European Union Committee of Experts on Rare Diseases

2011 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE

OF THE EUROPEAN UNION COMMITTEE OF EXPERTS ON RARE DISEASES

PART II : EUROPEAN COMMISSION AND OTHER EUROPEAN ACTIVITIES

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

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

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GENERAL INTRODUCTION

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

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan drugs up to the end of 2010. A range of stakeholders in each Member State have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive, and is not an official position of either the European Commission or national health authorities

The report is split into three parts:

Part I: Overview of Rare Disease Activities in Europe and Key Developments in 2010
Part II: European Commission and other European activities
Part III: Activities in EU Member States and other European Countries

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

1. METHODOLOGY AND SOURCES

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

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

[1] http://ec.europa.eu/health/rare_diseases/policy/index_en.htm
[2] http://cordis.europa.eu/home_fr.html
[3] www.ema.europa.eu
[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e30

- **OrphaNews Europe**
  Data from the OrphaNews Europe[5] newsletter for the period 2007-2010 was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France[6] (which focuses particularly on developments in the field of rare diseases in France) was carried out in order to collect information for the section concerning France.

- **Rare Diseases Task Force publications**
  Various reports of the RDTF have been used as sources of data to collect information on the state of affairs at both EU and Member State levels pre-2010, notably the reports of the RDTF WG on Standards of Care (concerning European Centres of Reference) produced between 2005-2008, including the *RDTF Final Report – Overview of Current Centres of Reference on rare diseases in the EU - September 2005*[7] and the *RDTF Meeting Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – September 2006*[8], as well as the *RDTF Final Report – State of the Art and Future Directions – March 2008*[9]**.**

- **EUCERD Publications**
  Parts II and III of this report presents an update of the information previously published in the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*[10] (July 2010). The methodology for the production of this previous report is outlined in the introduction. Information on the state of the art of centres of expertise at MS level was also collected during the EUCERD workshop on national centres of expertise and ERNs for rare diseases (8-9 December 2010[11] and 21-22 March 2011[12]).

- **Minutes of the EUCERD**
  The minutes of the first meeting of the EUCERD held on 9-10 December 2011 (and previous minutes of the RDTF meetings) was used in order to identify upcoming initiatives and incentives in the field of rare diseases, and to report on the events held to mark Rare Disease Day 2010.

- **Reports on orphan drugs**
  The information provided for each Member State concerning the state of affairs in the field of Orphan Drugs is taken, when referenced, from the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*[13] published in 2006 by the European Commission and produced using data collected by the EMA and Orphanet. This information has been updated when information is available and quoted when still applicable. Another valuable source of information on Orphan Drug policy, at EU and Member State levels was the 2009 KCE 112B report published by the KCE-Belgian Federal Centre of Healthcare Expertise (*Federaal Kenniscentrum voor de Gezondheidszorg/Centre federal d'expertise des soins de santé*) entitled *"Orphan Disease and Orphan Drug Policies" [Politiques relatives aux maladies orphelines et aux médicaments orphelins)*[14]. This report notably provided information for the 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*

[5] http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews
[6] http://www.orpha.net/actor/cgi-bin/OAhome.php
[7] http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf
[8] http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf
[9] http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf
[10] http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf
[11] http://www.eucerd.eu/upload/file/WorkshopReport/EUCERDWorkshopReportCECERN.pdf
[12] http://nestor.orpha.net/upload/file/EUCERDReport220311.pdf
[13] http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf
[14] *Politiques relatives aux maladies orphelines et aux médicaments orphelins*
http://www.kce.fgov.be/index_fr.aspx?SGREF=3460&CREF=13646

Comparative Study of Selected European Countries (No. 52 October 2009)" also provided information on orphan drug availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Information for the overview was also taken from the *Nature Reviews: Drug Discovery* article produced by the COMP/EMA Scientific Secretariat, *European regulation on orphan medicinal products: 10 years of experience and future perspectives*[15].

- **Eurordis website and websites of patient organisation alliances**
  The site of the European Organisation for Rare Diseases[16], 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[17] surveys), were used to provide information on Eurordis activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national patient alliances were also consulted for information. In addition to this the Rare Disease Day 2010 site[18], maintained by Eurordis, also provided information on events at Member State level[19] concerning Rare Disease Day.

- **EUROPLAN questionnaire to collect information on rare disease activities**
  In the context of the European Project for National Plans Development (EUROPLAN), the partners of the project (who include representatives of national health authorities, expert researchers and clinicians, national alliances of rare disease patient organisations from all MS, and a number of other experts from national health authorities) were addressed a questionnaire and asked to provide detailed information, especially information from sources in their languages, which is more difficultly accessible on the state of rare diseases activities in their country. The structure of the questionnaire (a sample of this questionnaire is included in Annex IV of the *2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*[20]) followed the structure of the Commission Communication on an action in the field of rare diseases[21]: 19 main questions were formulated in order to collect key data on a number of actions in their country. Since the detail of the answers to these questionnaires varied depending on the information available and the actions specific to the Country, a session of telephone interviews was also carried out to improve the information available, where appropriate. The collection of the information was concluded in October 2009.

- **EUROPLAN national conferences final reports**
  In the context of the EUROPLAN project, 15 national conferences were organised in collaboration with Eurordis and national rare disease patient alliances in 2010 in order to present the Council Recommendation on an action in the field of rare diseases, as well as discuss the Europlan recommendations/guidance document for the development of national plans and strategies in the field of rare diseases[22] and its application at national level. These conferences were attended by a range of stakeholder groups at national level and the final reports[23] of these conferences were presented in a common format for ease of comparison. Information provided in these reports has helped update the information provided in this document. Readers of this report are encouraged to refer to these reports in addition to the present report as they provide further detail of the discussions of national approaches to rare disease policy.

[15] http://www.ncbi.nlm.nih.gov/pubmed/21532564
[16] http://www.eurordis.org/secteur.php3
[17] http://www.eurordis.org/article.php3?id_article=1960
[18] http://www.rarediseaseday.org/
[19] http://www.rarediseaseday.org/country/finder
[20] http://www.eucerd.eu//upload/file/Reports/2009ReportInitiativesIncentives.pdf
[21] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on "Rare Diseases: Europe's challenges" (COM(2008) 679 final)
[22] http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf
[23] http://www.eurordis.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN%20%20National%20Conference%20Final%20Reports

- **Orphanet**
  The Orphanet database was exploited to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials and rare disease/orphan drug policies outside of Europe for Part I. Orphanet also provides links[24] 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[25], in particular the report *Rare diseases research, its determinants in Europe and the way forward*[26] was also used as a source for Part I.

- **OrphaNetWork News**
  OrphaNetWork News is the internal newsletter of Orphanet, which communicates information to partners on Orphanet activities in each partner country. The data for this newsletter is collected through a systematic query of Orphanet Country Coordinators and Information Scientists in order to collect information concerning Orphanet country teams' involvement in rare disease meetings and conferences, as well as participation in Rare Disease Day events and partnerships. This surveillance at national level was exploited to provide information for the events section for each Member State.

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

2. REPORT PREPARATION, REVISION AND VALIDATION

The present report provides a compilation of information from the previous report of the EUCERD on the state of the art of rare diseases activities in Europe (*2009 Report on initiatives and incentives in the field of rare diseases of the EUCERD*) elaborated in 2010, which has been updated in 2011 to take into account advances and activities in the field of rare diseases and orphan drugs at EU and MS level in 2010.

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

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

Part II of the report on activities at European Union level was sent for validation, to the best of their ability, by the representatives at the EUCERD of the European Commission Directorate Generals for Health, Research and

[24] http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN
[25] http://www.rdplatform.org/
[26] http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf

Innovation, Enterprise and Industry, as well as the EMA: this process was carried out in May/June 2011 by the Scientific Secretariat of the EUCERD. The European Commission is not responsible, however, for the completeness and the correctness of the information presented in this report.

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

3. REPORT STRUCTURE

The report is structured into three main parts: Part I consists of an overview of the activities in the field of rare diseases in Europe at EU and MS level as well as a short summary of key developments at EU and MS level in 2010; Part II concerns activities at EU level; Part III concerns activities at EU MS level, as well as five other non-EU European countries where information was available. Each part is followed by a selected bibliography outlining the sources used to produce the 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 is a list of contributors the report, organised by country with mention of the validating authority in each country, and stating their contribution to the current and/or previous report. A list of frequently used acronyms has also been included in each part to ease reading.

Part I provides an overview of the state of the art of rare disease activities in the field of rare diseases in Europe and key developments in 2010 at EU and MS level. This part thus serves as a summary to highlight key areas of the Parts II and III, which serve to provide more detailed background information at EU and MS level. The overview is structured into a number of topics: political framework, expert services in Europe research and development, orphan drugs and therapies for rare diseases, patient organisations and information services.

Part II of the report on activities at EU level is organised slightly differently to the last edition of the report where activities were presented in sections corresponding to the European Commission Directorates General (DG) of the European Commission implicated in the field of rare diseases. In the present report, activities concerning rare diseases and orphan drugs at EU level are split into four sub-sections:

1. EC activities related to rare diseases in the field of public health
2. EC activities related to rare diseases in the field of research
3. EC activities in the field of orphan drugs and therapies for rare diseases
4. Other European rare disease activities (i.e. meetings at European level and selected transversal EU activities).

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

The sub-section concerning EC activities in the area of orphan drugs and advanced therapies for rare diseases is organised accordingly: European legislation concerning orphan medicinal products and related activities, European Medicine Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare

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

The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU-level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2010.

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

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

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise[27]
- Registries
- Neonatal screening policy
- Genetic testing[28]
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines;
- Best practice guidelines
- Training and education initiatives
- Europlan national conference
- National rare disease events in 2010[29]
- Hosted rare disease events in 2010[30]
- Research activities and E-Rare partnership
- Participation in European projects[31]
- Orphan drugs (Orphan drug committee, Orphan drug incentives, Orphan drug availability[32], Orphan drug reimbursement policy, Other initiatives to improve access to orphan drugs, Orphan drug pricing policy)
- Orphan devices
- Specialised social services

The choice of categories of information for inclusion in this year's report were discussed by the EUCERD at their first meeting (9-10 December 2010): categories new to this year's edition include genetic testing, Europlan national conferences, orphan devices, other initiatives to improve access to orphan drugs and orphan drug pricing policy. The categories for which information is provided depends wholly on the information available following data collection from the described sources and contact with stakeholders. If no detail has been given for a topic, the mention "no specific activity/information reported" has been added.

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

[28] This section contains data extracted in May 2011 from the Orphanet database of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term 'estimated' is used as the concept of a single disease is a variable one).

[29] As announced in OrphaNews Europe.

[30] As announced in OrphaNews Europe.

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

[32] Contacts were asked to provide information on availability of orphan drugs (i.e. which drugs are registered/marketed at national level): some countries instead provided information on which drugs are accessible (i.e. reimbursed, on a positive drug list etc.). It is explicitly explained in each case to which of these concepts is being referred.

ACRONYMS

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

INTRODUCTION: EUROPEAN COMMISSION AND OTHER EUROPEAN ACTIVITIES IN THE FIELD OF RARE DISEASES[33,34]

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 Drug 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 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[35]. 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' drugs for these conditions.

A. EUROPEAN COMMISSION ACTIVITIES IN THE FIELD OF RARE DISEASES AND ORPHAN DRUGS

The European Commission has a coordinated approach to the field of rare diseases and orphan drugs 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 drugs: 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 drugs up to the end of 2010 is provided below by theme: public health, research and orphan drugs and therapies for rare diseases.

[33] http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

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

[35] 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 a 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)[36]. According to the DG Public Health 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[37] 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[38] 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

[36] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF
[37] http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
[38] http://ec.europa.eu/health/ph_threats/non_com/docs/raredis_comm_draft.pdf

countries through the creation of European reference networks in order to share knowledge and expertise and, where necessary, to identify where patients should go when such expertise cannot be made available to them. The role of patients' organisations is also highlighted as particularly important.

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.[39]

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 drugs: reports were produced on European Centres of Reference (2005[40], 2006[41]), Assessing treatable rare diseases and the proportion of patients eligible for treatment (2007) [42], Assessing the European Added-Value of ERN (2008)[43].

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 (PHI) 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 heath indicators. The first meeting was in January 2006 with a report on the subject in March 2008[44]. A report was also produced following a 2008 workshop on Patient Registries and Databases[45].

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[46]. 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

[39] http://www.eucerd.eu/__PP__2.html (Subsection "Working groups")
[40] http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf
[41] http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf
[42] http://www.eucerd.eu/upload/file/Publication/RDTFOD2007.pdf
[43] http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf
[44] http://www.eucerd.eu/upload/file/Publication/RDTFHI2008.pdf
[45] http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf
[46] 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 drugs, as well as to share clinical/therapeutic added-value assessment reports at the Community level.
- *VI. Empowerment of patient organisations* – calls on MS to consult patient representatives on policy development; facilitate patient access to updated information on rare diseases; promote patient organisation activities.
- *VII. Sustainability* – highlights that long-term sustainability in the field of information, research and healthcare of infrastructures must be ensured.

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 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. The deadline for submitting an expression of interest for any of these representative roles was 21 December 2009. 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.

The new Committee may establish temporary Working Groups consisting of external experts for specific missions. 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 National Centres of Expertise for Rare Diseases and European Reference Networks (8-9 December 2010).

OrphaNews Europe[47] 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 drugs. The newsletter has over 13'000 registered readers from all over the world and representing all stakeholder groups. In 2010, a reader satisfaction survey 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. Readers requested a search engine for sifting through the archives of the newsletter, the possibility to build a customised letter that targets the specific items of interest to an individual reader and an RSS Feed providing punctual updates. These features should be developed in 2011. The full results of the survey are available online[48].

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[49] implementing the second programme of Community action in the field of health (2008-2013). Amongst the rare disease initiatives

[47] http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews
[48] http://www.orpha.net/orphacom/cahiers/docs/GB/Orphanews_survey2010.pdf
[49] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:053:0041:0073:EN:PDF

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[50] implementing the second programme of Community action in the field of health (2008-2013) which will continue the support to rare disease projects and networks. Amongst the rare disease initiatives earmarked for funding are 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 drugs which is run by a large consortium of European partners and which is the most important rare diseases database in the world: in order to implement the establishment of a dynamic EU inventory of rare diseases it will be necessary to further develop the database, and 2) a technical action to support the European Surveillance on Congenital Anomalies (EUROCAT) network which is run by a large consortium of European partners in order to create a sustainable prevalence data system for 95 congenital anomaly subgroups which are to be updated annually. In order to improve procedures to access orphan medicinal products a call for tender concerning the creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines will be also launched.

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[51] 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 drugs. This

[50] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:340:0001:0046:EN:PDF

[51] More information can be found on www.eucerd.eu section "Activities".

joint action also aims to contribute to the revision of the International Classification of Diseases in the field of rare diseases.

The specific aims of the project include:

- the 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;
- the 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;
- liaising between EU agencies and services and major stakeholders to enhance collaboration and maximise input and outcomes;
- the 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 will also be improved thanks to this Joint Action by: assigning International Classification of Diseases codes (ICD10) to all rare diseases; proposing changes to improve the classification in view to the future adoption of the ICD11; using the technical platform developed by the WHO and with the assistance of an international expert group that will be established; and cross-referencing with other classification systems such as MedDRA and SNOMED-CT.

Workshops have been organised within the scope of the project around three working groups: indicators for rare diseases, initiatives and incentives for rare diseases and the coding and classification of rare diseases.

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

EUROCAT[52], 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 1.5 million births per year in Europe, with 43 registries present in 20 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 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.

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

Orphanet[53] is the reference portal for information on rare diseases and orphan drugs 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

[52] http://www.eurocat-network.eu/
[53] www.orpha.net

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 drugs; 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*[54]. Reports in the series include lists of rare diseases with their prevalence[55], lists of orphan drugs in Europe[56], lists of rare disease registries in Europe[57] and lists of collaborative research projects and clinical networks in the field of rare diseases funded by the European Commission[58]. 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 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 2,878 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.
- An inventory of orphan drugs at all stages of development, from EMA 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 drugs

- A range of other services for specific stakeholders:
  - For health care professionals: an assistance-to-diagnosis tool (search by signs and symptoms);
  - 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.

[54] http://www.orpha.net/consor/cgi-bin/Education_Home.php?lng=EN
[55] http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
[56] http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf
[57] http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf
[58] http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf

- 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 2010that Orphanet will 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 drugs. 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.

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[59] for 1 January 1999 to 31 December 2003, the EU Public Health Programme 2003-2008[60] and the Second EU Public Health Programme 2008-2013[61] 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 Public Health are[62]: 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, Surveillance of rare cancers in Europe (RARECARE), 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), the European Haemophilia Safety Surveillance System (EUHASS), 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

Pilot European Reference Networks for Rare Diseases (ERN)[63]

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

[59] http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf
[60] http://www.orpha.net/testor/cgi-bin/OTmain.php?PHPSESSID=43c50b5eec72a9b89f68faad7a33b30d&UserCell=workingGroup
[61] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:301:0003:0013:EN:PDF
[62] http://ec.europa.eu/health/rare_diseases/projects/index_en.htm
[63] Information taken from http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm#fragment1

groups of this High Level Group, in collaboration with the RDTF, focused on reference networks of centres of expertise for rare diseases[64].

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;
- 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[65].

EU Projects supporting cooperation between rare diseases organisations

Projects were supported in the framework of the Programme of Community Action on Rare Diseases[66] from 1 January 1999 to 31 December 2003 and the EU Public Health Programme 2003-2008[67] in order to strengthen

[64] http://ec.europa.eu/health/archive/ph_overview/co_operation/mobility/docs/highlevel_2005_013_en.pdf
[65] http://www.eucerd.eu/EUCERD/upload/file/Reports/ERNAnalysis2011.pdf
[66] http://eur-lex.europa.eu/pri/en/oj/dat/1999/l_155/l_15519990622en00010005.pdf
[67] http://eur-lex.europa.eu/pri/en/oj/dat/2002/l_271/l_27120021009en00010011.pdf

collaboration at European level among patient organisations, develop partnerships among all alliances and develop European recommendations and national action plans[68].

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[69].

The Rare Disease Patient Solidarity project (RAPSODY[70]) 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[71] 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 Krakow, Poland (13-15 May 2010).

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

The Council Recommendation on an action in the field of rare diseases[72] 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 drugs, 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 is 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 recommendations will provide information on the different steps to develop a strategic plan and, more importantly, it will highlight priority areas and actions of intervention in the field of rare diseases.

The project aims to collect and disseminate information on EU MS national initiatives on rare diseases, on expectations on national plans for rare diseases and on best practices contributing to share experiences, data and effective strategies to address rare diseases

[68] Projects financed to support this action include RAPSODY, PARACELSUS, EU PARD, POLKA and OPERA.
[69] http://www.eurordis.org/
[70] www.rapsodyonline.eu
[71] http://img.rarediseaseday.org/polka/polka_brochure_final.pdf
[72] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

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.

It is expected that the EUROPLAN project will: stimulate a discussion and reach a consensus on the importance of national plans for structuring all relevant actions in the field of rare diseases; list priority areas and actions of intervention to address rare diseases; promote the development of national plans for rare diseases within EU MS and provide an instrument to support countries in designing national plans for rare diseases according to the EU Communication on Rare Diseases[73].

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[74] at national and European level, a guidance document containing the EUROPLAN recommendations for the elaboration of the national plans or strategies for rare diseases[75], a report on indicators for monitoring the implementation and evaluating the impact of national plan or strategy for rare diseases[76], 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 has been published after each event[77]. A final conference, presenting the outcomes of the project and these national conferences was held on 25 February 2011 in Rome, Italy.

Continuity of some of the EUROPLAN activities especially those related to technical assistance to Member States experiencing particular difficulties in the preparation of their national plan or strategy on rare diseases is scheduled under the foreseen Joint Action on Rare Diseases 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 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. drugs, 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 is expected to be 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.

[73] http://ec.europa.eu/health/rare_diseases/policy/index_en.htm
[74] http://www.orpha.net/nestasso/EUCERD/upload/file/Reports/2009ReportInitiativesIncentives.pdf
[75] http://www.europlanproject.eu/public/contenuti/files/Guidance_Doc_EUROPLAN_20100601_final.pdf
[76] http://www.europlanproject.eu/public/contenuti/files/EP-D6-Indicators.pdf
[77] http://www.eurordis.org/content/europlan-guidance-national-plans-and-conferences#EUROPLAN20%20National%20Conference%20Final%20Reports

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

The general objective of this initiative 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 drugs 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.

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 the end date is 29 July 2011.

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

The expected outcomes of the evaluation are: 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 will be organised in June 2011 to finalise the report on NBS practices and the expert opinion containing recommendations on best practices.

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[78] 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 expert outcomes include: a report on the regulatory process followed by an orphan drug, from orphan designation at the European level to reimbursement in the Member State including Health Technology Assessment expertise used at national level; a questionnaire to compare the Orphan Designation and Marketing Authorisation processes of the EMA and at Member State level; forecasts and simulations of expected future budget impact of orphan drugs including clinical and economic evidence provided in the context of the registration and

[78] http://ec.europa.eu/eahc/documents/health/tenders/2010/EN/EAHC_2010_05_tenderSpecifications_EN.pdf

reimbursement procedures; expert opinion critically analysing and summarising positions on Common Assessment Report for CAVOD at EU institutional level and EU stakeholders; a Final Recommendation (including a format for the implementation of Common Assessment Report for CAVOD at EU level).

Key stakeholders in the field of rare diseases (including the EUCERD, EC competent units, the EMA Committee for Orphan Medicinal Products the EMA Committee for Human Medicinal Products, the EMA Committee of Advanced Therapies, and the EMA Paediatric Drugs Committee) will be implicated in the elaboration of these outcomes.

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 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).

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

Cross-border Healthcare Directive

The final steps to the approval of amendments of the European Parliament to the Cross-border Healthcare Directive[79] by the the Council of the European Union were taken in 2010, with the Directive finally approved in early 2011 to coincide with Rare Disease Day (28 February 2011). Highly relevant to rare disease patients suffering from scarce and scattered resources for care and diagnostics, the Directive seeks to facilitate access to health care for EU citizens and encourage cooperation between EU Member States in the field of health. The amended text reflects an agreement reached on 15 December between the Belgian Presidency of the Council of the European Union and the European Parliament. Upon publication in the *Official Journal of the European Union*, expected in April 2011, the Member States will have 30 months to put the provisions of the Directive into national legislation. A Council press release notes that *"the new directive provides clarity about the rights of patients who seek healthcare in another member state and supplements the rights that patients already have at EU level through the legislation on the coordination of social security schemes (regulation 883/04). It meets the Council's wish to fully respect the case law of the European Court of Justice on patients' rights in cross-border healthcare while preserving member states' rights to organise their own healthcare systems"*[80].

The Directive will have no impact on the rights of each Member State to determine which health benefits they will provide. Thus, if a particular treatment is not reimbursed in a patient's home country, it will not be reimbursed if accessed in another Member State. Member States would be able to require prior authorisation for "hospital care" – a term that Parliamentarians prefer Member States to define, rather than the Commission - and reimbursement would match the amount that patients would receive in their home country. However, Article 13 of the Directive specifically addresses the commitment of the Commission on behalf of rare disease patients: "*The Commission shall support Member States in cooperating in the development of diagnosis and treatment capacity in particular by aiming to:*

[79] http://register.consilium.europa.eu/pdf/en/11/pe00/pe00006.en11.pdf
[80] http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/119514.pdf

(a) make health professionals aware of the tools available to them at Union level to assist them in the correct diagnosis of rare diseases, in particular the Orphanet database, and the European reference networks;
(b) make patients, health professionals and those bodies responsible for the funding of healthcare aware of the possibilities offered by Regulation (EC) No 883/2004 for referral of patients with rare diseases to other Member States even for diagnosis and treatments which are not available in the Member State of affiliation."

European Commission's Alzheimer Communication
The European Commission adopted in late July 2009 a Communication[81] on a European initiative for Alzheimer disease and other dementias along with a proposal for a Council Recommendation[82] 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[83] 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 (7 July 2010)
A directive[84] adopted on 7 July 2010 established common standards for safety and quality in the area of organ donation and transplantation – an issue pertinent to the scores of rare diseases that affect organs such as the heart, liver or kidneys. The new legislation seeks to level the playing field across Europe and offer protection to poor citizens vulnerable to illegal organ trafficking schemes. The European Parliament voted in mid-May 2010 to pass the directive, which is pending adoption by the Council of Ministers. The European Commission has also set forth a ten point action plan for organ transplantation and donation, which has been backed by the 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.

EC public consultation on the revision of the Directive of the European Parliament and Council of 27 October 1998 on *in vitro* diagnostic medical devices (July 2010)
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. Due to both technological advances and identified emerging weaknesses identified in the regulatory framework, a public consultation was launched in 2008 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. The IVD Directive 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.

[81] http://ec.europa.eu/health/ph_information/dissemination/documents/com2009_380_en.pdf
[82] http://ec.europa.eu/health/ph_information/dissemination/documents/rec2009_379_en.pdf
[83] http://ec.europa.eu/health/ph_information/dissemination/diseases/docs/com_2009_291.en.pdf
[84] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:207:0014:0029:EN:PDF

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.

The EU-funded Network of Excellence EuroGentest[85] has produced a position paper[86] 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[87] 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 to the consultation robustly supports the retention of the exemption, while emphasising that patient safety should be ensured by restricting it to accredited laboratories. The results of the public consultation were published in February 2011[88].

[85] http://www.eurogentest.org/web/index.xhtml
[86] http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/public_consultation_ivd_final_en.pdf
[87] http://www.eurogentest.org/laboratories/qau/info/public/unit1/qmanagement/accreditation.xhtml
[88] http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/ivd_pc_outcome_en.pdf

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[89] and the *Orphanet Report Series* lists EU-funded collaborative projects in the field of rare diseases[90].

The FP6 ERA-Net for research programmes on rare diseases (E-Rare)[91] 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.

[89] http://cordis.europa.eu/lifescihealth/major/rare-diseases-projects-1.htm
[90] http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf
[91] http://www.e-rare.eu/

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

The Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7, 2007-2013 [92]) 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 2007–2010, 50 research projects with an EU contribution of over €237 million are being supported. They will ultimately lead to better diagnostic methods, new treatments, better care and prevention strategies for rare diseases.

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

The "Cooperation" 2010 work programme of the Health Theme[93] also called for an ERA-Net on rare diseases. The ERA-Net project E-Rare-2[94], 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.

A list of FP7 projects is provided on the Cordis website[95] and the *Orphanet Report Series* lists EU-funded collaborative projects in the field of rare diseases[96].

2.3. The International Rare Disease Research Consortium (IRDiRC[97]) (2010)

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[98] 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

[92] http://cordis.europa.eu/fp7/home_en.html
[93] ftp://ftp.cordis.europa.eu/pub/fp7/docs/wp/cooperation/health/a_wp_201001_en.pdf
[94] http://www.e-rare.eu/
[95] http://ec.europa.eu/research/health/medical-research/rare-diseases/projectsfp7_en.html
[96] http://www.orpha.net/orphacom/cahiers/docs/GB/Networks.pdf
[97] http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html
[98] http://ec.europa.eu/research/health/medical-research/rare-diseases/events-03_en.html

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[99], the Human Metagenome Consortium[100], the Cancer Genome Consortium[101] and the International Human Epigenome Consortium[102], 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 a future 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 failure rate (currently 85% after Orphan Drug 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[103] 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 who 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.

[99] http://www.knockoutmouse.org/
[100] http://www.metagenome.jp/
[101] http://www.icgc.org/
[102] http://www.epigenome.org/
[103] www.erditi.org

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[104] and official launch of the International Rare Disease 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.

Governance

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. Membership of the Executive Committee will require a minimum investment of $10 million over 5 years. To be considered, calls for proposals need to explicitly indicate the contribution towards IRDiRC objectives. Investments from 1 January 2010 contributing to the initiative objectives will be considered for membership. "Letters of Intent" concerning IRDiRC membership must be signed by the authorising official committing the research funds, and the letter should be addressed to the Interim Chair. A template letter of intent is made available through the EC website.

Policy Development

Working groups to develop the draft policy document have been established. These groups will develop the necessary policies that will foster international collaboration and ensure that results from invested research can rapidly be translated to diagnostics and treatments benefiting the patients.

Such policies include: harmonization and standardisation of data and research results, access to data, best practices, communication and intellectual property aspects. These policies will support the development of biomarkers for diagnosis and therapy development, model systems (in vitro and in vivo models), pre-clinical development and clinical trials.

A short summary of the overarching policies was developed, while the complete draft policy document should be available by September 2011 for further discussion at the next meeting. A number of working groups have been identified: genomic analyses, animal and *in vitro* models, ontologies, natural history, biomarkers, patient registries/biorepositories, preclinical research/clinical trials, communication of the consortium (also to deal temporarily with IPR and centralise information from other working groups on data sharing policies), information on rare diseases.

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 next call for proposals (Work Programme 2012).

[104] http://ec.europa.eu/research/health/medical-research/rare-diseases/events-04_en.html

The next meeting of IRDiRC will be organised by CIHR in Montreal on 8 and 9 October 2011. Governance procedures should be agreed, and the draft policy document developed by working groups will be reviewed.

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

The Open Access Infrastructure for Research in Europe (OpenAIRE[105]) 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[106] describes the launch as *"… an important step towards full and open access to scientific papers that could, for example, allow patients with rare illnesses to have access to the latest medical research results, or provide scientists with real-time updates about developments in their field"*. The new structure is part of a larger bid to develop research infrastructures and e-infrastructures that can help boost Europe's competitiveness. According to the press release, only 15%-20% of some 2.5 million research articles published annually are available via open access journals or repositories. OpenAIRE originates from a European Commission pilot initiative that was launched in August 2008. FP7-funded projects *"are requested to deposit peer-reviewed papers in online repositories and to provide open access within 6 or 12 months after publication depending on the thematic area"*. Increasing access is particularly good news for the fields of rare disease and orphan drug 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.

[105] www.openaire.eu

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

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

Before 2010, responsibility for pharmaceuticals at EC level lay with the EC Directorate General (DG) Enterprise and Industry. It was announced at the end of 2009 that the portfolio of the EC Directorate General for Public Health and Consumers would be expanded to take responsibility for pharmaceuticals, including the European Medicines Agency (EMA)[107]. This change is in line with the political organisation of Member States, where policy for medicinal products is generally the responsibility of the country's health department.

The European Commission is responsible for proposing pharmaceutical legislation. The European Parliament and the Council as the Community legislators then adopt and maintain legislation in this field.

The European Commission adopts decisions on the marketing authorisation for medicinal products at EU level and on the designation of orphan medicinal products.

3.1. European legislation concerning orphan medicinal products and related activities

Orphan Medicinal Product Regulation (16 December 1999)

The orphan medicinal product regulation (Regulation (EC) No 141/2000)[108] was adopted in December 1999 and came into force in the European Union in 2000.

The Orphan Drug Regulation addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides for incentives for products receiving an orphan designation. The incentives contained in the legislation aim to assist sponsors receiving orphan drug designations in the development of medicinal products with the ultimate goal of providing medicinal products for rare diseases to patients.

Orphan designation is based on a number of criteria: the prevalence of the condition; the return generated by the product would be insufficient to justify investment; the severity of the condition; and the existence of alternative products. The first two criteria are mutually exclusive, whilst the third and fourth criteria always have to always be addressed. To receive designation, a product must target a life-threatening or chronically debilitating condition that affects no more than five in 10,000 persons (which currently corresponds to about 250,000 persons in the EU). Many rare conditions have a much lower prevalence.

Alternatively to the rarity of the condition, sponsors can also apply if they are able to justify that without incentives the development costs of the product will not be recovered by the return obtained once the product is on the market. Any application for orphan drug designation must also describe all authorised methods of treatment (or diagnosis or prevention, as applicable) existing for the orphan indication being applied for; in cases where authorised products already exist for the condition, the sponsor is asked to justify what the significant benefit would be for patients who would receive the proposed orphan product. For example, what would be the clinically relevant advantage for patients, or how would the drug contribute to their care[109]? Normally the criterion of significant benefit is assessed at a very early stage in the drug development process, therefore at the time of designation the arguments are usually based on assumptions

[107] This section is based on and includes information from http://www.ema.europa.eu/ and www.emea.europa.eu. Before 2010 the EMA was known as the EMEA.

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

[109] This is the definition of significant benefit, as defined in the implementing regulation (EC) No 847/2000.

that will have to be confirmed at the time of marketing authorisation, when also efficacy and safety data are available.

The economic and regulatory incentives laid down in this regulation aim to assist sponsors in the development of medicinal products for rare diseases and include: the direct access to the Centralised Procedure for Marketing Authorisation, a 10 year period of market exclusivity 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.

Reduced fees for designated orphan drugs (1 February 2009)

As of 1 February 2009, designated orphan medicinal products are now 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 states: *"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"*[110].

10th Anniversary of the Orphan Medicinal Product Regulation (May 2010)

In May 2010 the European Medicines Agency (EMA) celebrated the tenth anniversary of Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products (Orphan Drug Regulation), along with Commission Regulation (EC) No 847/2000 defining the provisions for implementation of the criteria for orphan designation.

The EMA's Committee for Orphan Medicinal Products (COMP[111]), created in the year 2000 to review designation applications, has received some 1'235 applications for orphan designation in the past decade. Of these, more than 850 have been granted orphan status by the European Commission, and 63 products have crossed the finish line to receive marketing authorisation in the European Union based on a positive opinion from the COMP[112]. The number of applications for orphan designation has steadily increased, from 72 in the year 2000 to 174 in 2010. While oncology products receive the greatest share of COMP positive opinions (40%), immunology, cardiovascular and respiratory, metabolism, musculoskeletal, nervous system, and anti-infectious indications are also represented. The EMA celebration in London brought together participants from the European Parliament, the European Commission, international and European regulatory agencies, COMP members, patient groups, health professionals, and members of the biopharmaceutical industry. During the two-day event, participants reviewed the impact of the Orphan Drug regulation and examined future challenges.

The conference participants agreed that the orphan legislation in Europe has been an unprecedented success. The continued interest in the orphan designation process shown by the pharmaceutical industry indicates that orphan-designated medicines will keep coming to the market at a steady rate and therefore providing new treatment options for patients with rare diseases. The Agency expects that an increasing number of new marketing authorisation applications will relate to complex, innovative medicines, such as advanced therapies medicinal products (gene therapy, somatic cell therapy or tissue engineered products). Nevertheless the number of diseases without satisfactory treatments or even a single pharmacological therapeutic option is still extremely high and needs continuous support in terms of scientific and economic resources.

While the future for authorised orphan-designated medicines is promising, there is some concern that not all patients, who need to, have access to these medicines in the European Union because of the high costs

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

[111] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000123.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028e32

[112] Source: *Nature Reviews: Drug Discovery "European regulation on orphan medicinal products: 10 years of experience and future perspectives"* COMP/EMA Scientific Secretariat, Volume 10, May 2011: http://www.ncbi.nlm.nih.gov/pubmed/21532564

of treatment. Increased transparency of scientific decision-making and collaboration between Health Technology Assessment (HTA) bodies to identify the best ways to share information is of paramount importance to address tensions about the pricing of orphan medicines. Moreover, making more and better treatments available for patients with rare diseases will require global collaboration. Participants also celebrated the growing collaboration between Europe and the USA, resulting in the harmonisation of administrative procedures, the most recent of which is the streamlined procedure for the annual report for orphan designated products.

The workshop participants agreed that other aspects such as post-marketing safety surveillance studies or handling of supply issues would also benefit from increased multi-national cooperation and should be tackled at a global scale.

Another topic of discussion concerned the post-marketing studies for products granted conditional authorisation. How to best organise registries and how to enhance access to the vital data they contain? The issue becomes more complex when there is more than one product on the market or under development for the same indication. How to promote collaboration within industry and encourage data sharing between industry and academia and the patient organisations? Another consideration involves incorporating data from untreated patients. The data from registries could provide national authorities with crucial information for cost assessment and reimbursement purposes. It was suggested that the EMA could take a regulatory role in establishing and managing post-marketing registries.

There was also the perspective of the patients, offering their analysis of what is still needed to encourage the development of more products for rare conditions. The desire for a "one-stop shop" to chaperone products through the entire development procedure was echoed. Patient representatives also called for improvements to the current pricing and reimbursement systems. This is a challenge that needs to address the current system of assessing drugs at the national level, which results in marked disparity in availability between countries.

Participants also celebrated the growing collaboration between Europe and the USA, resulting in the harmonisation of administrative procedures, the most recent of which is the streamlined procedure for the annual report for orphan designated products.

In honour of the Regulation's tenth birthday, staff from the Orphan Section at the EMA published an article in the journal *Drug News and Perspectives* entitled *European Medicines Agency Support Mechanisms Fostering Orphan Drug Development*[113]. Offering a review of how the orphan drug legislation operates and a consideration of the impact the regulation has had over the past decade.

Molecules and other substances receiving an orphan designation are entered in the Community Register for Orphan Medicinal Products[114]. The EMA issues a detailed report listing positive opinions following each COMP meeting, including summaries for the public. Orphanet also keeps close tabs on orphan drug activity. The List of Orphan Designations in the Orphanet database includes all substances which have been granted an orphan designation for disease(s) considered rare in Europe, whether or not they have been developed into drugs with marketing authorisation. The Orphanet Report Series[115] itemises all medicinal products in Europe with marketing authorisation for rare conditions and provide indication details. Data on products with marketing authorisation and/or orphan designation are cross-referenced by trade name, authorisation date; Anatomical Therapeutic Chemical (ATC) classification; and by authorisation holder. Available in English, French, German, Italian and Spanish, this information is regularly updated.

It is expected that all the various registers and listings for orphan designated substances and market authorised products will expand significantly in the next ten years of the Orphan Drug Regulation under the efficient guidance of the COMP, the CHMP, the CAT and the entire EMA. Many of the keynote lectures from the 10 Years of the Orphan Regulation in Europe workshop are available for consultation on the EMA website[116].

[113] http://www.ncbi.nlm.nih.gov/pubmed/20155221
[114] http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm
[115] http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf
[116] http://www.ema.europa.eu/meetings/conferences/03may10.htm

3.2. The European Medicines Agency's (EMA) activities in the field of orphan medicinal products and therapies for rare diseases

European Medicines Agency[117]

The European Medicines Agency (EMA) is a decentralised body of the European Union, located in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

The Agency is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines (centralised procedure). Under the centralised procedure, companies submit a single marketing-authorisation application to the Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralised procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.

The Agency constantly monitors the safety of medicines through a pharmacovigilance network, and takes appropriate actions if adverse drug reaction reports suggest that the benefit-risk balance of a medicine has changed since it was authorised.

The Agency also plays a role in stimulating innovation and research in the pharmaceutical sector. The Agency gives scientific advice and other assistance to companies for the development of new medicines. It publishes guidelines on quality-, safety- and efficacy-testing requirements. A dedicated SME Office, established in 2005, provides special assistance to small and medium-sized enterprises.

Six scientific committees, composed of members of all EU and EEA-EFTA states, some including patients' and doctors' representatives, conduct the main scientific work of the Agency: the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT). In 2012 a new committee (Pharmacovigilance Risk Assessment Committee) will start working at the Agency as a result of the implementation of the new pharmacovigilance legislation, which amends existing legislation. This was adopted in the European Union in December 2010. The legislation aims to strengthening the European-wide system for monitoring the safety of medicines. The new legislation amends existing pharmacovigilance legislation contained in Directive 2001/83/EC and Regulation (EC) No. 726/2004. The Pharmacovigilance Risk Assessment Committee will be responsible for providing recommendations to the Committee for Medicinal Products for Human Use and the coordination group on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems and it will be responsible for monitoring the effectiveness of those risk management systems.

The Agency works with a network of over 4,500 'European experts' who serve as members of the Agency's scientific committees, working parties or scientific assessment teams. These experts are made available to the Agency by the national competent authorities of the EU and EFTA states.

The Agency can be considered as the 'hub' of a European medicines network comprising over 40 national competent authorities in 30 EU and EEA-EFTA countries, the European Commission, the European Parliament and a number of other decentralised EU agencies. The Agency works closely with its European partners to build the best possible regulatory system for medicines for Europe and protect the health of its citizens.

In view of the continuing globalisation of the pharmaceutical sector, the Agency works to forge close ties with partner organisations around the world, including the World Health Organization and the regulatory authorities of non-European nations. The Agency is continually involved in a wide range of cooperation activities with its international partners, designed to foster the timely exchange of regulatory and scientific expertise and development of best practices in the regulatory field.

[117] Information reproduced from http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028a42

The Agency is also involved in referral or arbitration procedures relating to medicines that are approved or under consideration by Member States in non-centralised authorisation procedures.

EMA re-organisation in 2010

The EMA has undergone a significant shift in structure in 2009. In a press release issued in December 2009, the EMA describes the re-organisation as encompassing *"the integration of human pre- and post-authorisation activities into one unit, to guarantee seamless lifecycle-management of medicines. The creation of a new unit for patient health protection further strengthens the Agency's focus on safety-monitoring of medicines. In addition, a dedicated group for the management of product data and documentation will improve the efficiency of data management processes throughout the Agency"*. Furthermore, the acronym changed from EMEA to EMA, reflecting the shortening of the agency's original name, from the *"European Medicines Evaluation Agency"*, which has not been used for several years now, to the *"European Medicines Agency"*.

EMA Work Programme 2010

The EMA adopted its work programme for 2010[118] in December 2009. The work programme cited a number of new issues and trends in relation to the field of orphan drugs, including the increasing percentage of molecular and personalised medicines and of advanced therapies in the orphan product segment, and the continued international collaboration with regulatory authorities (i.e. implementation of EMA/USFDA common application form, expected increase in parallel submissions with the US FDA, and analysis of different designation practices between the US FDA and the EMA). Amongst the objectives cited for 2010 were to increase communication related to orphan designation activities and to review and analyse the first 10 years' of activities in the field of rare diseases since the entry into force of the Regulation (EC) No 141/2000 on orphan medicinal products.

EMA Work Programme 2011

The European Medicines Agency (EMA) adopted its Work Programme for 2011[119] in December 2010. The 2011 Work Programme outlines its strategic and budgetary agenda for the year. Section 2.1 is dedicated to Orphan Medicinal Products. Amongst new issues figuring in 2011's work programme is the anticipated increase in the volume of applications stemming from the consequence of the Agency's rare diseases policy (including due to collaboration with the FDA and continuous support to rare diseases provided by DG Research and DG Health and Consumers).

The work programme also highlights the development of activities following the Pharmaceutical Forum conclusions on health technology assessment bodies for orphan medicines, in particular through the Clinical Added Value of Orphan Drugs (CAVOD) initiative. The Work Programme estimated that some 180 applications for orphan designation will be received in 2011, revealing a sustained, slightly increasing volume (173 were received in 2010). Amongst the objectives and initiatives for the year are the maintenance of core activities and reaching an agreement on the framework for collaboration as part of the developing collaboration with the Commission and Member States HTA bodies on added value of orphan medicinal products. In terms of Scientific Advice and Protocol Assistance, the EMA anticipates growth in the number of applications with 73 in 2011 compared to 68 in 2010. The work programme points at adaptive and other innovative designs of clinical trials and use of biomarkers as endpoints in clinical trials as topics to be particularly relevant for 2011. Also it is expected an increase uptake of biomarker qualification and the novel-methodologies procedures. Interactions with health technology assessment bodies and with national authorities providing scientific advice will become more important.

EMA Road Map to 2015

In late 2010, the EMA's Management Board adopted the new Road Map to 2015 that takes into account the public consultation[120] held in the first half of 2010 that brought responses from *"EU institutions, Member States, and organisations representing patients and consumers, healthcare professionals, pharmaceutical industry, academia and health technology assessment bodies"*. The new plan builds upon the accomplishments made from the objectives of the 2005-2010 strategy and continues to focus on the *"high-quality delivery of the Agency's core business in an increasingly complex regulatory and scientific environment"*. In the new plan, three priority areas have been identified: Addressing public health, Facilitating access to medicines, and Optimising

[118] http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2010/03/WC500075892.pdf
[119] http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2010/01/WC500046686.pdf
[120] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf

the safe use of medicines. The proposed vision also specifies that *"another aspect which will remain high on the public health agenda relates to the availability of medicines for rare diseases and other current unmet medical needs such as medicines for the paediatric population"*. Particularly relevant to rare diseases, Strategic Area 1 includes amongst its objectives the stimulation of medicine development in the areas of unmet medical needs, including rare disorders. To address the challenge of existing gaps in medicine development, the EMA proposes undertaking an analysis of *"the reasons for discontinuation of the development of medicines for human use starting with selected designated orphan medicines and propose remedial action. Any solution should favour a holistic approach, including the use of novel endpoints, different study designs and a more appropriate use of the accelerated assessment scheme for medicines intended for unmet medical needs, rare diseases and neglected diseases in the EU and beyond"*.

The final Road Map was published in January 2011[121] and detailed information on the implementation of the road map will be provided in the document 'From vision to reality', to be published in the course of 2011.

EMA annual reports (2010)

The European Medicines Agency Annual Report for 2010 recognises the increasing volume of core business activities and the achievement of a number of "important milestones" such as the launching of the new website, the publication of new rules on conflicts of interests and the new policy on access to documents. Another important development in 2010 was the publication of a report on the evaluation of the Agency and the European medicines network carried out by Ernst & Young on behalf of the European Commission. The report shows that the European medicines network, i.e. the Agency, the European Commission and the national competent authorities in the Member States, has been successful in delivering high-quality scientific opinions on medicines for human and veterinary use in an efficient and effective manner.

In 2010 the EMA received 174 orphan designation applications, of which 123 positive opinions were issued by the Committee for Orphan Medicine Products (COMP). Of these, oncology products once again were in the majority. In 2010, almost half of orphan designations concerned products for paediatric populations. In terms of marketing authorisation, there were 12 orphan drug applications amongst the total 91 requests, quite similar to 2009 (11 applications). Of the 53 new products receiving marketing authorisation in 2010, six were new orphan medicines. Amongst the medicines of notable public-health interest that received a positive opinion from the CHMP in 2010 the report highlights a designated orphan medicine intended for the treatment of Gaucher disease (major public-health interest in the light of the shortage of the authorised medicine for the treatment of this disease) , designated orphan medicines intended for the treatment of pulmonary conditions (one for suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in cystic fibrosis, and another for idiopathic pulmonary fibrosis), a designated orphan medicine intended for the treatment of inborn errors in primary bile acid synthesis due to enzyme deficiencies and an orphan medicine intended for the treatment of patients with chronic lymphocytic leukaemia.

The report also documents the ongoing protocol assistance for orphan medicinal product development, continued support for small and medium-sized enterprises (SMEs development). Finally, the report outlines the considerable activities undertaken to strengthen and expand European and international cooperation and to further engage consumers, patients, and health professionals. The actions to improve communication and transparency are also detailed. A full report is available online[122].

EMA evaluated for efficiency and efficacy (2010)

The European Medicines Agency (EMA) underwent a year-long evaluation process conducted by global auditors Ernst and Young of which the results were published in early 2010[123]. Designed to assess the effectiveness and efficiency of the EMA, the evaluation, consisting of interviews, surveys, observations and case studies, shined a light into every corner of the EMA, examining the centralised and decentralised procedures of the agency. Working closely with EMA staff, National Competent Agencies (NCA), experts, industry, patient organisations and external stakeholders, recommendations to optimise the agency's operations and strategies emerged around eight main topics: the organisation of the various EMA committees; NCA involvement in EMA work; the role of the EMA Secretariat; Procedures; Communication; Industry fees; Telematics; and Future challenges.

According to the audit, the EMA *"appears to be a learning organisation that shows a permanent willingness to develop an ongoing improvement process. However the higher complexity and enlarged scope of*

[121] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf
[122] http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2011/06/WC500108073.pdf
[123] http://ec.europa.eu/enterprise/dg/files/evaluation/final_report_emea_january_2010_en.pdf

responsibility and activities reveal some weaknesses associated with their specific risks. The system is progressively attaining its maximum capacity."

The audit singles out the Committee for Orphan Medicinal Products (COMP) as a success: *"Both the industry and other stakeholders tend to agree that the creation of COMP and related incentives have had a positive impact on research and development for specific products for orphan diseases. The procedure showed immediate success, with 83 submissions in 2001. This number has increased until 2005, when it stabilized around 120 submissions per year (with the exception of 2006). This coincided with a global increase and stabilisation in the number of authorised medicinal products for orphan diseases, with an average of 12.5 new medicinal products/year receiving approval from the CHMP for orphan diseases during the 2001-2008 period (range: 7-18, vs. only 2 in 2000)".*

The report observes that *"... the careful consideration of whether a population can be considered as an orphan population may become a more complex issue in the future. Indeed, the trend towards the development of targeted therapies and personalised medicine could lead to more and more segmentation of patient populations into sub-populations. The rationale for such segmentation should be carefully monitored, as these subgroups may end up meeting the criteria for orphan status, while being sub-indication of a non-orphan disease. More applications of this type may lead to an increase of COMP's workload in the near-future"*. Furthermore, the COMP's *"sustainability may be put at stake both because the system may not appropriately compensate NCAs for their involvement ... Although the current orphan products policy is unanimously recognized as having very positive outcomes, most stakeholders have expressed their concern over two subjects. First, some interviewees doubt the sustainability of a system that does not allow directly Rapporteurs and Co-Rapporteurs' compensation and which budget has significantly increased in recent years. ... Second, although orphan medicines do reach the market more easily than they used to, their reimbursement is a raising issue at the national level. While this matter does not strictly enter the scope of the EMA, the unwillingness of national reimbursement bodies to pay for medicines that end up being very expensive and treating a very small population may on the long run undermine EMA efforts to provide all patients with new and accessible medicines".*

While the EMA has contributed to the harmonisation of the EU internal market for medicines, the audit reports that *"many stakeholders regret that medicines' distribution falls out of the EMA scope. However, the industry provides already the EMA with some data about the distribution of authorised products according to the so-called "Sunset clause" (requirement for centrally authorised products to be placed on the European market within three years of the authorisation being granted). Monitoring such data with a look on the availability of authorised products in each Member State may allow the EMA to identify main weaknesses of the system. As pointed out in the first objective of the EC Communication on the future of the pharmaceutical sector, adopted on December 10th, 2008, this challenge may require political actions both at EU and Member States level: options to improve the availability of medicinal products for patients in need, with a particular focus on smaller markets should be developed in close cooperation with Member States by 2010"*.

3.3. EMA Committee for Orphan Medicinal Products' (COMP) activities

EMA Committee for Orphan Medicinal Products (COMP)

Since 2000, there is a Committee for Orphan Medicinal Products[124] (COMP) at the European Medicines Agency (EMA). The COMP is comprised of health professionals representing each of the Member States, three patient representatives, and three other representatives nominated by the EC after recommendation from the EMA. The Committee meets once a month and it is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union. The Commission adopts decisions on designation based on an opinion from the COMP. The EMA maintains a searchable list of opinions on rare disease (orphan) designations[125]. The full list of orphan designations granted by the European Commission is available in the Community register of orphan

[124] This section reproduces information from http://www.ema.europa.eu/htms/general/contacts/COMP/COMP.html

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

medicinal products for human use held by the European Commission[126]. The COMP is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU, and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products.

The development of orphan medicinal products is supported by incentives for development and placement on the market as provided for in the Orphan Regulation. The Scientific Advice Working Party in collaboration with the COMP offers protocol assistance to provide advice on the development of orphan drugs with regards to regulatory, quality, safety and efficacy issues.

The COMP is presently chaired by Professor Kerstin Westermark (Sweden) and co-chaired by Ms Birthe Byskov Holm (Patient Representative, Denmark). The COMP was a pioneer in including patient representatives as full members and the experience has illustrated the great added-value of this collaboration, which contributes to the quality of the opinions adopted for orphan designation.

Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (March 2010)

The COMP adopted in March 2010 a Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMEA/COMP/15893/2009)[127] after a public consultation launched in January 2009. This document is a review of an earlier document, aiming at outlining the level of evidence normally required to support the medical plausibility of using the product in the applied condition, and the evidence required to support the assumption of significant benefit. The document is based on the experience accumulated by the COMP with several hundred orphan drug designation applications, of which around 70% included a discussion on significant benefit since satisfactory methods for diagnosis, prevention or treatment existed in the EU at the time of the submission of the application for orphan designation. General guidance on what is considered necessary support 'medical plausibility' at the time of the submission of an orphan designation application and on what is necessary for the justification of the assumption of 'significant benefit' if this criterion applies. This is included in the "Commission Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another" (ENTR/6283/00) and in the "Communication from the Commission on Regulation (EC) 141/2000 of the European parliament and of the Council on orphan medicinal products" (Commission Communication 2003/C 178/02 of 29 July 2003). The Recommendation adopted by the COMP should thus be read in conjunction with these documents and is aimed at being incorporated into the above mentioned guideline on format and content.

COMP makes public outcomes of reviews for orphan designation (April 2010)

In the April 2010 monthly report[128] of the European Medicine Agency's Committee for Orphan Medical Products (COMP), the intention to make public the outcomes of the reviews for orphan designation was announced. As part of an effort to enhance transparency, the EMA will publish a document Designed to *"…summaris[ing] the review of the orphan designation carried out by the Committee for Orphan Medicinal Products (COMP) whenever an orphan medicine reaches marketing authorisation …the review is carried out to check that the criteria underpinning the medicine's orphan designation still apply"*. A discussion of the justification of significant benefit over existing authorised treatments will be included in these public "Review of orphan designation" documents.

In mid-September 2010, the first published review document was announced for the product Vpriv (velaglucerase alfa)[129], which received marketing authorisation in late August of this year for the treatment of Gaucher disease. As part of the its effort to enhance transparency of the orphan designation process, the EMA has completed the publication of reports for all products reviewed in 2010 and is publishing prospectively a review document for each orphan-designated product at the time marketing authorisation is granted, as well as for all approved extensions of indication for orphan-designated products already on the market.

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

[127] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf
http://www.orphandrugexperts.com/downloads/COMP%20paper%20on%20medical%20plausability.pdf

[128] http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2010/04/WC500089471.pdf

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

Annual report guidance for orphan designations updated (2010)

Sponsors of designated orphan medicinal products are required to submit to the European Medicines Agency an annual report on the development of their product. The note for guidance[130] on the format and content of this annual report has been updated by the COMP in early 2010, taking into account the new harmonised procedures between the EU and the USA.

3.4. EMA Committee on Human Medicinal Products (CHMP) activities

EMA Committee on Human Medicinal Products (CHMP) and compassionate use

Before a medicinal product can be marketed in the European Union (EU) by a pharmaceutical company, the product must receive a marketing authorisation. However, for patients suffering from a disease for which there is no satisfactory authorised alternative therapy, Article 8 of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European medicines Agency, provides for the possibility to allow pharmaceutical companies to supply a product which has not received a marketing authorisation via a compassionate use programme[131]. This is intended to facilitate the use of new treatment options under development. Such usage is particularly pertinent in the field of rare diseases, where the lack of existing treatments and the chronic nature of many disorders can be critical for patients.

While the implementation of compassionate use falls within the competence of each Member State, Article 83 of Regulation (EC) No 726/2004 complements national legislation and provides for an option of adoption by the European Medicine Agency's Committee on Human Medicinal Products (CHMP) Opinion concerning the compassionate use of a particular medicinal product. Article 83 specifically seeks to *"facilitate and improve the access of patients in the EU to compassionate use programmes; favour a common approach regarding the conditions of use, distribution and the patients targeted for the compassionate use of unauthorised new medicinal products; and increase transparency between member states in terms of treatment availability"*. While the implementation of these recommendations is not mandatory, Member States can take them into consideration when setting up compassionate use programmes.

CHMP opinions in 2010 concerning orphan medicinal products

In 2010, the CHMP issued positive opinions for applications for extensions of the therapeutic indications, adding new treatment options for medicines that are already authorised in the European Union, to Sprycel (dasatinib) to include the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in the chronic phase and to Sutent (sunitinib) to include the treatment of unresectable metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

In 2010, the CHMP also recommended[132] that physicians switch back to prescribing the full dose of Fabrazyme according to the authorised product information, depending on the availability of enzyme replacement therapy and the severity of the disease. Temporary treatment recommendations to manage patients relying on this medicine have been in place since the start of the supply shortage and have been regularly updated.

[130] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/12/WC500025681.pdf

[131] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058007e691&jsenabled=true

[132] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/10/news_detail_001136.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

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

Regulation of Clinical Trials[133]

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"[134]). In its Communication of 10 December 2008 to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on "Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector", the Commission announced that an assessment would be made of the application of the Clinical Trials Directive. This assessment would consider, in particular, various options for improving the functioning of the Clinical Trials Directive with a view to making legislative proposals, if appropriate, while taking the global dimension of clinical trials into account.

The Clinical Trials Directive was reinforced by the "Commission Directive 2005/28/EC[135] 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[136] 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[137]).

A European database – EudraCT[138] – contains all ongoing or completed interventional clinical trials of medicinal products falling within the scope of Directive 2001/20/EC, i.e. with at least one investigator site in the EU (including the European Economic Area) and commencing after implementation of the Directive 2001/20/EC by the Member States. This database gives the competent authorities of the Member States, EMA and the Commission the necessary information to communicate on clinical trials and to maintain oversight of clinical trials and IMP development. This provides for enhanced protection of clinical trial subjects and patients receiving IMPs.

Paediatric clinical trials that form part of a Paediatric Investigation Plan (PIP)[139], but that are conducted in third countries, will also be included in the near future (paediatric clinical trials with sites in the EU/EEA are already available).

Assessment of the EC Clinical Trials Directive (2008-2009)

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 came under fire from 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[140]. 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

[133] This section reproduces information from http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index_en.htm (March 2010)
[134] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF
[135] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF
[136] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0067:EN:PDF
[137] http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_en.htm
[138] https://eudract.ema.europa.eu/
[139] http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true
[140] http://www.orpha.net/actor/EuropaNews/2006/060409.html#EUPol

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[141] 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 drug trials. The survey detected a significant increase from 2003 to 2007 in the number of biotechnology product and orphan drug trials, considered to reflect more the new orphan drug 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.

Following, amongst other things, the results of ICREL project, the European Commission has consequently issued a legislative proposal[142] on a Regulation/Directive amending the Clinical Trials Directive 2001/20/EC. Whether the current legislation is to be amended or an entirely new regulation will be introduced is still uncertain. With the particular challenges and cost concerns of the average rare disease clinical study, the revision of the Clinical Trials Directive is a matter of great importance.

Reflection paper on ethical and good clinical practice considerations for trials in third countries (2010)

There are a significant number of clinical studies that recruit patients from several regions – including countries outside the European Economic Area – for products that will be submitted for marketing authorisation within the EU. The European Medicines Agency issued a reflection paper[143] in 2010 considering ethical and good clinical practice aspects for such trials conducted in third countries. The paper, open for consultation until 30 September 2010, sought to ensure that so-called third country trials (countries beyond the European Economic Area) are conducted in accordance with existing principles of good clinical practice and ethical requirements. Such considerations are relevant to rare disease clinical trials, which, due to sparse and scattered patient populations, may indeed involve third country participation. For this population, post-trial treatment access is a particularly pertinent topic, especially for the often-expensive orphan drugs.

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

Regulation on Advanced Therapies (13 October 2007)[144]

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

[141] http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf
[142] http://ec.europa.eu/governance/impact/planned_ia/docs/47_sanco_clinical_trials_directive_en.pdf
[143] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/06/WC500091530.pdf
[144] This section reproduces information from http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/advanced-therapies/

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 Therapies (Regulation (EC) 1394/2007[145]) 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.

EMA scientific committee for advanced therapy products (CAT)

The EMA announced at the start of 2009 the formation of the Committee for Advanced Therapies (CAT)[146] – the EMA's sixth scientific committee. Created following new European Union legislation concerning the regulation of advanced-therapy medicinal products, the CAT met for the first time on 15 January 2009. Three types of advanced therapy products defined in the EU legislation: gene therapy products, somatic cell therapy products and tissue engineered products. Such developments offer great potential for the treatment of rare diseases. The CAT will "prepare a draft opinion on each advanced-therapy medicinal product (ATMP) submitted to the EMA for evaluation as part of a marketing-authorisation application, prior to the adoption of a final opinion by the Committee for Medicinal Products for Human Use (CHMP)" which will be submitted to the European Commission for decision.

Three ATMP applications have been received since the CAT was created, of which one was for a rare condition: Cerepro, which received an orphan medicinal designation on 6 February 2002 for the treatment of high-grade glioma with subsequent use of ganciclovir sodium, received a negative draft opinion from the CAT. A press release issued for the CAT's anniversary stated that the committee received 22 requests for classification in 2009 – a procedure that allows companies to verify whether the product they are developing meets the definition of an advanced therapy product and can benefit from the new regulatory pathway for these products. The press release also discloses that one *"request for certification of quality and non-clinical data from small and medium-sized enterprises (SMEs) developing ATMPs has been received. This is another new procedure introduced by the legislation on ATMPs and is aimed at providing an incentive to SMEs to conduct necessary studies to further develop their product"*. Companies developing advanced therapy medicinal products can obtain reductions in certain EMA fees including: *"65% for a request for scientific advice (90% for small and medium-sized companies); and 50% for an application for a marketing authorisation, in cases where the applicant is a hospital or small/medium-sized company and can prove that its product is of a particular public-health interest"*. The experts making up the CAT also offer scientific advice as requested.

The European Medicines Agency and its Committee for Advanced Therapies issued in April 2010 a statement[147] of concern over the practice of offering unregulated stem cell products to patients for a variety of

[145] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

[146] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac05800292a4&jsenabled=true

[147] http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/04/WC500089472.pdf

disorders - including rare conditions. While such treatments are available under limited, strictly controlled circumstances - including clinical studies, compassionate use programmes, and hospital exemption - the use of such products outside these circumstances could be harmful. The statement reminds the public that no stem-cell product has been authorised by the EMA in the European Union to date.

The European Medicine Agency's Committee for Advanced Therapies (CAT) and the CAT Scientific-Secretariat contributed an opinion piece to *Nature Reviews Drug Discovery* in March 2010[148] in which the authors demonstrate the complexity involved with the burgeoning field of advanced therapy medicinal products (ATMP), encompassing gene therapy products, somatic cell therapy products and tissue-engineered products. Working within the regulatory parameters established under Regulation (EC) No 1394/2007, the CAT illustrates some of the complex issues inherent in both the development and the evaluation of ATMPs. As the authors point out, *"Many ATMPs will be developed for rare diseases. At the EMA, the Committee for Orphan Medicinal Products (COMP) is responsible for reviewing applications seeking orphan medicinal product designation for products that diagnose, prevent or treat life-threatening or serious conditions that affect less than 5 in 10,000 persons in the European Union. The CAT considers it important that there is an active and early link with the COMP for exchange of information on orphan ATMPs, which may qualify for orphan designation, and initial discussions have already commenced. Some of the CAT members were formerly members of the COMP, so there is already a clear understanding of the needs of orphan drugs in the CAT"*. The article underscores the regulatory advice that the EMA and CAT offer to drug developers stepping into this promising new field of drug development.

The European Medicines Agency's Committee for Advanced Therapies (CAT) has tested in 2010 its new certification system[149] created to facilitate the process of advanced therapy product development amongst small and medium sized enterprises (SMEs). The CAT's new certification procedure does not guarantee a marketing authorisation, but it sends a signal to potential investors that a sponsor is on the right track in terms of product development. An EMA press release elaborates that the certificate procedure, delineated in Commission Regulation (EC) No 668/2009 *"… foresees that an SME submits to the Agency data on the quality and where available non-clinical data generated with an ATMP from an early stage of development. The CAT carries out a scientific evaluation of these data and may recommend the issuing of a certificate confirming to what extent the data generated so far comply with the review standards that would be applied for the evaluation of a marketing authorisation application"*. This first certification opinion has been issued for a suspension of 5-50 107 mononuclear cells in 11 ml X-Vivo-10 medium containing 20 % autologous serum, indicated for acute myocardial infarction and chronic ischaemic heart disease.

The CAT released its Work Programme for 2010-2015 in 2010[150] with the overarching goal of bringing more advanced therapy products to the market. Measures, some of which are already underway, include "training and early dialogue" with relevant stakeholders and an examination of the existing regulatory framework with an eye to making it *"…more accessible for small and medium-sized enterprises, academia, patient groups, hospitals, charity foundations and trusts developing ATMPs".*

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

Regulation on Medicinal Products for Paediatric Use (26 January 2007)[151]

New legislation governing the development and authorisation of medicines for paediatric use (Regulation (EC) N° 1901/2006)[152] 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

[148] http://www.ncbi.nlm.nih.gov/pubmed/20190786

[149] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000300.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058007f4bd&jsenabled=true

[150] http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/11/WC500099025.pdf

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

[152] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF

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[153];
- 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 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.

Advances in the process of increasing transparency in clinical trials for children (February 2009)

New measures were moved forward in February 2009 to expand the transparency of information on clinical trials for medicinal products involving paediatric populations. The *Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMA), in accordance with Article 41 of Regulation (EC) No 1901/2006*[154], 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[155], 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

[153] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF
[154] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF
[155] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf
http://ec.europa.eu/health/files/clinicaltrials/technical_guidance_en.pdf

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[156]. 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[157].

3.8. Other EMA activities and initiatives relevant to rare diseases and orphan drugs

ENCePP E-Register of Studies (2010)

The European Medicines Agency (EMA) has announced the launch of the ENCePP E-Register of Studies, a publicly available electronic register developed with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[158] allowing users to consult the pharmaco-epidemiological and pharmacovigilance studies that are undertaken by academic centres and other research organisations. The E-Register offers a database resource of information on the safety and effectiveness of medicinal products. An added dividend of the E-Register is the contribution to the reduction of publication bias by *"…handling both positive and negative study results in the same manner and promote exchange of information, thereby facilitating collaboration within the scientific community and preventing unnecessary duplication of research"*. While the registration of a study in E-Register is completely voluntary, studies applying for the 'ENCePP Studies' seal that is *"awarded to wholly or partially EU-based, benefit/risk studies that are carried out in compliance with the ENCePP Code of Conduct for independence and transparency and the ENCePP Checklist of Methodological Research Standards"* need to register before they commence.

EMA Public Register for SMEs (2010)

The European Medicines Agency has launched in 2010 a public register[159] for small-and medium-sized enterprises (SMEs) that *"aims at facilitating and promoting interaction amongst SMEs"* by furnishing data, including contact information, areas of activity and number of employees, for SMEs registered with the agency. A second phase of the registry, available from the end of March 2011, will provide further details, including pipelines and product profiles. The new registry is part of a larger initiative to enhance transparency. It also reflects an ongoing effort of the EMA to support SMEs. The agency's SME Office, established in 2005, encourages smaller European companies developing innovative new medicines, which are particularly promising to the field of rare diseases, by providing incentives and assistance, such as regulatory assistance, aid with translations, fee reductions, exemptions, and deferrals. The SME Office was the recipient of a 2010 European Mediscience Award for *"Most significant contribution to the mediscience sector*".

[156] https://www.clinicaltrialsregister.eu/

[157] 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.

[158] http://www.encepp.eu/encepp/studiesDatabase.jsp

[159] http://fmapps.emea.europa.eu/SME/

3.9. EU-USA collaboration in the field of orphan medicinal products[160]

The European Union (EU), including the European Commission and the European Medicines Agency, has had confidentiality arrangements with the United States Food and Drug Administration (FDA) since September 2003. Under the agreement, both the EMA and the FDA can exchange confidential information pertaining to scientific advice, orphan drug designation, paediatric development, good manufacturing practice and good clinical practice inspection planning and reports, marketing authorisation procedures and subsequent changes to the marketing authorisations together with post-marketing surveillance as part of their regulatory and scientific processes. This includes information on advance drafts of legislation and regulatory guidance documents, as well as non-public information related to ensuring the quality, safety and efficacy of medicinal products for human and veterinary use. The agreement extends to medicines that are authorised at the national level by individual EU Member States, as well as those undergoing the centralised process. The extension is considered good news by the rare disease community, which counts on international cooperation to bring treatments to patients. The confidentiality agreements between the EU and the FDA were extended in 2005 and again in 2010[161]. They are now effective for an indefinite period without the need for further renewal.

As part of the ongoing confidentiality agreement between the European Commission, the European Medicines Agency, and the US Food and Drug Administration, a new initiative was launched for an 18 month pilot phase on 1 September 2009. The Good Clinical Practice Initiative - a reflection of both the increasing globalisation of clinical studies and limited inspection resources - defines its objectives as *"the sharing of information on inspection planning, policy and outcomes and the conduct of collaborative inspections"*. The small patient populations typically available for rare disease medicinal product trials dispose such trials to international participation. By harmonising inspection procedures, the new initiative is expected to play a key role in ensuring that trials are conducted under safe, ethical, and uniform conditions. One of the principle objectives for the pilot phase of the initiative includes the exchange of Good Clinical Practice-related information *"contained in applications for scientific advice, orphan medicines designation, paediatric investigational plans, marketing authorization or post-authorization activities of significant public health interest"*. In a press release, the FDA and EMA announced that they *"are looking to partner with applicants/sponsors who are willing to volunteer during the pilot phase of the initiative to engage in dialogue and planning of joint inspections involving applications that are anticipated to be submitted fairly simultaneously to both regulatory agencies within the next 12 months"*. The pilot phase will concentrated on a subset of regulated products, specifically those regulated by the Center for Drug Evaluation and Research (CDER) of the FDA and by the Agency for the centralised procedure in the EU.

The interaction between the Agency and the FDA has been supported further by the transatlantic administrative simplification action plan[162,163]. This plan was set up in November 2007 by the European Commission and the FDA, with the collaboration of the Agency and the Heads of Medicines Agencies. The plan aims to remove administrative burden in the interaction between medicines regulators in Europe and in the USA, while maintaining or increasing levels of public-health protection. In addition, since 2009, the FDA has seconded a permanent representative to the Agency's office in London. Since early 2010, this has been mirrored by the Agency seconding its own representative to the FDA's offices.

The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) moved their collaborative effort another step forward in late February 2010 with the introduction of an agreement that permits one single annual report to be submitted for orphan products designated in both the EU and the USA. Prior to this, sponsors with designations in both places were required to submit two separate reports detailing the progress of drug development, including *"a review and status of ongoing clinical studies, a*

[160] Information taken from the page http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000228.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176e&jsenabled=true#section2 (accessed 22/04/2011).

[161] http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000228.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176e&jsenabled=true#section2

[162] http://ec.europa.eu/health/files/international/doc/eu_fda_action_plan_200806_en.pdf

[163] http://ec.europa.eu/health/files/international/2009_tas_implementation_report.pdf

description of the investigation plan for the coming year, any anticipated or current problems in the process, difficulties in testing, and any potential changes that may impact the product's designation as an orphan product." In a press release, Professor Kerstin Westermark, the Chair of the EMA Committee for Orphan Medicinal Products observed that this new measure will provide each agency *"with information in real time on any challenges arising during the development of products for rare diseases and will help identifying and acting on bottlenecks."* Each regulatory body will continue to conduct its own assessment of the reports filed in order to appraise whether information satisfies the legal and scientific requirements of each agency. The option of submitting a single annual report to both agencies benefits sponsors by reducing the duplication of efforts. The new measure, unveiled on the occasion of Rare Disease Day 2010, is one of several streamlined initiatives the two agencies have undertaken in recent years as part of a transatlantic agreement designed to enhance cooperation between the two agencies.

Other initiatives include a pilot programme on joint good-manufacturing-practice (GMP) inspections for manufacturers of medicinal products in August 2010, and a three-year pilot was announced for April 2011, which will allow the parallel evaluation of 'quality by design' aspects of applications submitted to the Agency and the FDA at the same time. Quality by design is an enhanced systematic and science-based approach to the development and manufacture of medicines that ensures better quality of medicines.

3.10. Other EC activities and initiatives in the field of orphan drugs

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

The Directorate General of Enterprise and Industry announced[164] in 2010 the launch of a process on corporate responsibility[165] in the pharmaceutical industry. 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 will be created: one of these projects will look into the possibility to establish a mechanism of coordinated access to orphan medicinal products. For this project, *"Members will be 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 contractual agreements for innovative medicines and another on facilitating the supply in small countries. A number of stakeholder organisations will be invited to 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 EuropaBio. In a press release, 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*".

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

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

B. OTHER EUROPEAN RARE DISEASE ACTIVITIES

1. Pharmaceutical Forum (2005-2008)

The Pharmaceutical Forum[166] was set up in 2005 as a three year process by Vice-President Verheugen and Commissioner Kyprianou, in order to find relevant solutions to public health considerations regarding pharmaceuticals, while ensuring the competitiveness of the industry and the sustainability of the national health-care systems. This high-level ministerial platform for discussion between Member States, EU institutions, industry, healthcare professionals, patients and insurance funds focused its work on three main topics: information to patients on diseases and treatment options; pricing and reimbursement policy and relative effectiveness. The last Ministerial meeting, on 2 October 2008, concluded the three year exercise with the adoption of the final report gathering Final Conclusions and Recommendations. It also included all technical documents and projects developed by the three working groups to support implementing actions addressed to the European Commission, Member States and interested stakeholders.

In that framework, the members of the working group on pricing and reimbursement decided to examine how access to orphan medicines may be improved. Indeed, Orphan medicines amplify the common tensions in the field of pricing and reimbursement: assessing and rewarding innovation is difficult, budget optimisation is challenged and access for patients is limited in several countries. In spite of many policy initiatives increasing the number of newly developed orphan medicines, many of these are not available for all EU citizens.

Based on the paper "Improving access to orphan medicines for all affected EU citizens"[167] developed by its members, The High Level Pharmaceutical Forum recommended the following[168]: Member State authorities, stakeholders and the Commission should strengthen their efforts to ensure access to orphan medicines in all EU Member States. They are therefore called upon to take up the appropriate ideas developed in the Working Group Pricing regarding i) early dialogue on research and development, ii) exchange of knowledge on the scientific assessment of the clinical added value, iii) specific pricing and reimbursement mechanisms and iv) increased awareness on orphan diseases.

2. Actions undertaken by recent European Union presidencies

French presidency of the European Union (July-December 2008)

During the French presidency of the European Union running from July to December 2008, a range of conferences and events were held concerning the field of rare diseases in Paris. The first event, the "European Symposium on Rare Diseases", notably contained an affirmation from French President Nicolas Sarkozy that France would renew its national rare disease plan (2004-2008) following a period of reappraisal and reprioritisation. At the European level, the President expressed support for the EC Communication, Rare Diseases: Europe's Challenges, indicating that under the current patronage of the French EU Presidency the contents of this vital document would receive priority status. The Symposium featured presentations from rare disease experts on the performance of the French rare disease plan, considered a model by many other countries. At the European level, recent advances and perspectives in the field were presented and the benefits of European orphan drug regulation were reviewed. Other sessions of the day-long event emphasised the value of European rare disease and orphan drug research; considered the need for pan-European organisation for managing patient needs; and reiterated the crucial role patient organisations play in forwarding rare disease initiatives.

[166] http://ec.europa.eu/pharmaforum/index_en.htm
[167] http://ec.europa.eu/pharmaforum/docs/pricing_orphans_en.pdf
[168] Conclusions and Recommendations of the High Level Pharmaceutical Forum 2005-2008, Recommendation 7.3 on Access to medicines for EU citizens http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf

The second event, "European Health at the Service of Patients", featured presentations on improving access to diagnostics and quality healthcare, emphasising that there could be no equal rights for patients without EU-level collaboration. The session also brought home the point that individual Member States need to commit to sharing resources. Shared expertise can foster harmonised standards of care – considered critical in view of the rarity of disorders and the dispersion of expertise. A key discussion considered how the rare disease community could access primary care physicians to furnish them with resources to help determine when and where to refer rare disease patients. Orphanet, with its roster of partners in all 27 EU Member States (and beyond), was evoked as the leading example of successful pan-European collaboration.

Finally, the European Platform for Patients' Organisations, Science and Industry (EPPOSI) held a workshop at the Assemblée Nationale, hosted by the French deputies representing the country's working group for rare diseases within the French government. The theme of the workshop was "Partnering along the chain and across the borders: Sharing strategies and tools for access to diagnosis and treatment". Several topics came under fiery debate during the two day event: the first considered whether permissive off-label practices hinder drug development for specific indications, whilst another d centred on the current procedures for appraising clinical added-value for products that have received marketing authorisation. Another pertinent point arose around the transparency of clinical trials. Finally, the value of innovation was evoked. High prices for many orphan medicinal products result from small patient populations for the development and eventual sales of products, but also are caused by the unknowns of the market. Orphan medicinal products are frequently innovative products, produced for markets that are unknown and unshaped. Innovation boosts research for unmet medical needs and thus its rewards are merited. French Minister of Health Roselyne Bachelot brought the workshop to an end with an encouraging affirmation of her commitment to renewing the national plan for rare diseases. She also echoed President Sarkozy's support for European-level action as delineated in the EC Communication.

The last official rare disease event taking place under the patronage of the French EU Presidency is the *European Conference on National Strategies on Rare Diseases in Europe, "State of the art and sharing experiences: toward EU Recommendations*[169]*"* was held on 18 November 2008 at the French Ministry of Health in Paris.. The conference followed the announcement exactly one week earlier of the European Commission's adoption of the Communication and a proposal for a Council Recommendation on Rare Diseases that delineates a strategy designed to support Member States (MS) in diagnosing, treating and caring for their rare disease patients. The daylong event started with French Ministry of Health Roselyne Bachelot-Narquin reiterating France's support of an EU-coordinated effort and a reminder that the French national plan for rare diseases is available to use as a model. Presentations were given by some of the leading stakeholders in the field, each contributing their knowledge and expertise geared to move forward and keep the initiative in motion. A historical perspective of European actions on rare diseases and orphan drugs was given as well as an overview of the various rare disease initiatives taking place nationally across Europe. Four countries (Bulgaria, Italy, the Netherlands, and Portugal) illustrated European diversity by outlining how each organises their efforts on behalf of their rare disease patients. The body of the morning's events were summed up in twelve key themes: tailor-made plans suiting each country's specifications; a European vision; establishing a baseline for identifying centres of expertise; defining clear and measurable objectives; creating indicators to measure progress; building networks of centres of expertise; training of medical professionals; coordination; multi-disciplinarity; evaluation; funding; and patient involvement. The afternoon focussed on the European Project for Rare Diseases National Plans Development (Europlan). Funded for a three-year period that began in April 2008, Europlan seeks to elaborate recommendations on how to define a strategic plan for rare diseases at the national level. The conference concluded with a discussion from a "panel of policy makers" who offered their understanding of the urgency of the Communication and recommendations, and their commitment to guard its "priority status".

Czech presidency of the European Union (January-June 2009)

Under the term of the Czech EU Presidency that ran from January to June 2009, several conferences and workshops were held in relation to rare diseases, including an international conference[170] in Prague to address the treatment of rare diseases in relation to EU legislation. This event was devoted to a discussion of the objectives of the EU in the area of diagnosis and treatment of rare diseases and to the respective tasks ascribed

[169] http://www.eu2008.fr/webdav/site/PFUE/shared/import/1118_Conference_maladies_rares/Rare_diseases_Summary_EN.pdf

[170] http://vzacna-onemocneni.cz/

to the individual EU member states in the EU Council Recommendation on European Action adopted under the Czech presidency at the meeting of EU27 Ministers of Health in Luxembourg on 9 June 2009.

An outcome of the ministerial conference entitled *eHealth for Individuals, Society, and Economy* that took place in Prague from 18–20 February 2009 was the adoption of the Prague Declaration[171] on eHealth and a call for action on building an eHealth area for European citizens. The principal objective of the Prague Declaration *"is to sum up the current state of the Europe-wide effort to use information and communication technologies (ICT) in healthcare for the benefit of patients as well as economic efficiency of the health sector. It also aims to determine further steps to be taken at the level of Member States as well as European institutions. At the same time, a common European eHealth area should be built, where individual national systems will be able to communicate with one another. Integrating eHealth solutions into national health strategies of the Member States will also be of great importance"*. The Prague Declaration was prepared in cooperation with the EU Member States. The ministerial conference targeted the various impacts of the eHealth solutions and processes. Amongst the presentations, ICT tools for rare diseases demonstrated how rare diseases provide a perfect example of the relevance of ICT tools in improving access to services and providing information at the European level. This presentation demonstrated the value of the various eHealth applications Orphanet has on offer for patients, health professionals, researchers, policy makers, and industry, across Europe and beyond. Other EU-funded rare disease electronic informational projects were cited including ECORN-CF, a shared knowledge database answering patient and professional queries on cystic fibrosis, and DYSCERNE, which provides an electronic forum for experts to submit cases of difficult-to-classify developmental anomalies.

Swedish presidency of the European Union (July-December 2009)

On 1 July 2009, Sweden took over the Presidency of the European Union (EU), completing the 18-month troika started under France and continued by the Czech Republic. The country holding the EU Presidency acts as the driving force behind the EU's legislative and political activities and works to broker compromises between the EU Member States. The most important task for the three-Presidency team was to establish a common 18-month programme for all three presidencies. Following on the momentum initiated by France and sustained by the Czech Republic, during which the historical adoption of the Council Recommendation on an Action in the Field of Rare Diseases was achieved in June 2009, Sweden, less than one month into its turn at the helm of the EU Council Presidency, organised a conference of experts to push the envelope further. The conference "Assessing Drug Effectiveness – Common Opportunities and Challenges for Europe" (28-29 July 2009) gathered stakeholders from throughout Europe to discuss how to develop cooperation across Europe for the collection and sharing of data on drug effectiveness and safety following marketing authorisation. Speakers included Thomas Lönngren, Executive Director of the EMA, along with representatives from government, industry, research, and patient organisations. A workshop specific to orphan drugs – an area for which cooperation is considered critical as most individual countries have too few patients and resources to sustain a comprehensive follow-up scheme – brought together a panel of experts. The conference moved forward the process of post-marketing assessment harmonisation via the decision to develop a pilot model "for structured follow-up for initial testing on an orphan drug" for which several candidate products were proposed by the workshop panellists. A meeting took place in autumn bringing together stakeholders interested in participating in the pilot project.

Spanish presidency of the European Union (January – June 2010)

No specific events linked to the field of rare diseases were organised by the Spanish presidency in 2010.

Belgian presidency of the European Union (July 2010 – December 2010)

During the Belgian presidency of the European Union (July 2010 – December 2010), MEP Frieda Brepoels hosted a lunch meeting in the European Parliament on problems with development and availability of orphan drugs for rare cancers. The meeting was organised by the Association of European Cancer Leagues, the Foundation Against Cancer and the Flemish League Against Cancer. The aim was to raise the awareness about this issue and motivate the parliament to take action. MEP Frieda Brepoels concluded the meeting, by calling upon the MEPs to: 1) make proposals to keep regulatory requirements for clinical trials on orphan drugs to a minimum without endangering patient safety; 2) ensure that there is EU funding for networks of centres of clinical and scientific excellence; 3) support the development of EU-wide registries, amongst others by securing full interoperabilty of national e-Health services, by creating a regulatory and legal framework; 4) support close collaboration between member states during the phase of deciding on the reimbursement so that common

[171] http://www.ehealth2009.cz/Pages/108-Prague-Declaration.html

arguments are used and comparable prices can be negotiated with industry; and to 5) install a non-binding European evaluation of the clinical added value of a new orphan drug, as one way to improve European collaboration in the reimbursement decision.

3. E-Rare

E-Rare, the ERA-NET for rare diseases launched two Joint Transnational Calls in the first phase of the project (2006-2010). The aim of the first call was to enable scientists in different countries to build an effective collaboration on a common research project based on complementarities and sharing of expertise. Six E-Rare partnering countries joined the first call in 2007 (France, Germany, Italy, Israel, Spain and Turkey). These National Institutions funded multilateral transnational research projects on rare diseases. The partners of E-Rare, ERA-Network for research programmes on rare diseases, launched the second joint transnational call (JTC) at the end of 2008/beginning of 2009. The ten countries that joined the 2nd Transnational Call are France, Germany, Israel, Spain, Turkey, the Netherlands, Portugal, Italy, Austria and Greece: 4 additional funding organisations from 4 Member States joined the 2nd JTC. The financial input of each partner research funding agency/ministry has allowed for the funding for 16 transnational research consortia with 75 participating research teams from 10 countries for a total research budget of €9.6 million. A list of funded projects is available[172].

A new E-Rare project (E-Rare-2) (2010-2014) aims at deepening and extending the cooperation among the E-Rare-1 and four new partner countries by systematic exchange of information, yearly launched joint calls, thorough assessment of the funding mechanisms and results of the funded research projects and, finally, strategic activities aiming at a sustainable development and extension of the network. Special attention will be given to the outreach and knowledge exchange with new Member States, countries outside of the European Union and key stakeholders/initiatives important for rare diseases. E-Rare-2 activities will thus further contribute to reducing fragmentation of research and resources through the enhanced coordination and transnational funding of excellent research on rare diseases, thereby shaping the European Research Area for rare diseases. E-Rare-2 will expand to include 16 funding agencies and ministries from twelve countries – Austria, Belgium, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and Turkey.

E-Rare-2 launched at the end of 2010 its third Joint Transnational Call for proposals. Research groups from nine countries (Austria, Belgium, France, Germany, Greece, Israel, Italy, Spain and Turkey) were eligible to participate in this call that seeks to promote transnational research collaboration on rare diseases. Proposals must cover at least one of the following areas: definition of new nosological entities, epidemiological studies, genotype/phenotype correlations, natural history of diseases; characterisation of the genetic/molecular basis of specific diseases; pathophysiological and genetic studies of rare diseases; and diagnostic and therapeutic research (interventional clinical trials are excluded). There will be a two-stage submission procedure: joint pre-proposals (in English) must be received by the Joint Call Secretariat no later than 31 January 2011 and only pre-proposals selected by the international Scientific Evaluation Committee will be invited to submit a full proposal (deadline 16 May 2011).

4. Proposal to harmonise qualifications for clinical genetics as medical specialty adopted by European Union of Medical Specialists

The European Union of Medical Specialists (UEMS), a non-profit organisation founded in 1958 to determine high quality standards harmonising specialist training for European physicians, represents some 1.5 million European medical specialists in 38 specialist sections throughout 35 national member associations. In April 2009, the UEMS Council adopted the text entitled *Description of Clinical Genetics as a Medical Specialty in EU: Aims and objectives for specialist training*[173]. The document, which defines educational goals for a specialisation in genetic medicine, has already been endorsed by the European Society of Human Genetics, the UEMS Multidisciplinary Joint Committee for Clinical Genetics, and the UEMS Specialist Sections & European Boards. This is good news for rare disease patients in countries where clinical genetics is not yet recognised: Belgium, Greece and Spain.

[172] http://www.e-rare.eu/images/stories/e-rarejtc2009fundedprojects.pdf
[173] http://admin.uems.net/uploadedfiles/1305.pdf

5. International Rare Disease Conferences In 2010

Rare Diseases Day 2010 (28 February 2010)

Held on the last day of February, Rare Disease Day debuted in 2008 - a leap year – in a handful of countries. Organised by the European Organisation for Rare Diseases (Eurordis) on 28th February 2010, the 2010 International Rare Disease Day has taken the theme *"Bridging Patients and Researchers"* with the slogan *"Patients and Researchers – Partners for Life"*. Specifically, 2010's Rare Disease Day sought to promote collaboration between patients and researchers and influence public policy and the European research agenda. Eurordis organised several activities to promote and encourage rare disease research – and emphasise the vital role patients can play - including a workshop co-organised with E-Rare, in partnership with The European Commission, Orphanet and Europlan on 1 March 2010 in Brussels[174] that invited policy-makers, researchers, patient organisations, and members of the biopharmaceutical industry to join together to create a European research agenda in which patients play an active role. The workshop examined in particular the pertinent topic of *Bridging Patients and Researchers to Build the Future Agenda for Rare Disease Research in Europe*. Over 100 key stakeholders attended the workshop, which sought to identify the priorities and the means to developing a truly collaborative framework for forwarding research in the field of rare diseases and orphan drugs.

Other activities hosted by Eurordis include the creation of a Research Hall of Fame, to which patient organisations are invited to nominate scientists who have pushed forward research on rare diseases, as well as the rare disease video and photograph competition which already proved popular at the previous editions of the Day. Meanwhile, rare disease organisations across the world hosted a range of functions designed to raise awareness.

In total, participants from at least thirty-five countries on six different continents have signed up to host events in celebration of the Day. A detailed review of national activities in the EU MS is provided in Part III of this report. In 2010 there were additional events in Canada, the United States, Brazil, Argentina, Hong Kong, the Philippines, Taiwan, China, South Africa and Cameroon. Events from around the globe were posted on the Rare Disease Day website (http://www.rarediseaseday.org/)

European Conference on Rare Diseases 2010 (13-15 May 2010, Krakow)

600 international stakeholders attended the Fifth European Conference on Rare Diseases[175] that took place in Krakow, Poland in 13-15 May 2010. The event, organised by European patient umbrella organization Eurordis was deemed a *"magical moment"* in the history of the European rare disease movement. With the European Commission Communication on Rare Diseases: Europe's challenges and the European Council Recommendation on an action in the field of rare diseases firmly established, the atmosphere was jubilant and the agenda practical: *From Policies to Effective Services for Patients*. Each of the eight themes of the conference, divided into twenty-four sessions, sought to address different aspects of the topic. With over 35% of participants coming from Central and Eastern Europe, expectations were high that individual Member State (MS) strategies would be moved forward during the sessions, for which simultaneous translations were available in up to five languages.

The first session of the conference exposed the *Dynamic of National Initiatives for Rare Diseases*. Co-chaired by Dr. Rys and Avril Daly (Genetic and Rare Disorders Organisation, Ireland) after a brief and excellent film in which Nick Fahy (DG Sanco) called for *"efficiency, solidarity, and innovation"*, Eurordis president Terkel Andersen took stock of the current situation, offering a brief tutorial on the history of rare disease advocacy in Europe, starting with Norway in the 1970s (the first RD conference took place in Oslo in 1979). He defined the main challenges in developing national plans as 1) the decentralised health care systems of some countries; 2) the need for supportive EU policies; and 3) sustainability. He also made reference to the European community's three "founding texts" (Regulation (EC) No 141/2000 on Orphan Medicinal Products; the Council Recommendation on an action in the field of rare diseases; and the European Commission Communication on Rare Diseases: Europe's challenges). The Chair of the EUCERD, Ségolène Aymé presented some current problems: each country needs to have an adequate healthcare infrastructure in place, on top of which expert services can be built. Services need to be available and affordable. Amongst the various elements to be

[174] http://www.eurordis.org/content/european-workshop-rare-disease-research
[175] http://www.rare-diseases.eu

considered are genetic services; disability and rehabilitation services; neonatal screening for at least PKU and hypothyroidism; academic research; laboratory networks; information; centres of expertise; funding for networks; patient group support; and access to innovative therapies. Networks are needed for developing clinical guidelines. A process that allows submitting questions to experts must be elaborated. Registry networks, which should be public/private partnerships, are crucial strategic tools. Genetic testing needs a reliable, workable cross-border mechanism.

After the opening of the conference, attendees were forced to choose between sessions addressing various aspects of the key theme offered simultaneously over the next two days, including the Added Value of Centres of Expertise; Improving Access to Orphan Drugs; Help Lines for Rare Diseases; National Plans and Centres of Expertise in Eastern countries; Access to Cross Border Care; Making the Best Use of Funds for Genetic Testing; Orphan Drug Development, Paediatric Investigation Plans and Advanced Therapies; Medical Education; The International Classification of Diseases Revision; Centres of Expertise for Ultra Rare Diseases; Involvement of Patients in Clinical Trials; and Databases and Registries.

A Poster Session allowed for networking - one of the most satisfying aspects of the conference. Two of the 70 posters displayed were singled out for special recognition: one based on a pan-European study of cystic fibrosis (Mehta et al[176]) and the other describing data from a longitudinal study involving patients with congenital neutropenia from 23 countries.

There were also audience participatory sessions of the PlayDecide[177] game, a method for introducing complex scientific and medical topics into the arena of public debate. PlayDecide allows patients to learn more about policy issues while fostering their ease in contributing to the discussion in multi-stakeholder events.

The final session of the conference regrouped the participants together again to learn more about the European Union Committee of Experts for Rare Diseases (EUCERD). In the Road Map 2010-2015 for the implementation of the Commission Communication session, Antoni Montserrat (Policy Officer for Rare and Neuro-developmental Diseases, European Commission) evoked the little known science of “commitology” – how to best organise a new committee.

The *Orphanet Journal of Rare Diseases* (OJRD) has published its first supplementary issue[178], containing the oral and poster presentations from the Fifth European Conference on Rare Diseases that took place in Krakow, Poland in May. Amongst the highlights are discussions on the various national strategies for rare disease patients, including the French and German experiences, as well as presentations on centres of expertise for rare conditions, different research considerations, orphan drugs and health technology assessment, genetic testing, classification, organisation of resources very rare disorders, and registries. The supplement also contains some thirty poster presentations from the conference focusing on a wide assortment of rare disease and orphan drug related topics. The OJRD is an open access electronic publication.

6th International Conference on Rare Diseases (18-20 March 2010, Buenos Aires)

The International Conference on Rare Diseases and Orphan Drugs (ICORD) crossed the equator for the first time to convene in Argentina in 18-20 March 2010. Hosted by the Latin American and Caribbean countries patient organisation GEISER, the conference capitalised on the efforts already underway to raise visibility and activity in the region. ICORD is an annual event conceived to promote global collaboration in the field of rare diseases and orphan drugs. The first meeting was held in 2005 in Stockholm and subsequent meetings have taken place each year in Madrid, Brussels, Washington, and Rome. This year’s theme *“Global Approaches to Research and Patient Access to Diagnosis, Information and Care, And the Common Issues with Neglected Diseases in Developing Countries”* has particular relevance in the region. With sixteen formal sessions and five additional activities, some 350 participants hailing from over 25 different countries (including Australia, Brazil, Chile, China, Colombia, Ecuador, Japan, Mexico, Panama, Peru and Uruguay) were in attendance. One plenary session chaired by ICORD president Stephen Groft and Kerstin Westermark explored *From Pioneer Countries to the Rest of the World*; and another, chaired by Ségolène Aymé and Sharon Terry focused on *The Development of Information*. In addition, nine round table sessions featured topics such as *Turning rare diseases into an international priority; Initiatives from the public institutions; Research; Patients and family care; Best practices in the approval of orphan products; Bioethics; Linking needs with neglected diseases; Strategies for accessibility*; and *International initiatives*. Furthermore, several Working Groups gathered to explore *Regulatory needs; Research; Patient/Family; Diagnosis; Accessibility;* and other topics. A satellite symposium proposed by the Pan American Health Organization (PAHO/WHO) on *The impact of high cost drugs in developing countries* was also

[176] http://www.orpha.net/actor/EuropaNews/2010/100512.html#EUPol
[177] http://www.playdecide.eu/
[178] http://www.ojrd.com/supplements/5/S1/?page=1

held. Other notable presentations included those by GEISER founder Virginia Llera on *Including the Developing Countries in the International Scenario of Rare Diseases and Orphan Drugs*; Orphanet director Ségolène Aymé on *A Review of the International Classification of Diseases*; and Tim Coté describing *The FDA Foreign Offices and its Impact in the Orphan Drugs Field*. A series of related courses were also on offer from the Latin American Society for Rare Disease Medical Research (SLADIMER). Significantly, the event was declared of national importance by the Argentinean Government, and was supported by the Pan American Health Organization as well as the local Embassies of the USA and Sweden, among others. These official connections related to rare diseases are unprecedented in the region. Tokyo, Japan has tentatively been proposed as the location for ICORD 2011 conference. Dr. Domenica Taruscio from Italy has been newly elected as president of the organisation and Dr. Virginia Llera from Argentina will serve as the President-Elect for a two-year period.

EPPOSI Workshops in 2010

EPPOSI (European Platform for Patients' Organisations, Science and Industry) is an EU patient-led partnership between patients' organisations, science and industry, founded in 1994 for the exchange of information and discussion of policies in EU human healthcare. EPPOSI's primary mission is to establish a strong European alliance of patients' organisations, academic science and industry jointly working on healthcare policies towards treatment and prevention of serious diseases.

EPPOSI focuses on building dialogue, consensus positions and policy recommendation for the benefit of EU patients and consumers. These consensus positions have provided building blocks for: the establishment of the European Orphan Medicinal Products Regulation; the advancement of biomedical research and the value of innovation; the timely access to innovative medicines; several rare-disease therapy developments and partnerships; East-West European collaboration amongst patient groups; and biobanking.

The eleventh Workshop on Partnering for Rare Disease Therapy Development of EPPOSI took place on 29-30 November 2010 in Prague, Czech Republic[179]. The theme *"Working together to define Research, Regulation and Realities for the EU Rare Disease Community"* comes as EU Member States put together strategies for their rare disease patients that include collaboration and coordination with other Member States and with EU-level experts. Stakeholders from over 20 countries gathered for the annual event, held this year under the auspices of the Czech Ministry of Health. A press release noted that *"…holding the event in Prague was particularly apt as it is countries from Central & Eastern European countries which, it emerged, are leading the way in putting in place the integrated frameworks to make this happen"*. While it was agreed that EU-level regulation was functioning, participants evoked the bottlenecks that exist at the Member State (MS) level. A plea for each of the 27 EU MS to elaborate a plan for rare diseases that includes cooperation and coordination was made. Professor Milan Macek, head of a leading Centre of Expertise in the Czech Republic (Charles University Prague) and President of the Czech Medical Genetics Society, commented that, *"It is only by working together in this field that we stand any chance of moving forward. No one has all the solutions alone and where patients are rare, knowledge is rare and resources are rare, we need to put it all together to be successful"*. Eight specific recommendations were elicited to achieve this goal. These include the need for national plans that *"…focus on a small number of key actions, integrated both vertically in the country as well as horizontally across countries, to create a true network that will make the most of scarce information and resources".* Other recommendations include the role of patients in *"bridging the gap between physicians and politicians"*; the *"responsible engagement"* of the biopharmaceutical industry; improved dialogue and collaboration between players; earlier communication between Health Technology Assessment bodies, regulators and payers; a mechanism to facilitate early access to orphan drugs against *"a commitment to gather in-life data, conditional pricing and reimbursement"*; the sharing of best practices; and safeguarding the successful EU Orphan Regulation (141/2000).

In 2010, EPPOSI published the official report[180] of its *Tenth Workshop on Partnering for Rare Disease Therapy Development*, entitled *Ten Years After the Adoption of the EU Orphan Medicines Regulation: Where Do We Go*[181]*?* The event took on three diverse yet equally critical issues: What is the impact of the economic crisis on the field of rare diseases – and what is the vision on further progress in R&D, diagnosis and patient care?; Building on the public policy base of the last 10 years: how to advance policies in the next five years?; and Rare cancers: specific challenges within rare diseases.

[179] http://www.epposi.org/upl/1/default/doc/EPPOSI%2011th%20PRDTD_Presentations.pdf
[180] http://www.epposi.org/upl/1/default/doc/EPPOSI-10th%20PRDTD-Report_low.pdf
[181] http://www.epposi.org/index.php/rare-diseases-publications

European Medical Devices Workshop (25-27 November 2010)

The *European Medical Devices Workshop* took place 25-27 November 2010 in La Ciotat, France. This biennial event considers ongoing issues relating to medical devices, defined as any *"instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any accessories or software for its proper functioning, intended by the manufacturer to be used for human beings in the: diagnosis, prevention, monitoring, treatment or alleviation of disease or injury; - investigation, replacement or modification of the anatomy or of a physiological process; - control of conception; and which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but which may be assisted in its function by such means"*. Many such devices have been developed for rare conditions. The 2010 workshop agenda paid particular attention to medical devices containing cell or tissue engineered material which fall within the scope of the European Medicine Agency's Committee for Advanced Therapies. A symposium during the Workshop discussed the implementation of post-marketing evaluation for medical devices – required under the EU Directive 2007/47[182]. Participants debated the elements post-marketing follow-up should contain. Would a European registry be advantageous and feasible? The Workshop also provided an interesting session comparing the way in which Europe and the Unites States define, encourage and manage devices for rare conditions. European medical devices are currently awarded EC marking when they meet criteria of specific European Council Directives. In contrast, the USA has the Humanitarian Device Exemption to facilitate access for small patient populations. Other incentives exist for medical devices developed for rare diseases. One problem that was pointed out with this system is that many devices can be applicable to both rare and common disorders. The next workshop will take place in 2012.

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

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