multidisciplinary expert Committee (Committee for Advanced Therapies), within the European Medicines Agency (EMA), to assess advanced therapy products and follow scientific developments in the field.
- Technical requirements adapted to the particular characteristics of these products.
- Special incentives for small and medium-sized enterprises.

¹⁶⁸ http://ec.europa.eu/health/files/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf

¹⁶⁹ http://ec.europa.eu/health/files/clinicaltrials/2010_03_30_summary_responses.pdf

¹⁷⁰ http://ec.europa.eu/health/files/clinicaltrials/ctresp_2011-06/ct_summary.pdf

¹⁷¹ http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

¹⁷² http://ec.europa.eu/health/files/clinicaltrials/2012_07/press-releases/memo-12-566_en.pdf

¹⁷³ http://ec.europa.eu/health/files/clinicaltrials/2012_07/impact_assessment_part1_en.pdf (Volume I) and

http://ec.europa.eu/health/files/clinicaltrials/2012_07/impact_assessment_part2_en.pdf (Volume II)

¹⁷⁴ This section reproduces information from <http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/advanced-therapies/>

¹⁷⁵ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>

The regulation also marks the recognition that a number of advanced therapy products actually combine biological materials, such as tissues or cells, and chemical structures such as metal implants or polymer scaffolds. These combination products lie at the border of the traditional pharmaceutical area and other fields (e.g. medical devices). They therefore cannot be regulated as ‘conventional’ drugs and need adapted requirements. In addition, it should be borne in mind that a significant share of economic operators involved in this field are not large pharmaceutical companies, but rather small and medium-sized enterprises or hospitals.

First regulatory approval for a gene therapy drug in the European Union

On 2nd November, 2012, the European Commission announced the authorisation of Glybera (alipogene tiparvovec) for marketing in the European Union. The product is designed to treat patients with lipoprotein lipase deficiency (LPLD), a rare inherited disorder which disrupts fat production in the body. Due to a defective gene, patients with this disorder cannot produce enough lipoprotein lipase (LPL), an enzyme responsible for breaking down fats. Glybera uses an adeno-associated virus to infect muscle cells with working copies of the LPL gene to enable production of the enzyme in the cells. Backed by the recommendation of the European Medicines Agency, this is the first regulatory approval of a gene therapy drug in the European Union.

3.4. European legislation and activities in the field of medicinal products for paediatric use

Regulation on Medicinal Products for Paediatric Use (26 January 2007)¹⁷⁶

New legislation governing the development and authorisation of medicines for paediatric use (Regulation (EC) N° 1901/2006)¹⁷⁷ entered into force in the European Union on 26 January 2007. This regulation sets up a system of requirements, rewards and incentives together with horizontal measures to ensure that medicines are researched, developed and authorised to meet the therapeutic needs of children. The key objectives of the Regulation are: to ensure high-quality research into the development of medicines for children; to ensure, over time, that the majority of medicines used by children are specifically authorised for such use; and to ensure the availability of high-quality information about medicines used by children.

The key measures included in the EU Regulation are:

- the establishment of an expert paediatric committee within the EMA¹⁷⁸;
- a requirement at the time of marketing authorisation applications for new medicines and line-extensions for existing patent-protected medicines for data on the use of the medicine in children resulting from an agreed paediatric investigation plan;
- a system of waivers from the requirement for medicines unlikely to benefit children and a system of deferrals of the timing of the requirement to ensure medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;
- a reward for compliance with the requirement in the form of a six-month extension to the supplementary protection certificate - SPC (in effect, a six-month patent extension on the active moiety);
- for orphan medicines, a reward for compliance with the requirement in the form of an additional two-years of market exclusivity added to the existing ten-years awarded under the EU's Orphan Regulation;
- a new type of marketing authorisation, the PUMA, which allows ten years of data protection for innovation (new studies) on off-patent products;
- measures to increase the robustness of pharmacovigilance and to maximise the impact of existing studies on medicines for children;

¹⁷⁶ This section reproduces information from http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/paediatric-medicines/index_en.htm and <http://www.ema.europa.eu/htms/general/contacts/PDCO/PDCO.html>

¹⁷⁷ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

¹⁷⁸ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

- an EU inventory of the therapeutic needs of children to focus the research, development and authorisation of medicines;
- an EU network of investigators and trial centres to conduct the research and development required;
- a system of free scientific advice for the industry, provided by the EMA;
- a public database of paediatric studies;
- a provision on EU funding into research leading to the development and authorisation of off-patent medicines for children.

The main responsibility of the Paediatric Committee (PDCO) at the EMA is to assess the content of proposed paediatric investigation plans and adopt opinions on them in accordance with Regulation (EC) 1901/2006 as amended. This includes the assessment of applications for paediatric investigation plans with a full or partial waiver and assessment of applications for paediatric investigation plans with deferrals. The PDCO is not responsible for the evaluation of marketing-authorisation applications for medicinal products for paediatric use. This remains fully within the remit of the Committee for Medicinal Products for Human Use (CHMP). However, the CHMP or any other competent authority may request the PDCO to prepare an opinion on the quality, safety and efficacy of a medicinal product for use in the paediatric population if these data have been generated in accordance with an agreed paediatric investigation plan.

New measures were moved forward in February 2009 to expand the transparency of information on clinical trials for medicinal products involving paediatric populations. The *Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMA), in accordance with Article 41 of Regulation (EC) No 1901/2006*¹⁷⁹, published in the 4 February 2009 *Official Journal of the European Union*, is designed to “increase the availability of information on the use of medicinal products in the paediatric population and to avoid unnecessary repetition of studies”. The guidance delineates the information to be registered with EudraCT¹⁸⁰, the clinical trials database of the European Union and concerns both trial protocol and trial results. The data to be furnished are destined for both the general public and for professionals in the fields of medicine, research, and the pharmaceutical industry. The guidelines also set out the timeframe for providing information and the means through which information is to be made available. The European Medicines Agency has the task of revising EudraCT to render the specified information public. A draft of the guidance underwent a period of public consultation in 2008. With an estimated 80% of all rare disorders affecting children, this measure to increase transparency is expected to augment the safety and efficacy of treatment development for this population. From March 2011, the European Union Clinical Trials Registry became accessible to the general public¹⁸¹. The Register shows data entered in EudraCT by the national competent authorities, or, for paediatric trials wholly conducted outside the EU, by the applicants themselves¹⁸².

The Paediatric Committee (PDCO) is developing an inventory process aiming to identify areas in which further research and development specific to paediatric medicinal products are needed. Such an inventory could assist industry in identifying opportunities, provide a source of information for healthcare professionals and patients, and aid various PDCO assessment processes. The first inventory, in the area of cardiovascular medicines for use in children, was released for public consultation¹⁸³ in 2012.

Public consultation on the experience gained from five years of the Paediatric Regulation

Five years after the Paediatric Regulation came into being, the European Commission is preparing a general report presenting the experience acquired as a result of the application of the Paediatric Regulation and including an inventory of the medicinal products authorised for paediatric use since the regulation took effect. The Commission has released for public consultation¹⁸⁴ the *General Report on Experience Acquired as a Result*

¹⁷⁹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

¹⁸⁰ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf
http://ec.europa.eu/health/files/clinicaltrials/technical_guidance_en.pdf

¹⁸¹ <https://www.clinicaltrialsregister.eu/>

¹⁸² On 15 July 2011, the Register contained detailed information on 14944 clinical trials, of which 1894 include children and adolescents of under 18 years of age; historical data (information entered into the EudraCT database between 1 May 2004 and the release of version 8.0 of the EudraCT database on 10 March 2011) is being gradually published online, along with new trials.

¹⁸³

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/08/news_detail_001591.jsp&mid=WC0b01ac058004d5c1

¹⁸⁴ http://ec.europa.eu/health/human-use/paediatric-medicines/developments/index_en.htm

of the Application of the Paediatric Regulation: Experience Acquired and Lessons Learnt. The responses¹⁸⁵ to the public consultation were published in January 2013.

ERA-NET PrioMedChild projects related to orphan medicinal products and paediatric populations

Many of the medicines currently prescribed to children may never have been studied in paediatric populations, meaning that medicinal products are administered without precise information on dosage, potential toxicity and evidence of clinical safety and efficacy at the recommended dosages. The ERA-NET PrioMedChild¹⁸⁶ (Priority Medicines for Children) is a network of eleven research funding organisations from different EU Member States working on the development of research around medicines for children. Under the umbrella of ERA-NET PrioMedChild, the national funding organisations of the Netherlands, Estonia, Finland, France, Great Britain, Italy, Latvia and Poland jointly provided funds in the order of €8 million to support the European call. The research projects were funded for three years in consortia with a minimum of three participants from at least three countries and a maximum number of 8 research groups. Regardless of its size, each collaborative consortium should have the optimal critical mass to achieve ambitious scientific goals and should clearly show the added value from working together. The ERA-NET PrioMedChild received €1.7 million from the European Commission's DG Research to set up the network and collaboration, but no funds for research. The Joint Call was funded out of national research budgets. Partnerships between research funding organisations seek to bring coherence and cooperation to national research programmes and policies on research for Priority Medicines for Children. PrioMedChild aims to contribute to ensuring more effective and safer medicines for children. At the end of 2010 seven projects were granted, the majority of which are directly related to the field of rare diseases and orphan medicinal products: New drugs for rare diseases: cost-effectiveness modelling in cryopyrin associated periodic syndromes; Rare diseases: use of clinical trial simulation for the choice and optimisation of study design; A faster and better tool for clinical decisions in children with leukaemia ; and Developing an effective treatment for childhood cancer with fewer side effects. The other projects of the PrioMedChild network will look at Validating non invasive imaging of the serotonergic- and dopaminergic system and adult neurogenesis with MRI; towards a better insight in the neurobiological mechanisms underlying psychiatric disorders in the paediatric population; Paediatric Accelerator Mass Spectrometry Evaluation Research Study; and Neonatal Exposure to Excipients. These seven projects contribute to making medication use safer for paediatric populations, including children with rare conditions.

3.5. Other EC activities and initiatives relative to the field of orphan medicinal products

Launch of a process on corporate responsibility in the field of pharmaceuticals (2010)

The Directorate General for Enterprise and Industry announced¹⁸⁷ in 2010 the launch of a process on corporate responsibility¹⁸⁸ in the field of pharmaceuticals. In a press release¹⁸⁹, Commission Vice President Antonio Tajani stated that it is time *“to launch a specific consultation at European level in [the pharmaceutical sector] so that commercial imperatives can be combined with the needs of society”*. Three separate platforms: ethics and transparency; access to medicines in Africa; and access to medicines in Europe will *“examine the major challenges of access to medicines in Europe and Africa in the light of the issues of price and reimbursement.”* A number of projects have been launched: one of these projects will look into the possibility to establish a mechanism of coordinated access to orphan medicinal products. For this project, *“Members are invited to develop the concept of a coordinated access to orphan medicinal products based on the set up of programmes between companies and groups of competent authorities and results of the ongoing project on a mechanism for clinical added value on orphan medicinal products. A pilot project could be set up in a second stage”*. Other projects that could be relevant to the field of rare diseases include one on capacity building on managed entry agreements for innovative medicines and another on facilitating the supply in small markets. Together with Member States, a number of stakeholder organisations take part in the platform, including the European Patients Forum, the European Hospital and Healthcare Federation, the European Federation of Pharmaceutical

¹⁸⁵ http://ec.europa.eu/health/files/paediatrics/2012-09_publicconsultation_en.pdf

¹⁸⁶ <http://www.priomedchild.eu/home/>

¹⁸⁷ <http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/10/442&format=HTML&aged=0&language=EN&guiLanguage=en>

¹⁸⁸ http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/index_en.htm

¹⁸⁹ <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/10/1170&format=HTML&aged=0&language=EN&guiLanguage=en>

Industries and Associations, and the European Association for Bioindustries. Results of most working groups under the platform “Access to medicines in Europe” will be submitted to the Steering Group members for endorsement at their meeting in April 2013.

EMINET Report (2011)

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*¹⁹⁰. This new report, commissioned by the European Commission DG Enterprise and Industry, presents a country-by-country survey of accessibility to orphan medicines, with an emphasis on product distribution through Centres of Expertise and derogatory procedures for accessing products in situations of restricted availability (typically Compassionate Use-type programmes). Taking Pompe disease and pulmonary arterial hypertension as examples, the EMINet report surveys both the availability of treatments across Europe and the distribution of centres of expertise for the diseases. The EMINet findings, combined with the results of the Ernst & Young CAVOD report, which focuses on developing a coordinated approach to providing orphan medicinal product information to all Member States prior to price negotiation in order to streamline health technology assessment and facilitate pricing decisions, contribute to the debate on efficient and equitable distribution of orphan medicinal products. Both reports seek to further the understanding of product access and availability for rare disease treatments across Europe. This feeds in to the reflection on a coordinated system for accessing orphan medicinal products.

¹⁹⁰ http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access_orphans_initialinvest_052011_en.pdf

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¹⁹¹ 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.

¹⁹² Disclaimer: the European Commission is not responsible for the completeness and correctness of the information included in this report.

SELECTED BIBLIOGRAPHY AND SOURCES¹⁹³

WEBSITES

European Commission & EMA websites

- Rare Diseases information on the EC Public Health portal
http://ec.europa.eu/health/rare_diseases/policy/index_en.htm
- Public health initiatives and other institutions responsible for rare diseases on the DG Sanco
http://ec.europa.eu/health/ph_threats/non_com/rare_9_en.htm
- Europe for patients: rare diseases
http://ec.europa.eu/health-eu/europe_for_patients/rare_diseases/index_en.htm
- Eudra-CT (European Clinical Trials Database)
<https://eudract.ema.europa.eu/>
- CORDIS: the gateway to European Research and development
http://cordis.europa.eu/home_fr.html
- European Commission research and innovation
<http://ec.europa.eu/research/index.cfm?lg=en>
- European Medicines Agency Committee for Orphan Medicinal Products
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000123.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e32

Other European websites

- Orphanet
<http://www.orpha.net>
- OrphaNews Europe [archives](#)
<http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>
- EURORDIS
<http://www.EURORDIS.org>
- Eurocat
<http://www.eurocat-network.eu/>
- EUROPLAN: Final National Conference Reports
http://www.europlanproject.eu/_newsite_986987/events22.html

KEY TEXTS

Directives, Regulations, Communications, Council Decisions, Council Recommendations and other related documents

- Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf

¹⁹³ All websites and documents were last accessed in May 2013.

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Clinical Trials Directive)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Good Clinical Practice Directive)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:EN:PDF>
- Regulation on advanced therapies (Regulation (EC) 1394/2007)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>
- Regulation on medicinal products for paediatric use (Regulation (EC) N° 1901/2006)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>
- EMA Public Statement on Fee Reductions for Designated Orphan Medicinal Products
http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/09/WC500003876.pdf
- Council Decision No 1982/2006/EC of 18 December 2006 concerning the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007-2013)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:412:0001:0041:EN:PDF>
- Communication from the Commission on Rare Diseases: Europe's Challenge
http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
- Summary of the Impact Assessment Accompanying the Communication on Rare Diseases: Europe's challenges
http://ec.europa.eu/health/ph_threats/non_com/docs/impact_assessment_exs_en.pdf
- Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>
- Commission Decision of 30 November 2009 establishing a European Union Committee of Experts on Rare Diseases (2009/872/EC)
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:315:0018:0021:EN:PDF>
- European Commission Communication on Action Against Cancer: European Partnership
http://ec.europa.eu/health/ph_information/dissemination/diseases/docs/com_2009_291.en.pdf
- European Commission Communication on a European initiative on Alzheimer's disease and other dementias
http://ec.europa.eu/health/ph_information/dissemination/documents/com2009_380_en.pdf
- Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare
http://ec.europa.eu/health/ph_information/dissemination/documents/com2009_380_en.pdf

Programmes of Community Action, Work Programmes and Calls

- EU Programme of Community Action in the Field of Health 2003-2008
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>
- EU Second Programme of Community Action in the Field of Health 2008-2013
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:301:0003:0013:EN:PDF>
- DG Sanco Work Plan 2011
http://ec.europa.eu/health/programme/docs/wp2011_en

- DG Sanco Work Plan 2012
http://ec.europa.eu/health/programme/docs/wp2012_en.pdf
- DG Research and Innovation FP7 Calls
http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.FP7ActivityCallsPage&id_activity=1
- EMA Work Programme 2011
http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2011/02/WC500102044.pdf
- EMA Work Programme 2012
http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2012/02/WC500122955.pdf

KEY DOCUMENTS

DG Enterprise and Industry

- Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)
http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf
- Final Conclusions and Recommendations of the High Level Pharmaceutical Forum (2nd October 2008)
http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf
- Initial investigation to assess the feasibility of coordinated system to access orphan medicines (Gesundheit Österreich GmbH, May 2011)
http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access_orphans_initialinvest_052011_en.pdf

DG Health and Consumers

RDTF Publications

- RDTF Report – Overview of Current Centres of Reference on rare diseases in the EU - 12 September 2005
<http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>
- RDTF Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – 1 September 2006
<http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>
- RDTF Report – State of the Art and Future Directions – 11 March 2008
<http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>
- RDTF Report: Health Indicators for Rare Diseases: State of the art and future directions – June 2008
<http://www.eucerd.eu/upload/file/Publication/RDTFHI2008.pdf>
- RDTF Report: How many drugs for how many patients – July 2007
<http://www.eucerd.eu/upload/file/Publication/RDTFOD2007.pdf>
- RDTF Report: Health Indicators For Rare Diseases I - Conceptual Framework And Development Of Indicators From Existing Sources – April 2010
<http://www.eucerd.eu/upload/file/RDTFIndicators2010.pdf>

EUCERD Publications

- EUCERD Report: Initiatives and Incentives in the field of rare diseases – July 2010
<http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>
- EUCERD Report: Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for rare diseases - May 2011
<http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

- EUCERD Report: 2012 Report the State of the Art of Rare Disease Activities in Europe of the EUCERD - Part I: Overview of Rare Disease Activities in Europe and Key Developments in 2010 – July 2012
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf>
- EUCERD Report: 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD - Part II: Key developments in 2011 – July 2012
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesII.pdf>
- EUCERD Report: 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD - Part III: European Commission activities in the field of rare diseases – July 2012
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf>
- EUCERD Report: 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD - Part IV: European Medicines Agency activities and other European Activities in the field of rare diseases – July 2012
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIV.pdf>
- EUCERD Report: 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD – Part V: Activities of European Member States and other European Countries in the field of rare diseases
<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesV.pdf>
- [EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States – October 2011](#)
<http://www.eucerd.eu/upload/file/EUCERDRecommendationCE.pdf>
- Recommendations of the EUCERD to the European Commission and Member States on Improving Informed Decisions Based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow - September 2012
http://www.eucerd.eu/?post_type=document&p=1446
- [EUCERD Recommendations on European Reference Networks for Rare Diseases - 31 January 2013](#)
http://www.eucerd.eu/?post_type=document&p=2207

DG Research and Innovation

- International Rare Disease Research Consortium (IRDiRC) First Workshop Summary Report
http://ec.europa.eu/research/health/medical-research/pdf/reykjavik-workshop-report_en.pdf
- International Rare Disease Research Consortium (IRDiRC) Second Workshop Summary Report
http://ec.europa.eu/research/health/medical-research/pdf/rare-diseases/executive-summary_en.pdf

European Medicines Agency

- European Medicines Agency Annual Report for 2010
http://www.ema.gov.sg/media/files/annual_reports/EMA_Annual_Report_2010.pdf
- COMP Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009)
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf

Joint Research Centre

- European Workshop on Genetic Testing Offer in Europe (November 2012)
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

OTHER DOCUMENTS

- Orphanet Report Series: Prevalence of reported number of published cases listed by alphabetical order by disease
http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

- Orphanet Report Series: Prevalence by decreasing prevalence or number of published cases
http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf
- Orphanet Report Series: Patient registries in Europe
<http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>
- Orphanet Report Series: List of orphan drugs in Europe
http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf
- Orphanet Report Series: European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases and European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases
<http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>
- RDPlatform Report: Rare Disease research, its determinants and the way forward (May 2011)
http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf
- EURORDIS report: The Voice of 12,000 Patients: Experiences & Expectations of Rare Disease Patients on Diagnosis & Care in Europe
http://www.EURORDIS.org/article.php3?id_article=1960
- EURORDIS report: Rare Diseases: Understanding this Public Health Priority” (November 2005)
http://www.EURORDIS.org/IMG/pdf/princeps_document-EN.pdf
- EURORDIS report: Results of the 4th EURORDIS Survey on Orphan Drug Availability in Europe (2007)
<http://www.EURORDIS.org/IMG/pdf/2007ODsurvey-EURORDIS.pdf>

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