

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



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

This work was financed by the EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01

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

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

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**To quote this document:**

Aymé S., Rodwell C., eds., “2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases”, July 2012.

ISBN : 978-92-79-25358-4

DOI : 10.2772/52980

<http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesIII.pdf>

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## ACRONYMS

### General

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

### Pilot European Reference Networks

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

## GENERAL INTRODUCTION

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

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2011. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of either the European Commission, its Agencies or national health authorities.

The report is split into five parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2011

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

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

### 1. METHODOLOGY AND SOURCES

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

- **European Commission websites and documents**

Information and documentation from the European Commission was used in order to establish this report, principally accessed through the rare disease information web pages of the Directorate General Public Health<sup>1</sup> and Directorate General Research CORDIS website<sup>2</sup> as well as the site of the European Medicines Agency<sup>3</sup>, in particular the pages of the COMP<sup>4</sup> (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**

Data from the OrphaNews Europe<sup>5</sup> newsletter for the period 2007-2011 was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission

<sup>1</sup> [http://ec.europa.eu/health/rare\\_diseases/policy/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/policy/index_en.htm)

<sup>2</sup> [http://cordis.europa.eu/home\\_fr.html](http://cordis.europa.eu/home_fr.html)

<sup>3</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

<sup>4</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000263.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac0580028e30](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30)

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

and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France<sup>6</sup> (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

- **EUCERD Publications**

Parts III, IV and V of this report present an update of the information previously published in the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*<sup>7</sup> (July 2010) and the *2011 EUCERD Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases*<sup>8</sup>. The methodology for the production of these previous reports is outlined in their respective introductions.

- **Reports of the EUCERD meetings**

The reports of 2011 meetings of the EUCERD (22-23 March 2011 and 24-25 October 2011) were used in order to identify upcoming initiatives and incentives in the field of rare diseases, and to report on the events held to mark Rare Disease Day 2011.

- **Rare Diseases Task Force publications**

Various reports of the RDTF have been used as sources of data to collect information on the state of affairs at both EU and Member State levels pre-2010, notably the reports of the RDTF WG on Standards of Care (concerning European Centres of Reference) produced between 2005-2008, including the *RDTF Final Report – Overview of Current Centres of Reference on rare diseases in the EU – September 2005*<sup>9</sup> and the *RDTF Meeting Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – September 2006*<sup>10</sup>, as well as the *RDTF Final Report – State of the Art and Future Directions – March 2008*<sup>11</sup>.

- **Reports on orphan medicinal products**

The information provided for each Member State concerning the state of affairs in the field of orphan medicinal products has been elaborated, when referenced, from the basis of the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*<sup>12</sup> published in 2006 by the European Commission and produced using data collected by the EMA and Orphanet. This information has been updated when information is available and quoted when still applicable. Another valuable source of information on Orphan Drug policy, at EU and Member State levels was the 2009 KCE 112B report published by the KCE-Belgian Federal Centre of Healthcare Expertise (*Federaal Kenniscentrum voor de Gezondheidszorg/Centre federal d'expertise des soins de santé*) entitled "*Orphan Disease and Orphan Drug Policies*" (*Politiques relatives aux maladies orphelines et aux médicaments orphelins*)<sup>13</sup>. This report notably provided information for the Member State sections on Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The Office of Health Economics Briefing Document "*Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries (No. 52 October 2009)*" also provided information on orphan medicinal product availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V has been provided for this year's edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding &*

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

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

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

<sup>9</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>

<sup>10</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

<sup>11</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

<sup>12</sup> [http://ec.europa.eu/health/files/orphanmp/doc/inventory\\_2006\\_08\\_en.pdf](http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf)

<sup>13</sup> *Politiques relatives aux maladies orphelines et aux médicaments orphelins*  
[http://www.kce.fgov.be/index\\_fr.aspx?SGREF=3460&CREF=13646](http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646)

*Market Access Issues, 2011 Edition*<sup>14</sup> by Donald Macarthur: this report is referenced in footnotes when used. Information for the overview was also taken from the *Nature Reviews: Drug Discovery* article produced by the COMP/EMA Scientific Secretariat, *European regulation on orphan medicinal products: 10 years of experience and future perspectives*<sup>15</sup>.

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

The site of EURORDIS the European Organisation for Rare Diseases<sup>16</sup>, and the book *The Voice of 12,000 Patients: Experiences & Expectations of Rare Disease Patients on Diagnosis & Care in Europe* (produced using the results of the EURORDISCare<sup>17</sup> surveys), were used to provide information on EURORDIS activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national patient alliances were also consulted for information. In addition to this the Rare Disease Day 2011 site<sup>18</sup>, maintained by EURORDIS, also provided information on events at Member State level<sup>19</sup> concerning Rare Disease Day.

- **EUROPLAN national conferences final reports**

In the context of the EUROPLAN project (2008-2011), 15 national conferences were organised in collaboration with EURORDIS and national rare disease patient alliances in 2010-2011 in order to present the Council Recommendation on an action in the field of rare diseases, as well as discuss the Europlan recommendations/guidance document for the development of national plans and strategies in the field of rare diseases<sup>20</sup> and its application at national level. These conferences were attended by a range of stakeholder groups at national level and the final reports<sup>21</sup> of these conferences were presented in a common format for ease of comparison. Information provided in these reports has helped update the information provided in this document. Readers of this report are encouraged to refer to these reports in addition to the present report as they provide further detail of the discussions of national approaches to rare disease policy.

- **Orphanet**

The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links<sup>22</sup> to other web-based information services and help-lines which were used to collect information at country-level. The Orphanet Country Coordinators also provided valuable input into the elaboration of information at country level, notably via contributions to OrphaNetWork News. The report produced by the RDPlatform project<sup>23</sup>, in particular the report *Rare diseases research, its determinants in Europe and the way forward*<sup>24</sup> was also used as a source for Part I.

- **OrphaNetWork News**

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

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<sup>14</sup> <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf>

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

<sup>16</sup> <http://www.EURORDIS.org/secteur.php3>

<sup>17</sup> [http://www.EURORDIS.org/article.php3?id\\_article=1960](http://www.EURORDIS.org/article.php3?id_article=1960)

<sup>18</sup> <http://www.rarediseaseday.org/>

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

<sup>20</sup> [http://www.europlanproject.eu/public/contenuti/files/Guidance\\_Doc\\_EUROPLAN\\_20100601\\_final.pdf](http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf)

<sup>21</sup> <http://www.EURORDIS.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN%20%20National%20Conference%20Final%20Reports>

<sup>22</sup> [http://www.orpha.net/consor/cgi-bin/Directory\\_Contact.php?lng=EN](http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN)

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

<sup>24</sup> [http://asso.orpha.net/RDPlatform/upload/file/RDPlatform\\_final\\_report.pdf](http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf)

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

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

## 2. REPORT PREPARATION, REVISION AND VALIDATION

The present report provides an updated compilation of information from the previous reports of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD* and *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*) which have covered activities up to the end of 2010. The present edition takes into account advances and activities in the field of rare diseases and orphan medicinal products at EU and MS level in 2011.

Once this information from the previous report was updated using the sources cited above, a draft of each country section (Part V) was sent in February 2012 to EUCERD Member States representatives with a guidance document providing an explanation of the type of information to include if available for each category. The Member State representatives were asked to contact a range of identified key stakeholders in their country for input. The stakeholders identified for each country included: representatives at the EUCERD in the respective countries, and their alternates, the Orphanet Country Coordinators, National Alliances of rare disease patient alliances, partners of the E-Rare consortium, Member State representatives on the COMP, representatives of national competent authorities, coordinators of national plans for rare diseases and other rare diseases experts identified at national level. The Member State representatives integrated the stakeholder feedback into their report before returning it to the Scientific Secretariat for homogenisation and extraction of developments in 2011 to be included in Part II. Final validation of Parts II and V were sent to the EUCERD Member State representatives for final validation, to the best of their knowledge, in May 2012.

Part III and IV of the report on activities at European Union level was sent for validation, to the best of their ability, by the representatives at the EUCERD of the European Commission Directorate Generals for Health, Research and Innovation, Enterprise and Industry, and the EMA respectively: this process was carried out in March/April 2012 by the Scientific Secretariat of the EUCERD. The European Commission and its agencies are not responsible, however, for the completeness and the accuracy of the information presented in this report. The new activities in 2011 were extracted and added to Part II.

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

## 3. REPORT STRUCTURE

The report is structured into three main parts: Part I consists of an overview of the activities in the field of rare diseases in Europe at EU and MS level; Part II is an extraction of the developments at EU and MS level in 2011 based on Parts III, IV and V; Part III concerns activities of the European Commission; Part IV concerns European Medicines Agency activities and other European activities/events at European level apart from the activities of the European Commission; Part V concerns activities at EU MS level, as well as five other non-EU European countries where information was available.

Each part is followed by a selected bibliography outlining the sources used to produce that part of the report, which includes a list of the European Commission documents referred to in the report and a list of web addresses by country listing national sources of information on rare diseases and links to documents



concerning national plans or strategies for rare diseases when in place. Each part is also followed by a list of contributors to the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous report. A list of frequently used acronyms has also been included in each part to ease reading.

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

**Part II** is a new section of the report, providing information extracted from Parts III, IV and V, relative only to the new activities and initiatives reported for the year 2011.

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

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

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

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

- European Medicine Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases, EMA Committee for Orphan Medicinal Products' activities, EMA Committee on Human Medicinal Products' activities, European legislation and activities in the field of clinical trials, European legislation and activities in the field of advanced therapies, European legislation and activities in the field of medicinal products for paediatric use, other EMA activities and initiatives relevant to rare diseases and orphan medicinal products, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan medicinal products.
- The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2011.

**Part V** concerns the rare disease activities in the field of rare diseases in each of the 27 Member States plus Norway and Switzerland as EFTA countries, Croatia and Turkey as candidates for EU membership, and Israel: Iceland has chosen to not contribute a country report this year. These sections are organised in alphabetical order by country.

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

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise<sup>25</sup>

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<sup>25</sup> The term "official centre of expertise" used in this report means officially designated via a (ministerial) procedure.

- Pilot European Reference Networks
- Registries
- Neonatal screening policy
- Genetic testing<sup>26</sup>
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Good practice guidelines
- Training and education initiatives
- National rare disease events in 2011<sup>27</sup>
- Hosted rare disease events in 2011<sup>28</sup>
- Research activities (National research activities, Participation in European research projects<sup>29</sup>, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability<sup>30</sup>, Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products)
- Orphan devices
- Specialised social services

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

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<sup>26</sup> This section contains data extracted in September 2011 from the Orphanet database of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term ‘estimated’ is used as the concept of a single disease is a variable one).

<sup>27</sup> As announced in OrphaNews Europe.

<sup>28</sup> As announced in OrphaNews Europe.

<sup>29</sup> Past and ongoing participation in DG Research and Innovation financed projects. Some countries have added information on additional European projects.

<sup>30</sup> Contacts were asked to provide information on availability of orphan medicinal products (i.e. which drugs are launched on the market/sold at national level). As this information is often hard to identify, some countries instead provided information on which drugs are accessible (i.e. reimbursed, on a positive drug list etc.). It is explicitly explained in each case which of these concepts is being referred to.

## INTRODUCTION<sup>31,32</sup>

Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 people affected per 10'000 people in the European Union, as defined by the European Orphan Medicinal product regulation) 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. It is estimated that between 5'000 and 8'000 distinct rare diseases exist today, affecting between 6% and 8% of the population in total thus affecting between 27 and 36 million people in the European Union. Most of the people represented by these statistics suffer from less frequently-occurring diseases affecting one in 100 000 people or less. The definition of a rare disease as having a prevalence of not more than 5 in 10000 first appeared in EU legislation in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products<sup>33</sup>. The Community action programme on rare diseases including genetic diseases for the period 1 January 1999 to 31 December 2003 then applied this definition to the field of public health.

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 additional 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 2011 is provided below by theme: public health, research and orphan medicinal products and therapies for rare diseases.

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<sup>31</sup> [http://ec.europa.eu/health/rare\\_diseases/policy/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/policy/index_en.htm)

<sup>32</sup> Disclaimer: the European Commission is not responsible for the completeness and correctness of the information included in this report.

<sup>33</sup> [http://ec.europa.eu/health/files/eudralex/vol-1/reg\\_2000\\_141/reg\\_2000\\_141\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf)

# 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)<sup>34</sup>. 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 challenge<sup>35</sup> 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 consultation<sup>36</sup> 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,

<sup>34</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>

<sup>35</sup> [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/rare\\_com\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf)

<sup>36</sup> [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/raredis\\_comm\\_draft.pdf](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.<sup>37</sup>

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 (2005<sup>38</sup>, 2006<sup>39</sup>), Assessing treatable rare diseases and the proportion of patients eligible for treatment (2007)<sup>40</sup>, Assessing the European Added-Value of ERN (2008)<sup>41</sup>.

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 2008<sup>42</sup>. A report was also produced following a 2008 workshop on Patient Registries and Databases<sup>43</sup>.

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) will support the activities of the EUCERD. 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 diseases<sup>44</sup>. 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 Union and is the main decision-making agent. Every Council meeting is attended by one minister from each EU

<sup>37</sup> [http://www.eucerd.eu/PP\\_2.html](http://www.eucerd.eu/PP_2.html) (Subsection "Working groups")

<sup>38</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>

<sup>39</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

<sup>40</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFOD2007.pdf>

<sup>41</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf>

<sup>42</sup> <http://www.eucerd.eu/upload/file/Publication/RDTFHI2008.pdf>

<sup>43</sup> <http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf>

<sup>44</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

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 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 will supported by a dedicated Joint Action<sup>45</sup>.

### **Meetings and workshops**

Two workshops of the EUCERD (financed by the Joint Action for the support of the former RDTF/ EUCERD Scientific Secretariat) were organised in 2010 on Indicators for Rare Diseases (24 November 2010) and on National Centres of Expertise for Rare Diseases and European Reference Networks (8-9 December 2010). In 2011 the EUCERD met twice (22-23 March 2011<sup>46</sup> and 24-25 October 2011<sup>47</sup>) and held a number of workshops: Workshop on National Centres of Expertise for Rare Diseases and Networking Between Centres of Expertise (21-22 March 2011<sup>48</sup>), Workshop on Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States (8 September 2011), EUCERD/EMA Workshop "Towards a Public-Private Partnership for Registries in the Field of Rare Diseases" (4 October 2011<sup>49</sup>) and the EUCERD/EuroBioMed event "Sharing Data to Improve Health Care Management for Rare Diseases" (4 November 2011<sup>50</sup>).

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<sup>45</sup> See section on Joint Actions 1.2.1.

<sup>46</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/Meeting/EUCERD/EUCERDPublicSummaryReport230311.pdf>

<sup>47</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERD3Abstract.pdf>

<sup>48</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDReport220311.pdf>

<sup>49</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDWorkshopRegistries2011.pdf>

<sup>50</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/Rare2011.pdf>

### Reports and Recommendations

In 2011 the EUCERD issued a number of reports including the *Preliminary Analysis of the Outcomes and Experiences of Pilot European Reference Networks for Rare Diseases (May 2011)*<sup>51</sup>, the *EUCERD report on the State of the Art of Rare Disease Activities in Europe (July 2011)*<sup>52</sup> and the *EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States (24 October 2011)*<sup>53</sup>.

The *Preliminary Analysis of the Outcomes and Experiences of Pilot European Reference Networks for Rare Diseases*<sup>54</sup> considers the experience of EC-funded pilot European Reference Networks (ERNs) and other EC-funded networks for rare diseases. The report offers conclusions and recommendations which will help better define the objectives and goals of future ERNs, taking into account the specifics of the Council Recommendation and of the Cross-Border Healthcare Directive. The EUCERD report highlights that for the ERNs, specific concepts need to be defined and stabilised. National-level expertise needs to be identified and designated, and, in terms of organisation, the ERNs need to be genuine infrastructures, ideally “*coordinated by an expert in networking whose position is financed at European level*”. A mechanism for evaluating the ERNs also needs to be developed. How best to support existing ERNs and also identify new ones must be worked out, and the ever-present issues of financing and sustainability need to be addressed.

The 2011 “*Report on the State of the Art of Rare Disease Activities in Europe*” of the European Union Committee of Experts on Rare Diseases, provides a comprehensive overview of rare disease and orphan medicinal product activities at both the European Union (EU) and Member State (MS) levels up to the end of 2010. The lengthy report is a hybrid of updated data from the previous report and brand-new information that was carefully selected to enhance understanding of the rare disease activities across Europe. As such, it presents an informed overview of rare disease and orphan medicinal product activities, elaborated in concertation with a wide range of stakeholders from each of the MS and at the EU level. The information has been divided into three principal sections:

- Part I, available for the first time, presents the Overview of Rare Disease Activities in Europe and Key Developments in 2010<sup>55</sup>
- Part II delineates the European Commission and Other European Activities<sup>56</sup>
- Part III outlines Activities in EU Member States and Other European Countries<sup>57</sup>

The report outlines the political context that has spawned the growth of rare disease activities across Europe and also summarises the political frameworks of other regions across the world. Amongst the topics examined at both the MS and EU levels are the national strategies for rare diseases either implemented or under elaboration; centres of expertise; registries; newborn screening policies; genetic testing resources and activities; patient organisation activities; information resources; guidelines for best practice; educational initiatives; research and funding mechanisms and participation in EU-level projects; rare disease conferences and events; orphan medicinal product and device incentives, availability, reimbursement and pricing policies; and specialised social services. New to this year’s edition are the topics of genetic testing, Europlan national conferences, orphan devices, other initiatives to improve access to orphan medicinal products, and orphan medicinal product pricing policy. Each section of the report finishes with a bibliography of sources used, including a list of any European Commission documents referred to and a list of web addresses organised by country listing national sources of information on rare diseases and links to documents concerning national plans or strategies for rare diseases when appropriate. The report also furnishes a list of contributors, organised by country and with mention of the validating authority for each country. The report has 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 *EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States*<sup>58</sup> were the first set of recommendations to be elaborated and adopted by the EUCERD. Developing Centres of Expertise and European Reference Networks in the field of rare diseases has been proposed in the Council Recommendation on an Action in the Field of Rare Diseases, and more recently in the Cross-Border Healthcare Directive, as a means of organising care for the thousands of heterogeneous rare

<sup>51</sup> <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

<sup>52</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf>

<sup>53</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDRecommendationCE.pdf>

<sup>54</sup> <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

<sup>55</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf>

<sup>56</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf>

<sup>57</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

<sup>58</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDRecommendationCE.pdf>



conditions affecting scattered patient populations across Europe. In order to share knowledge and expertise more efficiently, the EUCERD recommendations seek to introduce harmonious standards of quality practices by elaborating criteria for the Member States to incorporate into their process to designate Centres of Expertise. The 45 recommendations build upon this work already achieved by the EUCERD and RDTF and assist the Member States to develop their healthcare pathways at both the national and EU levels in the field of rare diseases. The recommendations cover the Mission and Scope of the Centres of Expertise; the Criteria for Designating Centres of Expertise; the Process of Designating and Evaluating National Centres of Expertise; and the European Dimension of Centres of Expertise.

A report documenting the outcomes of the EUCERD workshop (4 October 2011) organised with the European Medicines Agency (EMA) on public-private partnership for registries in the field of rare diseases was published in Autumn 2011<sup>59</sup>. Experts from academia, the biopharmaceutical industry, patient organisations, and regulatory agencies, all lent their expertise to the event, which culminated in a consensus towards disease-based registries that could ultimately be shared amongst all relevant public and private partners. This consensus, shifting from the medicinal product- or patient-based designs to a larger-encompassing disease-based model, moves forward the challenge of how to coordinate, manage and share the goldmine of data that the disease registries potentially yield.

### **OrphaNews Europe**

*OrphaNews Europe*<sup>60</sup> 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 13'000 registered readers from all over the world and representing all stakeholder groups. In 2010, a reader satisfaction survey<sup>61</sup> 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 Italian<sup>62</sup> was launched in December 2011.

#### **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 2009<sup>63</sup> 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 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 2010<sup>64</sup> 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

<sup>59</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDWorkshopRegistries2011.pdf>

<sup>60</sup> <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

<sup>61</sup> [http://www.orpha.net/orphacom/cahiers/docs/GB/Orphanews\\_survey2010.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/Orphanews_survey2010.pdf)

<sup>62</sup> <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=ItaliaNews>

<sup>63</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:053:0041:0073:EN:PDF>

<sup>64</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:340:0001:0046:EN:PDF>

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 2011<sup>65</sup> 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 Plan<sup>66</sup>. 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 Plan<sup>67</sup> 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.

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 is 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 2011<sup>68</sup>. 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 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**

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

<sup>65</sup> [http://ec.europa.eu/health/programme/docs/wp2011\\_en](http://ec.europa.eu/health/programme/docs/wp2011_en)

<sup>66</sup> [http://ec.europa.eu/health/programme/how\\_does\\_it\\_work/call\\_for\\_proposals/index\\_en.htm](http://ec.europa.eu/health/programme/how_does_it_work/call_for_proposals/index_en.htm)

<sup>67</sup> [http://ec.europa.eu/health/programme/docs/wp2012\\_en.pdf](http://ec.europa.eu/health/programme/docs/wp2012_en.pdf)

<sup>68</sup> [http://ec.europa.eu/health/strategy/docs/midtermevaluation\\_euhealthstrategy\\_2011\\_report\\_en.pdf](http://ec.europa.eu/health/strategy/docs/midtermevaluation_euhealthstrategy_2011_report_en.pdf)

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 report<sup>69</sup> is available in English, French and German. Fact-sheets for each of the Member States are available in the country's EU language and also in English.

## 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 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 Action<sup>70</sup> 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:

<sup>69</sup> [http://ec.europa.eu/health/rare\\_diseases/eurobarometers/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/eurobarometers/index_en.htm)

<sup>70</sup> More information can be found on [www.eucerd.eu](http://www.eucerd.eu) section "Activities".

- 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 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)
- 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 Report<sup>71</sup>
- EUCERD Report: 2009 Report on Initiatives and Incentives in the Field of Rare Diseases of the EUCERD - July 2010<sup>72</sup>
- RDTF Report: Health indicators for rare diseases I - Conceptual framework and development of indicators from existing sources - April 2010<sup>73</sup>
- EUCERD Workshop Report: Centres of expertise and European Reference Networks for Rare Diseases (8-9/12/10)<sup>74</sup>

<sup>71</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/RDTFSummaryII.pdf>

<sup>72</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

<sup>73</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/RDTFIndicators2010.pdf>

<sup>74</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf>

- EUCERD Workshop Report: National centres of expertise for rare diseases and networking between centres of expertise for rare diseases (21-22/03/2011)<sup>75</sup>
- EUCERD Report: Preliminary analysis of the experiences and outcomes of pilot European Reference Networks for rare diseases - May 2011<sup>76</sup>
- RDTF Report: Patient Registries for Rare Diseases - April 2009, Update June 2011<sup>77</sup>
- 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 2011<sup>78</sup>
- 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 2011<sup>79</sup>
- 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 2011<sup>80</sup>
- EUCERD Report: Health indicators for rare diseases II - Conceptual framework for monitoring quality of care (September 2011)<sup>81</sup>
- EUCERD/EMA Workshop Report: Towards a public-private partnership for registries in the field of rare diseases (4 October 2011)<sup>82</sup>
- EUCERD Recommendations on Centres of Expertise for Rare Diseases in Member States (24 October 2011)<sup>83</sup>

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

EUROCAT<sup>84</sup>, 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 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.

On 17 June 2011 the 11<sup>th</sup> Eurocat International Symposium took place in Antwerp (Belgium) with prenatal and periconceptional care, environmental risks and long term outcomes as main topics.

<sup>75</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDReport220311.pdf>

<sup>76</sup> <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

<sup>77</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/RDTFRegistriesrev2011.pdf>

<sup>78</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivities.pdf>

<sup>79</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesII.pdf>

<sup>80</sup> <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesIII.pdf>

<sup>81</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDIndicators2011.pdf>

<sup>82</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDWorkshopRegistries2011.pdf>

<sup>83</sup> <http://www.orpha.net/nectasso/EUCERD/upload/file/EUCERDRecommendationCE.pdf>

<sup>84</sup> <http://www.eurocat-network.eu/>

As part of the Joint Action outcomes, EUROCAT systematically monitors the rates of birth defects over time. The *EUROCAT Statistical Monitoring Report 2009*<sup>85</sup> described trends in Europe for the ten year period 2000-2009.

Two major surveys are being conducted by EUROCAT: one on the 'Prevention on Congenital Anomalies by Folic Acid and Foliates' 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' will be launched in 2012.

#### **Joint Action to support the Orphanet database (2011-2013<sup>4</sup>)**

Orphanet<sup>86</sup> 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 encyclopaedia and the collection of data 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; OrphaNews France and Europe (newsletters about scientific and political progress in the field of rare diseases); and the thematic studies and reports offered by the *Orphanet Report Series*<sup>87</sup>. Reports in the series include lists of rare diseases with their prevalence<sup>88</sup>, lists of orphan medicinal products in Europe<sup>89</sup>, lists of rare disease registries in Europe<sup>90</sup> and lists of collaborative research projects and clinical networks in the field of rare diseases funded by the European Commission<sup>91</sup>. Orphanet data is collected in each European Member State and is expert validated.

The site gives access to:

- An inventory of diseases including 5,954 diseases and classifications of these diseases developed using existing published expert classifications. Each disease has a unique Orphan number and is indexed with ICD10 and OMIM, and its 'identity card' includes the relevant prevalence class, age of onset class, mode of inheritance and associated genes. At the moment, not every disease has a completed 'identity card'.
- An encyclopaedia covering 3,077 rare diseases, written by world-renowned experts and peer-reviewed. Systematically produced in both English and French, this encyclopaedia is partly translated into German, Italian and Spanish. 1148 new or updated abstracts or definitions were produced in 2011.
- An inventory of orphan medicinal products at all stages of development, from orphan designation to European market authorisation.
- A directory of specialised services in the 36 European partner countries, providing information on:
  - Specialised clinics and centres of expertise
  - Medical laboratories
  - Ongoing research projects
  - Clinical trials
  - Registries
  - Networks
  - Technological platforms
  - Patient organisations
  - Orphan medicinal products
- A range of other services for specific stakeholders:
  - For health care professionals: an assistance-to-diagnosis tool (search by signs and symptoms);

<sup>85</sup> <http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf>

<sup>86</sup> [www.orpha.net](http://www.orpha.net)

<sup>87</sup> [http://www.orpha.net/consor/cgi-bin/Education\\_Home.php?lng=EN](http://www.orpha.net/consor/cgi-bin/Education_Home.php?lng=EN)

<sup>88</sup> [http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence\\_of\\_rare\\_diseases\\_by\\_alphabetical\\_list.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf)

<sup>89</sup> [http://www.orpha.net/orphacom/cahiers/docs/GB/list\\_of\\_orphan\\_medicinal\\_products\\_in\\_europe.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_medicinal_products_in_europe.pdf)

<sup>90</sup> <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

<sup>91</sup> <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

- For professionals in the field of emergency health care: an encyclopaedia of emergency guidelines;
- For researchers and the pharmaceutical industry: availability of data from the database for research purpose;
- For all: newsletters with both scientific and political content;
- For all: regularly published thematic studies and reports on overarching subjects, downloadable from the site: “the Orphanet Report Series”.

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:

- 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 that Orphanet would be funded as a Joint Action between the European Commission and the Member States from April 2011. The expected outcomes of this Joint Action are a comprehensive and complete information will be made available, including: an inventory of rare diseases; an expanded encyclopaedia of rare diseases (translated into French, German, Spanish, Italian and possibly more) a directory of expert clinics, medical laboratories, networks, registries and patient organisations; information on orphan medicinal products. The Orphanet dataset will be available for re-use in different formats to ensure dissemination of the Orphanet nomenclature of rare diseases and maximise the use of collected information on expert services. Customised websites at national level in national language(s) will be available in order to disseminate national data at MS level. Orphanet will have the governance needed to ensure its mission at international level.

The Kick-Off Meeting of the Orphanet Joint Action, gathering all national country coordinators and Member State health representatives took place on 7 and 8 June 2011 in Paris. The 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 an 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. Polish and Flemish are amongst languages that could be added soon to the six official existing European languages of the site (English, French, German, Italian Portuguese, and Spanish). The Orphanet Clinical Guidelines were also amongst the documents considered a priority for translation into national languages. Capitalising on the newly developed Orphadata tools, the Joint Action country partners will be able to customise the popular Orphanet Report Series to feature national data. Orphanet country sites will also be 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. Orphanet will also become a more interactive site via the activities of the Joint Action. Indeed, the “IT side” of Orphanet was presented and discussed, including the new challenges expanded services and languages engender.

Putting in place appropriate governance is one the biggest changes the Joint Action ushers in, one which will encompass all the partner countries in the Steering Committee, in charge of supervising national activities and formulating future strategies. The Orphanet Joint Action now also has an external International Advisory Board which will report to the Steering Committee and review 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.

Other developments in 2011 included the launch of Orphadata<sup>92</sup>. Inspired by the growing number of requests for data from its database, Orphanet decided to create a comprehensive, high-quality and freely-accessible dataset related to rare diseases and orphan medicinal products that would be available in a reusable format. Launched in May 2011, was developed within the context of the RD Portal and the new Orphanet Europe joint action contracts funded by DG Sanco. Additional support is also provided by GSK. The dataset is a partial extraction of the data stored in Orphanet and will be updated monthly. For user convenience, the date of the last data release will be provided. Freely accessible in six languages (English, French, German, Italian, Portuguese and Spanish) the Orphadata dataset encompasses:

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

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

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

Orphadata provides a guide for users that defines and describes the elements of the dataset. Orphanet hopes that this latest offer will contribute to furthering research toward better understanding and treating rare diseases.

Another development Orphanet in 2011 was a partnership developed with Canada, extending Orphanet across the Atlantic for the first time. Negotiations are also ongoing with Japanese and Chinese stakeholders to explore the possibility of launching Orphanet into Asia, as well as with Brazil and Australia.

The 2010 Impact Factor for the *Orphanet Journal of Rare Diseases*<sup>93</sup> (OJRD) was announced in 2011: the Journal continues its steady ascent, increasing to 5.93 from 5.83 in 2009. The OJRD more than doubled its impact factor from 2007 to 2008 (from 1.30 to 3.14) and gained another impressive hike from 2008 to 2009. This year's increase moves the journal into tenth place out of the 106 journals in the 'Medicine, Research and experimental' category of the Journal Citation Reports.

### ***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 will start in March 2012. The Joint Action will kick-off in mid-March and 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 have already been planned in order to address the identified priority areas: national plans and strategies for rare diseases, rare diseases in international nomenclatures, specialised social services for rare diseases, quality of care for rare diseases and integration of European rare diseases initiatives. 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.

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<sup>92</sup> [www.orphadata.org](http://www.orphadata.org)

<sup>93</sup> [www.ojrd.com](http://www.ojrd.com)



### 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 Diseases<sup>94</sup> for 1 January 1999 to 31 December 2003, the EU Public Health Programme 2003-2008<sup>95</sup> and the Second EU Public Health Programme 2008-2013<sup>96</sup> 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 are<sup>97</sup>: 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) and the Information Network on Rare Cancers (RARECARENet) project.

#### ***Pilot European Reference Networks for Rare Diseases (ERN)***<sup>98</sup>

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 diseases<sup>99</sup>.

Some principles have been developed regarding European Reference Networks (ERNs) for rare diseases, 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 is 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.
- 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;

<sup>94</sup> [http://eur-lex.europa.eu/pri/en/oj/dat/1999/l\\_155/l\\_15519990622en00010005.pdf](http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf)

<sup>95</sup> <http://www.orpha.net/testor/cgi-bin/OTmain.php?PHPSESSID=43c50b5eec72a9b89f68faad7a33b30d&UserCell=workingGroup>

<sup>96</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:301:0003:0013:EN:PDF>

<sup>97</sup> [http://ec.europa.eu/health/rare\\_diseases/projects/index\\_en.htm](http://ec.europa.eu/health/rare_diseases/projects/index_en.htm)

<sup>98</sup> Information taken from [http://ec.europa.eu/health/rare\\_diseases/european\\_reference\\_networks/erf/index\\_en.htm#fragment1](http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm#fragment1)

<sup>99</sup> [http://ec.europa.eu/health/archive/ph\\_overview/co\\_operation/mobility/docs/highlevel\\_2005\\_013\\_en.pdf](http://ec.europa.eu/health/archive/ph_overview/co_operation/mobility/docs/highlevel_2005_013_en.pdf)

- 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 since been approved by the EUCERD and is available online<sup>100</sup>.

### **EU Projects supporting cooperation between rare diseases organisations**

Projects were supported in the framework of the Programme of Community Action on Rare Diseases<sup>101</sup> from 1 January 1999 to 31 December 2003 and the EU Public Health Programme 2003-2008<sup>102</sup> in order to strengthen collaboration at European level among patient organisations, develop partnerships among all alliances and develop European recommendations and national action plans<sup>103</sup>.

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 diseases<sup>104</sup>.

The Rare Disease Patient Solidarity project (RAPSODY<sup>105</sup>) 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 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 POLKA<sup>106</sup> project was launched in September 2008 and aims 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

<sup>100</sup> <http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

<sup>101</sup> [http://eur-lex.europa.eu/pri/en/oj/dat/1999/l\\_155/l\\_15519990622en00010005.pdf](http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf)

<sup>102</sup> [http://eur-lex.europa.eu/pri/en/oj/dat/2002/l\\_271/l\\_27120021009en00010011.pdf](http://eur-lex.europa.eu/pri/en/oj/dat/2002/l_271/l_27120021009en00010011.pdf)

<sup>103</sup> Projects financed to support this action include RAPSODY, PARACELUSUS, EU PARD, POLKA and OPERA.

<sup>104</sup> <http://www.EURORDIS.org/>

<sup>105</sup> [www.rapsodyonline.eu](http://www.rapsodyonline.eu)

<sup>106</sup> [http://img.rarediseaseday.org/polka/polka\\_brochure\\_final.pdf](http://img.rarediseaseday.org/polka/polka_brochure_final.pdf)

Krakow, Poland (13-15 May 2010). EURORDIS will organise the 2012 European Conference on Rare Diseases and Orphan Products in Brussels, Belgium (23-25 May 2012).

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

The Council Recommendation on an action in the field of rare diseases<sup>107</sup> 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 diseases<sup>108</sup> at national and European level, a guidance document containing the EUROPLAN recommendations for the elaboration of the national plans or strategies for rare diseases<sup>109</sup>, a report on indicators for monitoring the implementation and evaluating the impact of national plan or strategy for rare diseases<sup>110</sup>, 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 event<sup>111</sup>. A final conference, presenting the outcomes of the project and these national conferences was held on 25 February 2011 in Rome, Italy.

<sup>107</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

<sup>108</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

<sup>109</sup> [http://www.euoplanproject.eu/public/contenuti/files/Guidance\\_Doc\\_EUROPLAN\\_20100601\\_final.pdf](http://www.euoplanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf)

<sup>110</sup> <http://www.euoplanproject.eu/public/contenuti/files/EP-D6-Indicators.pdf>

<sup>111</sup> <http://www.EURORDIS.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN20%20National%20Conference%20Final%20Reports>

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 online<sup>112</sup>.

#### **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

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<sup>112</sup> <http://www.epirare.eu/quest4.html>

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 practices<sup>113</sup> and the expert opinion<sup>114</sup> containing recommendations on best practices which were published in 2012. An executive report<sup>115</sup> to the EC was also issued.

***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 tender<sup>116</sup> 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 2011<sup>117</sup>: 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.

**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 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 (e.g., EuroWilson).

<sup>113</sup> [http://ec.europa.eu/eahc/documents/news/Report\\_NBS\\_Current\\_Practices\\_20120108\\_FINAL.pdf](http://ec.europa.eu/eahc/documents/news/Report_NBS_Current_Practices_20120108_FINAL.pdf)

<sup>114</sup> [http://ec.europa.eu/eahc/documents/news/Expert\\_opinion\\_document\\_on\\_NBS\\_20120108\\_FINAL.pdf](http://ec.europa.eu/eahc/documents/news/Expert_opinion_document_on_NBS_20120108_FINAL.pdf)

<sup>115</sup> [http://ec.europa.eu/eahc/documents/news/Executive\\_Report\\_to\\_EC\\_20120108\\_FINALE.pdf](http://ec.europa.eu/eahc/documents/news/Executive_Report_to_EC_20120108_FINALE.pdf)

<sup>116</sup> [http://ec.europa.eu/eahc/documents/health/tenders/2010/EN/EAHC\\_2010\\_05\\_tenderSpecifications\\_EN.pdf](http://ec.europa.eu/eahc/documents/health/tenders/2010/EN/EAHC_2010_05_tenderSpecifications_EN.pdf)

<sup>117</sup> [http://ec.europa.eu/eahc/documents/news/CAVOD\\_Final%20Report\\_vf\\_corrected\\_281011.pdf](http://ec.europa.eu/eahc/documents/news/CAVOD_Final%20Report_vf_corrected_281011.pdf)

### 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**

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's Alzheimer and Dementias Communication**

The European Commission adopted in late July 2009 a Communication<sup>118</sup> on a European initiative for Alzheimer disease and other dementias along with a proposal for a Council Recommendation<sup>119</sup> 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**

The European Commission adopted on 24 June 2009 a Communication on Action Against Cancer<sup>120</sup> and created a European Partnership on cancer. 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.

#### **Directive regulating organ donations and transplantations**

A directive<sup>121</sup> 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

<sup>118</sup> [http://ec.europa.eu/health/ph\\_information/dissemination/documents/com2009\\_380\\_en.pdf](http://ec.europa.eu/health/ph_information/dissemination/documents/com2009_380_en.pdf)

<sup>119</sup> [http://ec.europa.eu/health/ph\\_information/dissemination/documents/rec2009\\_379\\_en.pdf](http://ec.europa.eu/health/ph_information/dissemination/documents/rec2009_379_en.pdf)

<sup>120</sup> [http://ec.europa.eu/health/ph\\_information/dissemination/diseases/docs/com\\_2009\\_291.en.pdf](http://ec.europa.eu/health/ph_information/dissemination/diseases/docs/com_2009_291.en.pdf)

<sup>121</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:PDF>

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 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 shall 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 2008<sup>122</sup> 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 2011<sup>123</sup>. 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 EuroGentest<sup>124</sup> 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 15189<sup>125</sup> 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 response<sup>126</sup> 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.

### **EU Disability Strategy 2010-2020: A Renewed Commitment to a Barrier-Free Europe**

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'<sup>127</sup> 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

<sup>122</sup> [http://ec.europa.eu/consumers/sectors/medical-devices/files/recast\\_docs\\_2008/public\\_consultation\\_ivd\\_final\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/public_consultation_ivd_final_en.pdf)

<sup>123</sup> [http://ec.europa.eu/consumers/sectors/medical-devices/files/recast\\_docs\\_2008/ivd\\_pc\\_outcome\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/ivd_pc_outcome_en.pdf)

<sup>124</sup> <http://www.eurogentest.org/web/index.xhtml>

<sup>125</sup> <http://www.eurogentest.org/laboratories/qau/info/public/unit1/qmanagement/accreditation.xhtml>

<sup>126</sup> [http://ec.europa.eu/health/medical-devices/files/ivd/50\\_ivd\\_en.pdf](http://ec.europa.eu/health/medical-devices/files/ivd/50_ivd_en.pdf)

<sup>127</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2010:0636:FIN:EN:PDF>

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**

In December 2011, the European Commission adopted a Decision<sup>128</sup> establishing an eHealth Network, as foreseen by the Directive on Patients' Rights in Cross-border Healthcare<sup>129</sup>. 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.

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<sup>128</sup> [http://ec.europa.eu/health/ehealth/docs/decision\\_ehealth\\_network\\_en.pdf](http://ec.europa.eu/health/ehealth/docs/decision_ehealth_network_en.pdf)

<sup>129</sup> [http://ec.europa.eu/health/ehealth/policy/index\\_en.htm](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 website<sup>130</sup> and the *Orphanet Report Series* lists EU-funded collaborative projects in the field of rare diseases<sup>131</sup>.

The FP6 ERA-Net for research programmes on rare diseases (E-Rare)<sup>132</sup> 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.

<sup>130</sup> <http://cordis.europa.eu/lifescihealth/major/rare-diseases-projects-1.htm>

<sup>131</sup> <http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf>

<sup>132</sup> <http://www.e-rare.eu/>

## 2.2. 7<sup>th</sup> 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, 2007-2013<sup>133</sup>) 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 already published several calls for proposals covering research on rare diseases in various thematic areas of FP7. For the period 2007–2011, 66 research projects with an EU contribution of over €325 million are being supported. They will ultimately lead to better diagnostic methods, new treatments, better care and prevention strategies for rare diseases.

Of these, 17 projects are specifically devoted to support research on the natural history and the pathophysiology of rare diseases (for a total of €71 million), and 8 projects cover the preclinical and clinical development of orphan medicinal products (for a total of €36 million).

The “Cooperation” 2010 work programme of the Health Theme<sup>134</sup> also called for an ERA-Net on rare diseases. The ERA-Net project E-Rare-2<sup>135</sup>, which aims at coordinating national research programmes on rare diseases, is being supported. Important aspects include exchanging information concerning research on rare diseases, and funding transnational collaborative research through joint transnational calls.

The European Commission released on 20 July 2011 the content of a new call for proposals<sup>136</sup> which opened several opportunities for rare diseases in the HEALTH theme of the work programme for 2012. The indicative budget for the rare disease activities is €108 million.

A list of FP7 projects is provided on the Cordis website<sup>137</sup> and the *Orphanet Report Series* lists EU-funded collaborative projects in the field of rare diseases<sup>138</sup>.

### **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*”<sup>139</sup>. 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.

<sup>133</sup> [http://cordis.europa.eu/fp7/home\\_en.html](http://cordis.europa.eu/fp7/home_en.html)

<sup>134</sup> [ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/health/a\\_wp\\_201001\\_en.pdf](ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/health/a_wp_201001_en.pdf)

<sup>135</sup> <http://www.e-rare.eu/>

<sup>136</sup> [http://ec.europa.eu/research/participants/portal/page/cooperation;efp7\\_SESSION\\_ID=QJMWPQCQHMZgQwqLihGhQY2XH6RRrTxDH4hwGkvQBz3NBsJYrW!1086760178?callIdentifier=FP7-HEALTH-2012-INNOVATION-1](http://ec.europa.eu/research/participants/portal/page/cooperation;efp7_SESSION_ID=QJMWPQCQHMZgQwqLihGhQY2XH6RRrTxDH4hwGkvQBz3NBsJYrW!1086760178?callIdentifier=FP7-HEALTH-2012-INNOVATION-1)

<sup>137</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/projectsfp7\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/projectsfp7_en.html)

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

<sup>139</sup> [http://asso.orpha.net/RDPlatform/upload/file/RDPlatform\\_final\\_report.pdf](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 (IRDIRC<sup>140</sup>)

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 workshop<sup>141</sup> 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.

The Icelandic workshop gathered 40 participants from the EC and the NIH administrations, as well as representatives from patient organisations, the biopharmaceutical industry, and academia. The discussions allowed a review of successful initiatives already taken on both sides of the Atlantic, and an exploration of what could be developed in common to speed up R&D. Currently, EU and US calls for research proposals are already open to transatlantic cooperation, but a large-scale international cooperative effort would be more efficient, as has been demonstrated by previous international consortiums such as the International Knock-out Mouse Consortium<sup>142</sup>, the Human Metagenome Consortium<sup>143</sup>, the Cancer Genome Consortium<sup>144</sup> and the International Human Epigenome Consortium<sup>145</sup>, among others.

This international programme will have ambitious goals, and will establish common policies and define shared resources, such as common Standard Operating Procedures, ontologies and data quality controls. It will ensure fair sharing of the workload and avoid funding overlap. The Reykjavik workshop was intended as a brain-storming session to review areas for cooperation which will serve to draft the outline of the consortium, to be further delineated at a second workshop in Washington in April 2011. The first area which was discussed in depth in Iceland, was the existing hurdles in the field of clinical research, specifically the lack of good clinical data on many diseases. The field of patient registries tops the list of areas to improve, including the constitution of repositories of data, data format and outcome variables (such as those of the PhenXtoolkit), templates for writing research protocols, informed consent forms, and rules on data sharing. This field would benefit from a public-private partnership, since, in any case, patient data must be collected when a product is marketed. Good practice guidelines to share data and access it need to be established and widely distributed. The factors of success and of failure during the R&D process were analysed both by European Medicines Agency and US Food and Drug Administration representatives. Most discussed were ways to decrease the

<sup>140</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html)

<sup>141</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/events-03\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/events-03_en.html)

<sup>142</sup> <http://www.knockoutmouse.org/>

<sup>143</sup> <http://www.metagenome.jp/>

<sup>144</sup> <http://www.icgc.org/>

<sup>145</sup> <http://www.epigenome.org/>

failure rate (currently 85% after Orphan Designation) as a means to both increase the number of marketed products and to decrease the cost of individual products. The example of the FDA Rare Disease Repurposing Database was cited. The issue of training was also discussed at length, particularly as it pertains to Small- and Medium-sized Enterprises and to the training of young clinicians who are not well enough informed of the regulatory aspects of clinical research. Industry representatives presented a concept currently under discussion between members of the group of research directors at the European Federation of Pharmaceutical Industries and Associations (EFPIA), named the “Cookie Jar”, into which each company could put promising products that they do not want or cannot develop, for another company to develop, under the condition that the other company also puts products into the Cookie Jar, to balance the benefits. This idea was thought very promising in order to ensure no waste of opportunities for patients. The ERDITI<sup>146</sup> initiative was also presented as an example of good practice. This led to a recommendation to push forward the Creative Commons concept as the right framework for the management of many platforms, seen as pre-competitive, as the only way to de-risk the R&D process, to both decrease costs and optimise the success of the R&D process.

The volume of new scientific data coming from the whole genome sequencing approach was also discussed as very promising for patients, many more of whom will be able to receive a diagnosis for their condition, and also positive for researchers and clinicians who will be able to better understand the underlying mechanisms. However, the changing situation requires a new approach as the tools to handle and interpret massive data do not yet exist. The proposal to establish a Human Phenome Consortium was made, which would include the current effort of the Human Variome project, the ‘ontologisation’ of various human disease databases to allow their interconnection with other biological ontologies, including the Mouse phenome ontology, and the establishment of an international nomenclature of clinical physical and functional anomalies, the development of multi-terminology servers and the implementation of a nomenclature of rare diseases in health information systems.

Participants were well aware of the difficulties to be faced in the current economic context. The setting up of this ambitious programme requires commitment of the Community of researchers and of the funding agencies. It will be a challenge to implement, to agree on its governance and to convince the Community of this approach.

In early April 2011, some 80 participants from research funding agencies, research organisations, industry, patient representatives and regulatory agencies gathered for the second meeting in Bethesda<sup>147</sup> and the official launch of the International Rare Diseases Research Consortium (IRDiRC).

Research funding agencies represented at this second workshop were:

- European Commission (DG Research and Innovation; DG Health and Consumers)
- National Institutes of Health - NIH (USA)
- Canadian Institutes of Health Research - CIHR (Canada)
- Instituto de Salud Carlos III (Spain)
- Istituto Superiore di Sanita (Italy)

To develop a policy document framing the international effort, different breakout sessions were organised to trigger the discussion on the different policy items:

- Understanding Pathophysiology of Rare Diseases (Genomics analyses and In vitro and animal models),
- Ontologies/Disease Classification/Natural History,
- Biomarkers,
- Patient Registries and Biospecimen Repositories,
- Preclinical Research and Clinical Trials,
- Communication/Publication/Information/Intellectual Property Rights/Data Policy.

The second reunion picked up the pace with the endorsement by members to fulfil certain goals, including, notably, a commitment to the development of 200 new rare disease treatments by the year 2020 and the development of diagnostics for most rare disorders. Related challenges identified include the need to establish and provide access to harmonised data and samples, perform the molecular and clinical characterisation of rare diseases, boost translational, preclinical and clinical research, and streamline ethical and regulatory procedures.

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<sup>146</sup> [www.erditi.org](http://www.erditi.org)

<sup>147</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/events-04\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/events-04_en.html)

The third workshop of the IRDiRC<sup>148</sup> was held in Montreal, Canada on 8-9 October 2011 and was hosted by the Canadian Institutes for Health Research and Genome Canada and co-organised with the European Commission and the US National Institutes of Health, just before the 12th International Congress of Human Genetics. Some 100 international participants representing public and private funding organisations, scientists, regulators, industry, and patient groups were onboard, working together to develop common scientific and policy frameworks that will guide the activities of the participating IRDiRC members. Identifying priority research areas was a principal topic, as well as addressing the regulatory challenges in an international context. Initial goals put forward by the IRDiRC founders include 200 new treatments for rare diseases by the year 2020 and have a diagnosis available for most rare diseases. A series of Round Table presentations provided an update of the current and planned actions by the funding agencies committed to IRDiRC.

### **Governance**

IRDiRC will be governed by an Executive Committee, three Scientific Committees and a number of working groups<sup>149</sup>. Until the end of 2012, IRDiRC will be run by an Interim Executive Committee with representatives of all participating funding agencies. It will be 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.

IRDiRC will have three Scientific Committees, one each for Diagnostics (including sequencing and characterisation), Therapies (including pre-clinical and clinical development) and Interdisciplinary aspects of rare diseases research (including ontologies, natural history, biobanking, registries etc). The Scientific Committees will advise the Executive Committee on research priorities and progress made from a scientific viewpoint. Nominations for the three IRDiRC Scientific Committees were opened at the end of 2011 and the first members were appointed on 29 February 2012.

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

### **Organisational 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-INNOVATION<sup>150</sup> call for proposals (Work Programme 2012).

### **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 Commission<sup>151</sup>.

## **2.4. Open Access Infrastructure for Research in Europe (OpenAIRE) (2010)**

The Open Access Infrastructure for Research in Europe (OpenAIRE<sup>152</sup>) 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 release<sup>153</sup> 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

<sup>148</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/events-05\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/events-05_en.html)

<sup>149</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/governance\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/governance_en.html)

<sup>150</sup> <http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-1> and <http://ec.europa.eu/research/participants/portal/page/cooperation?callIdentifier=FP7-HEALTH-2012-INNOVATION-2>

<sup>151</sup> [http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members\\_en.html](http://ec.europa.eu/research/health/medical-research/rare-diseases/committed-members_en.html)

<sup>152</sup> [www.openaire.eu](http://www.openaire.eu)

<sup>153</sup> <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/10/1644&format=HTML&aged=1&language=EN&guiLanguage=fr>

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.

## 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)<sup>154</sup> was adopted in December 1999 and came into force in the European Union in 2000.

The Regulation addresses the need to offer incentives for the development and 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.<sup>155</sup>

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 designation and marketing authorisation, a period of market exclusivity (normally 10 years) once the orphan product is authorised, 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.

The regulation on orphan medicinal products also set up the Committee for Orphan Medicinal Products<sup>156</sup> (COMP) at the European Medicines Agency (EMA) to assist the Commission. According to the regulation the

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

<sup>155</sup> 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](http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm)

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

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 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 2011, the Commission granted 107 orphan designations. In addition, the Commission authorised five orphan medicinal products in 2011.

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 Commission<sup>157</sup>. The EMA maintains a searchable list of opinions on orphan designations<sup>158</sup>.

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”*<sup>159</sup>. 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.

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

### Regulation of Clinical Trials<sup>160</sup>

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 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”<sup>161</sup>). 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

<sup>157</sup> <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>

<sup>158</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan\\_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d12b](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d12b)

<sup>159</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Public\\_statement/2009/09/WC500003876.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/09/WC500003876.pdf)

<sup>160</sup> This section reproduces information from [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index_en.htm) (March 2010)

<sup>161</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>



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/EC<sup>162</sup> 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/EC<sup>163</sup> 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 products<sup>164</sup>).

### 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 initiation<sup>165</sup>. 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 report<sup>166</sup> 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.

A European Commission public consultation was held in from 9 October 2009 to 8 January 2010<sup>167</sup> to assess the impact of the Directive and the replies were published soon after<sup>168</sup>. The Commission has scheduled adoption of the legislative proposal<sup>169</sup> for 2012. 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

<sup>162</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>

<sup>163</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0067:EN:PDF>

<sup>164</sup> [http://europa.eu/legislation\\_summaries/internal\\_market/single\\_market\\_for\\_goods/pharmaceutical\\_and\\_cosmetic\\_products/l21230\\_en.htm](http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm)

<sup>165</sup> <http://www.orpha.net/actor/EuropaNews/2006/060409.html#EUPol>

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<sup>167</sup> [http://ec.europa.eu/health/files/clinicaltrials/docs/2009\\_10\\_09\\_public-consultation-paper.pdf](http://ec.europa.eu/health/files/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf)

<sup>168</sup> [http://ec.europa.eu/health/files/clinicaltrials/2010\\_03\\_30\\_summary\\_responses.pdf](http://ec.europa.eu/health/files/clinicaltrials/2010_03_30_summary_responses.pdf)

<sup>169</sup> [http://ec.europa.eu/governance/impact/planned\\_ia/docs/47\\_sanco\\_clinical\\_trials\\_directive\\_en.pdf](http://ec.europa.eu/governance/impact/planned_ia/docs/47_sanco_clinical_trials_directive_en.pdf)

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 2011<sup>170</sup>.

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

#### **Regulation on Advanced Therapy Medicinal Products (13 October 2007)<sup>171</sup>**

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) 1394/2007<sup>172</sup>) 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.

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.

<sup>170</sup> [http://ec.europa.eu/health/files/clinicaltrials/ctresp\\_2011-06/ct\\_summary.pdf](http://ec.europa.eu/health/files/clinicaltrials/ctresp_2011-06/ct_summary.pdf)

<sup>171</sup> This section reproduces information from <http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/advanced-therapies/>

<sup>172</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>

### 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)<sup>173</sup>

New legislation governing the development and authorisation of medicines for paediatric use (Regulation (EC) N° 1901/2006)<sup>174</sup> 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 EMA<sup>175</sup>;
- 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;
- 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*

<sup>173</sup> This section reproduces information from [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/paediatric-medicines/index\\_en.htm](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>

<sup>174</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

<sup>175</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

*Regulation (EC) No 1901/2006*<sup>176</sup>, 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 EudraCT<sup>177</sup>, 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 public<sup>178</sup>. The Register shows data entered in EudraCT by the national competent authorities, or, for paediatric trials wholly conducted outside the EU, by the applicants themselves<sup>179</sup>.

### **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 PrioMedChild<sup>180</sup> (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.

<sup>176</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

<sup>177</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009\\_02\\_04\\_guideline.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf)  
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<sup>178</sup> <https://www.clinicaltrialsregister.eu/>

<sup>179</sup> 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.

<sup>180</sup> <http://www.priomedchild.eu/home/>

## 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 announced<sup>181</sup> in 2010 the launch of a process on corporate responsibility<sup>182</sup> in the field of pharmaceuticals. In a press release<sup>183</sup>, 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 Industries and Associations, and the European Association for Bioindustries.

### 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*<sup>184</sup>. This new report, commissioned by the European Commission DG Enterprise and Industry, presents a country-by-country survey of accessibility to orphan medicines, with an emphasis on product distribution through Centres of Expertise and derogatory procedures for accessing products in situations of restricted availability (typically Compassionate Use-type programmes). Taking Pompe disease and pulmonary arterial hypertension as examples, the EMINet report surveys both the availability of treatments across Europe and the distribution of centres of expertise for the diseases. The EMINet findings, combined with the results of the Ernst & Young CAVOD 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.

<sup>181</sup> <http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/10/442&format=HTML&aged=0&language=EN&guiLanguage=en>

<sup>182</sup> [http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process\\_on\\_corporate\\_responsibility/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/process_on_corporate_responsibility/index_en.htm)

<sup>183</sup> <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/10/1170&format=HTML&aged=0&language=EN&guiLanguage=en>

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<sup>185</sup> The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

<sup>186</sup> Disclaimer: the European Commission is not responsible for the completeness and correctness of the information included in this report.

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<sup>187</sup> All websites and documents were last accessed in May 2012.

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[http://ec.europa.eu/health/files/orphanmp/doc/inventory\\_2006\\_08\\_en.pdf](http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf)
- Final Conclusions and Recommendations of the High Level Pharmaceutical Forum (2<sup>nd</sup> October 2008)  
[http://ec.europa.eu/pharmaforum/docs/final\\_conclusions\\_en.pdf](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](http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access_orphans_initialinvest_052011_en.pdf)

### DG Health and Consumers

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### European Medicines Agency

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[http://www.ema.gov.sg/media/files/annual\\_reports/EMA\\_Annual\\_Report\\_2010.pdf](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](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf)

#### DG Research and Innovation

- International Rare Disease Research Consortium (IRDiRC) First Workshop Summary Report  
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- International Rare Disease Research Consortium (IRDiRC) Second Workshop Summary Report  
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#### 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](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](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](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  
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- EURORDIS report: Results of the 4<sup>th</sup> EURORDIS Survey on Orphan Drug Availability in Europe (2007)  
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ISBN 978-92-79-25358-4

