

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



**PART IV: EUROPEAN MEDICINES AGENCY  
ACTIVITIES AND OTHER EUROPEAN  
ACTIVITIES IN THE FIELD OF RARE DISEASES**

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

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## ACRONYMS

### General

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

### Pilot European Reference Networks

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

## GENERAL INTRODUCTION

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

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

The report is split into five parts:

Part I: Overview of rare disease activities in Europe

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

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

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

### 1. METHODOLOGY AND SOURCES

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

- **European Commission websites and documents**

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

- **OrphaNews Europe**

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

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

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

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

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

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

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

- **EUCERD Publications**

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

- **Reports of the EUCERD meetings**

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

- **Rare Diseases Task Force publications**

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

- **Reports on orphan medicinal products**

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

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

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

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

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

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

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

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

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

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

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

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

- **EUROPLAN national conferences final reports**

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

- **Orphanet**

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

- **OrphaNetWork News**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 2. REPORT PREPARATION, REVISION AND VALIDATION

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

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

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

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

## 3. REPORT STRUCTURE

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## A. EUROPEAN MEDICINES AGENCY ACTIVITIES

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

#### European Medicines Agency<sup>31</sup>

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<sup>32</sup>. 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<sup>33</sup> 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<sup>34</sup>, established in 2005, provides special assistance to small and medium-sized enterprises.

Six scientific committees<sup>35</sup>, 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 (PCDO) 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.

<sup>31</sup> 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](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)

<sup>32</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000109.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac0580028a47](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028a47)

<sup>33</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000049.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9)

<sup>34</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000059.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cc](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cc)

<sup>35</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000217.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac0580028c77](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000217.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c77)

The Agency works with a network of over 4,500 'European experts'<sup>36</sup> 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<sup>37</sup> 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<sup>38</sup>. 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.

The Agency is also involved in referral<sup>39</sup> or arbitration procedures relating to medicines that are approved or under consideration by Member States in non-centralised authorisation procedures.

The EMA underwent a significant re-organisation 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"*.

The agency also went through a year-long evaluation process conducted by global auditors Ernst and Young of which the results were published in early 2010<sup>40</sup>. 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 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*

<sup>36</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000105.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac0580028c32](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000105.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c32)

<sup>37</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000219.jsp&murl=menus/partners\\_and\\_networks/partners\\_and\\_networks.jsp&mid=WC0b01ac058003174e](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000219.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003174e)

<sup>38</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000214.jsp&murl=menus/partners\\_and\\_networks/partners\\_and\\_networks.jsp&mid=WC0b01ac058003176d](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000214.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176d)

<sup>39</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000150.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d0](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d0)

<sup>40</sup> [http://ec.europa.eu/enterprise/dg/files/evaluation/final\\_report\\_emea\\_january\\_2010\\_en.pdf](http://ec.europa.eu/enterprise/dg/files/evaluation/final_report_emea_january_2010_en.pdf)

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".

### Work programme

The European Medicines Agency (EMA) adopted its Work Programme for 2011<sup>41</sup> in December 2010. The 2011 Work Programme outlined 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 was 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 highlighted 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 were 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 anticipated growth in the number of applications with 73 in 2011 compared to 68 in 2010. The work programme highlighted 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 was 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 were expected to become more important.

The European Medicines Agency's Management Board, at its meeting on 15 December 2011, adopted the Agency's work programme<sup>42</sup> and budget for 2012 which are driven by the implementation of the pharmacovigilance legislation. The work programme forecasts a stable number of applications for marketing authorisation for human and veterinary medicines in 2012. The Agency expects some 112 applications in total (2011: 111), with 52 applications for new medicines for human use, in addition to 13 new orphan medicines and 39 generic applications (2011: 47, 13 and 45 respectively). The Board noted the 10% increase in expected requests for scientific advice for human medicines, which includes an increasing number of joint scientific advice with health technology assessment bodies (HTAs). New pharmacovigilance legislation, implementing revised policies on handling of conflicts of interests and ethical and good clinical practice (GCP) aspects of clinical trials, progress of Agency interaction with healthcare professionals, supply shortages of medicines caused by insufficient good manufacturing practice (GMP) compliance, are all listed as priority areas in the work plan.

<sup>41</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Work\\_programme/2011/02/WC500102044.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2011/02/WC500102044.pdf)

<sup>42</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500122955&mid=W0b01ac058009a3dc](http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500122955&mid=W0b01ac058009a3dc)

In the document it is noted that orphan medicinal product designations are expected to increase steadily in number and complexity as a consequence of the incentives for development and marketing of advanced therapies and innovative products for disease subsets. Continued collaboration with the FDA on joint designation assessment is also expected. Objectives for 2012 include the development of a pilot project on orphan medicines to explore how to better communicate and justify significant-benefit decisions reached by the Committee for Orphan Medicinal Products (road map initiative), a review of orphan medicines development to identify bottlenecks in development and provide feedback for the EU research policy on rare diseases, and the identification of advanced therapy medicinal products (ATMPs) designated as orphan medicinal products and their specific regulatory needs.

### **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<sup>43</sup> 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 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<sup>44</sup> and detailed information on the implementation of the road map was provided in the document 'From vision to reality'<sup>45</sup>.

### **EMA annual reports**

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 Medicinal 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.

<sup>43</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/01/WC500067952.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf)

<sup>44</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2011/01/WC500101373.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf)

<sup>45</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2011/10/WC500115960.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/10/WC500115960.pdf)

Six positive opinions were adopted by the Committee for Medicinal Products for Human Use (CHMP) recommending marketing authorisation for orphan-designated products in 2010. Indications include angioedema attacks, Gaucher disease, chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis, idiopathic pulmonary fibrosis, the treatment of inborn errors in primary bile acid synthesis due to enzyme deficiency and 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). Scientific Advice requests continued to increase in 2010, with the largest number (over half) relating to Clinical topics, and the remaining requests divided between Quality and Pre-Clinical issues. Protocol Assistance requests for orphan-designated products dipped to 68 for the year, after peaking at 77 requests in 2009.

Other highlights of the report include the adoption of two positive opinions for Compassionate Use; the activities of the Paediatric Committee and the Committee for Advanced Therapies, post-marketing activities, and the EU telematics strategy for pharmaceuticals.

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<sup>46</sup>.

### **Reduced fees for designated orphan medicinal products**

As of 1 February 2009, designated orphan medicinal products are eligible for reductions for all fees payable under Community rules pursuant to amended Regulation (EEC) 2309/93. Covered in the reductions, applicable to orphan products designated in accordance with Regulation (EC) 141/2000, are the fees for pre-authorisation activities (protocol assistance such as scientific advice), as well as for products using the centralised procedure: the application for marketing authorisation, inspections, and post-authorisation activities. The fee revisions reflect a policy of enhanced support for micro- small- and medium-sized enterprises (SMEs). An EMA press release 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”*<sup>47</sup>.

The EMA revised the fee reduction policy in April 2011 to ensure adequate incentives are still offered with the EU contribution received for 2011. The revised policy was adopted with an aim to ensuring that incentives for Small and Medium-sized Enterprises (SMEs) developing orphan medicinal products are maintained at the same level as previous years. In order to keep this objective the fee reductions for bigger pharmaceutical companies have been decreased.

The main changes introduced for 2011 are the following: 75% fee reduction for protocol assistance and follow-up procedures for non-SMEs. SMEs continue to benefit from a 100% reduction, as required by Article 7(3) of Regulation (EC) No 2049/2005. 10% fee reduction for initial marketing authorisation applications for non-SMEs. SMEs continue to benefit from a 100% reduction.

## **2. 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<sup>48</sup> (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

<sup>46</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Annual\\_report/2011/06/WC500108073.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2011/06/WC500108073.pdf)

<sup>47</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Public\\_statement/2009/09/WC500003876.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/09/WC500003876.pdf)

<sup>48</sup> This section reproduces information from <http://www.ema.europa.eu/htms/general/contacts/COMP/COMP.html>

COMP. The EMA maintains a searchable list of opinions on rare disease (orphan) designations<sup>49</sup>. The full list of orphan designations granted by the European Commission is available in the Community register of orphan medicinal products for human use held by the European Commission<sup>50</sup>. 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 medicinal products with regards to regulatory, quality, safety and efficacy issues. Protocol assistance activities have been increasing in number since its establishment, with 76 finalised procedures in 2010.

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.

Since its implementation, the Orphan Regulation has yielded more than 1005 positive opinions for orphan product designation, adopted from 1449 applications reviewed since 2000. To date, the distribution of the prevalence of conditions for which the designations have been adopted shows that the most frequently designated conditions have been those that affect between 1 and 3 in 10'000 patients, that is between approximately 50,000 and 150,000 people (receiving 52% of all orphan designations). Indeed, 37% of the orphan medicinal products having obtained market authorisation in the EU, are for the treatment of diseases affecting less than 1 in 10'000 patients (approximately 50,000).

The number of applications has increased steadily each year during the first decade of the Regulation with 166 applications received in 2011. Sixty-eight designated products had received marketing authorisation by the end of 2011, of which oncology is by far the most common therapeutic area (35%). Interestingly, the average time span between designation and authorisation is only 2.8 years, indicating that designated products were at an advanced developmental stage.

The COMP has also granted orphan medicinal product designations to various innovative product types (i.e. fusion proteins, monoclonal antibodies, cell and gene therapy products, tissue-engineered products, oligonucleotides): at the end of 2011, the COMP has given more than 70 positive opinions for advanced therapy products out of a total of 1005 positive opinions for orphan medicinal product designation.

#### **Positive opinions on orphan designations in 2011**

The COMP adopted 111 positive opinions on orphan designations in 2011. Over eighty diseases are covered by these designations. The European Commission then granted 107 of these orphan designations. Five orphan medicinal products received marketing authorisation in 2011.

#### **COMP publication in Nature Reviews (2011)**

The Committee for Orphan Medicinal Products (COMP) and the European Medicines Agency Scientific Secretariat have produced an article for *Nature Reviews: Drug Discovery* that details the progress made since the adoption of European Commission (EC) Regulation Number 141/2000, commonly referred to as the Orphan Drug Regulation in 2000. The first decade of the Orphan Drug Regulation yielded more than 850 positive opinions for orphan product designation, adopted from 1235 applications reviewed since 2000. The authors note that *“distribution of the prevalence of conditions for which the designations have been adopted to date shows that the most frequently designated conditions have been those that affect fewer than 1 in 10,000 patients (that is, ~50,000 patients in the EU)”*. The number of applications has increased steadily each year during the first decade of the Orphan Drug Regulation. The authors cite the economic climate and the growing collaborations between the EMA and the Food and Drug Administration (FDA) in the USA as possible contributing factors to the increase in applications. This perspective article reviews the designation criteria and the incentives available under the ODR. Other interesting statistics concern the number of designated products that have received authorisation. Sixty-three designated products had received marketing authorisation by the end of 2010, of which oncology is by far the most common therapeutic area (41%). Interestingly, the average time span between designation and authorisation is only 2.8 years, indicating that designated products were at

<sup>49</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan\\_search.jsp&url=menus/medicines/medicines.jsp&id=WC0b01ac058001d12b](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&url=menus/medicines/medicines.jsp&id=WC0b01ac058001d12b)

<sup>50</sup> <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>



an advanced developmental stage. Some of the incentives of the Orphan Drug Regulation, however, are geared to support the developmental process.

The article discusses other areas in which the COMP is active, including an advisory role to the EC “established in the EC Regulation Number 141/2000, Article 4(1) (b) — the COMP strongly supported the proposal from the EC Directorate-General for Research (DG Research) to fund the preclinical and clinical development of medicines for the treatment of rare diseases in the Seventh Framework Programme. Before this, the COMP had been regularly liaising with the DG Research and identifying areas in which research into rare diseases is particularly needed, taking into account the number of designations and the lack of development, or failures seen by regulators”. The COMP also is involved with the World Health Organization revision of the ICD 11 for rare diseases. The COMP also liaises internationally – particularly with the FDA in the USA. The two regulatory bodies are streamlining many procedures in a bid to accelerate the availability of rare disease products on both sides of the Atlantic.

Finally, the paper considers future challenges and opportunities, speculating on the possible role the COMP and the EMA might play to help get authorised products distributed to patients across Europe – a procedure that presently is the responsibility of the Member States. The paper looks at some ways to address the existing unmet medical needs of patients with rare diseases and gives a “resounding yes” to the question of whether the orphan medicinal product incentives will be needed ten years from now. The paper concludes that “the needs of many patients with rare diseases are far from fulfilled, and so continued committed efforts are required from the EU, its institutions and member states”.

#### **EMA’s Committee for Orphan Medicinal Products initiative to publish prevalence information (2011)**

The July 2011 Committee Report of the European Medicine Agency’s Committee for Orphan Medicinal Products includes the news that the COMP agrees to support an initiative to publish the prevalence data and data sources for the conditions for which products receive orphan designation. The measure is another action in an overall campaign designed to heighten transparency. Ascertaining prevalence can be extremely difficult, particularly for rare disorders. It is hoped that the initiative will aid future applications.

### **3. 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 83 of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use<sup>51</sup>, establishes that the CHMP can adopt opinions on the conditions for use and distribution of products under compassionate use and patients targeted. These provisions are 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.

<sup>51</sup>[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](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)

### **CHMP opinions in 2011 concerning orphan medicinal products**

In 2011, the CHMP issued positive opinions for marketing authorisation applications for Vyndaquel (tafamidis) for amyloidosis, Plenadren (hydrocortisone) for adrenal insufficiency, Votubia (everolimus) for astrocytoma, Tobi podhaler (tobramycin) for cystic fibrosis, and Esbriet (pirfenidone) for pulmonary fibrosis.

In 2011, the CHMP kept the recommendation 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 2010 due to a supply shortage and have been regularly updated.

### **EMA's first positive opinion for paediatric marketing authorisation (2011)**

In June 2011, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued its first positive opinion for a paediatric-use marketing authorisation (PUMA) for Buccolam (midazolam) from ViroPharma SPRL, intended to treat prolonged, acute, convulsive seizures in paediatric patients between 3 months and 18 years of age. According to Article 30 of Regulation (EC) No. 1901/2006, paediatric-use marketing authorisations can be granted for medicines which are already authorised, but no longer patented, and which will be exclusively developed for use in children. Such products benefit from 10 years of market protection as an incentive. A paediatric investigation plan (PIP) which sets out the development of the medicine in children and is subject to approval from EMA's Paediatric Committee (PDCO) is a prerequisite to obtaining a PUMA. The PIP for Buccolam was approved in August 2009. Many authorised medicines have not been studied adequately in children. The dedicated development of established medicines for children ensures that adequate information on the efficacy and the safety of a medicine is established and the correct dose and appropriate pharmaceutical form can be prescribed. To date, 26 applications for PIPs for PUMAs have been received and seven opinions have been issued by the PDCO. A large majority of rare diseases affect paediatric populations.

## **4. EMA activities in the field of clinical trials**

### **EudraCT Database**

A European database – EudraCT<sup>52</sup> – contains all ongoing or completed interventional clinical trials of medicinal products falling within the scope of “Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use” (known more commonly as the “Clinical Trials Directive”<sup>53</sup>, 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, available from March 2011, 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 with investigator sites inside the EEA or which form part of a Paediatric Investigation Plan (PIP)<sup>54</sup>, but that are conducted in third countries, are included (paediatric clinical trials with sites in the EU/EEA are already available). Following the guidelines published by the European Commission, all trials in the register have been authorised by the national medicine regulatory authority and have obtained a positive opinion from the ethics committee for clinical trials in the Member State concerned. Furthermore, clinical trials that include the paediatric population and have received a negative ethics committee opinion are being made public. Phase I clinical trials in adults will not be publicly available unless they form part of a PIP. The Clinical Trials Register contains historical data (all eligible trials contained in the EudraCT since its establishment in May 2004) and will contain all future trials recorded in the EudraCT.

<sup>52</sup> <https://eudract.ema.europa.eu/>

<sup>53</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

<sup>54</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/general/general\\_content\\_000302.jsp&url=menus/special\\_topics/special\\_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&url=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true)

Public access does not currently extend to data concerning trial results. However, there are plans to eventually include summaries of results, based on a guideline to be published by the European Commission, in late 2012 following the launch of an updated version of the EudraCT. The Clinical Trials Register does not provide data for non-interventional studies (observational, et al) for authorised products. Such data can be found via the website of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP<sup>55</sup>).

#### **EMA-NIH collaboration to harmonise clinical trial register data sets**

The EMA is working with the National Institutes of Health in the USA, which manages the ClinicalTrials.gov<sup>56</sup> registry of federally and privately supported clinical trials conducted in the United States and around the world as well as the Health Level 7 - Clinical Trial Registration and Results project<sup>57</sup> on the harmonisation of data sets submitted by the sponsor to clinical trial registers, as well as the World Health Organization. Such harmonisation is particularly welcomed by the rare disease community, which already faces the challenges of scattered patient populations and expertise.

#### **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<sup>58</sup> 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 medicinal products.

## **5. EMA activities in the field of advanced therapies**

#### **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)<sup>59</sup> – the EMA's sixth scientific committee. Created following new European Union legislation concerning the regulation of advanced-therapy medicinal products (Regulation (EC) 1394/2007<sup>60</sup>), 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. The experts making up the CAT also offer scientific advice as requested.

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

<sup>55</sup> <http://www.encepp.eu/>

<sup>56</sup> <http://clinicaltrials.gov/>

<sup>57</sup> <http://www.hl7.org/index.cfm?ref=nav>

<sup>58</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/06/WC500091530.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/06/WC500091530.pdf)

<sup>59</sup> [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](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)

<sup>60</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>

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 European Medicines Agency and its Committee for Advanced Therapies issued in April 2010 a statement<sup>61</sup> of concern over the practice of offering unregulated stem cell products to patients for a variety of 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<sup>62</sup> 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.

An Editorial article appearing in *Molecular Therapy* in March 2012 recalled the recent rejection of approval for Glybera (alipogene tiparvovec) by the EMA despite the approval by the CAT. In the case of Glybera, an AAV vector engineered to deliver a lipoprotein lipase cDNA to the muscle for the treatment of the rare disease lipoprotein lipase deficiency, the CHMP rejected the application despite the positive opinion of the CAT. The controversy involves the generation of statistically significant data in a small number of trial subjects, calling into question the long-term efficacy of Glybera. The Editorial article calls for clarification of the relationship between the CAT and the CHMP and for “greater emphasis” on the CAT opinion, citing the “very specific understanding of gene and cell therapy products” that the ATMPs require.

The European Medicines Agency’s Committee for Advanced Therapies (CAT) tested in 2010 its new certification system<sup>63</sup> 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<sup>64</sup> “... 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<sup>65</sup> 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

<sup>61</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Public\\_statement/2010/04/WC500089472.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/04/WC500089472.pdf)

<sup>62</sup> <http://www.ncbi.nlm.nih.gov/pubmed/20190786>

<sup>63</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000300.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac058007f4bd&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000300.jsp&url=menus/regulations/regulations.jsp&mid=WC0b01ac058007f4bd&jsenabled=true)

<sup>64</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:194:0007:0010:EN:PDF>

<sup>65</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2010/11/WC500099025.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/11/WC500099025.pdf)

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”.

## 6. EMA activities in the field of medicinal products for paediatric use

### European Network of Paediatric Research – Enpr-EMA

The European Medicines Agency (EMA) announced in 2011 the publication of the first membership list of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)<sup>66</sup>. Established to build a high-level network of existing research networks, investigators and centres with recognised expertise in performing clinical studies in children, the Enpr-EMA seeks to facilitate high-quality ethical research on medicines for use in children through networking and stakeholder collaboration with members from both within and outside the European Union as part of the EMA’s accordance with European Paediatric Regulation (EC) No 1901/2006. Enpr-EMA’s also aims to: coordinate studies relating to paediatric medicines and avoid unnecessary testing in children; build up scientific and administrative competence at a European level; help with the recruitment of patients for clinical trials; and promote European Commission framework programme applications. Enpr-EMA does not perform clinical trials or fund studies or research or decide on areas for paediatric research, as this is the responsibility of Member States, the European Commission or each individual network. The European Medicines Agency is responsible for ensuring collaboration within the network. The Enpr-EMA membership list<sup>67</sup> was compiled following a call for expressions of interest in 2010. Some 32 networks and centres have thus far applied for membership. Of these, 16 networks and centres have become members of Enpr-EMA. A second category of networks has been established for those “... undergoing clarification before membership of Enpr-EMA”. Networks grouped into a third category do not currently qualify for membership.

### Database of clinical studies involving children available via the EMA (2011)

In 2011 the European Medicines Agency made available a database<sup>68</sup> housing information on clinical studies of medicines authorised in the European Union that involved paediatric populations and were completed prior to the 2007 Paediatric Regulation came into effect. Via the Article 45 Paediatric Studies Database, it is possible to access information including the name and goal of the study, the medicinal product involved, and data on the patients, including age. Some trial outcomes are also available. The database is part of a global aim of the Agency to enhance transparency. The Agency is also specifically focused on improving information on medicinal products for paediatric populations.

## 7. Other EMA activities and initiatives relevant to rare diseases and orphan medicinal products

### ENCePP E-Register of Studies (2010)

The European Medicines Agency (EMA) announced in 2010 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)<sup>69</sup> 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

<sup>66</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000303.jsp&mid=WC0b01ac05801df74a](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a)

<sup>67</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/q\\_and\\_a/q\\_and\\_a\\_detail\\_000108.jsp&mid=WC0b01ac05802b9f0f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/q_and_a/q_and_a_detail_000108.jsp&mid=WC0b01ac05802b9f0f)

<sup>68</sup> <http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/>

<sup>69</sup> <http://www.encepp.eu/encepp/studiesDatabase.jsp>

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 launched in 2010 a public register<sup>70</sup> 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 Medicines Award for *“Most significant contribution to the medicines sector”*.

#### **EMA guidance for stem cell-based medicines (2011)**

The European Medicines Agency (EMA) has issued a reflection paper<sup>71</sup> on stem cell-based medicines that encompasses the different types of stem cells used in medicines, and addresses considerations for the development of stem cell-based medicines. In particular, the document *“stresses the fact that companies developing medicines including stem cells need to pay close attention to the way the medicines are manufactured, to make sure that the final medicine is as consistent and reproducible as possible”*. The reflection paper also offers consideration for pre-clinical and clinical testing. Adopted by the EMA's Committee for Advanced Therapies in January 2011, the reflection paper was open for public consultation in 2010 and was discussed at a public workshop last May 2010. Stem cell-based medicines could potentially be used in the treatment of many rare diseases.

#### **Good manufacturing practice database expands access to all Member States (2011)**

EudraGMP<sup>72</sup> is the Community database on manufacturing and import authorisations and Good Manufacturing Practice (GMP) certificates launched by the European Medicines Agency in April 2007. In July 2009 GMP non-compliance of manufacturers was added. Now a new version of the database has been developed that offers public access to information on manufacturing inspection by regulatory authorities from all the European Economic Area countries, including all the EU Member States, Iceland, Liechtenstein and Norway. The move represents a global effort of the EMA to increase transparency. According to a press release, the wider access will, *“...improve the sharing of information between regulators and industry; aid the coordination of activities related to manufacturing authorisations and GMP certificates between regulatory agencies in different European countries; eliminate the need for industry to submit applications in paper form; and facilitate the sharing of information on the outcome of inspections in the EU with regulatory authorities elsewhere in the world”*. The increased access is particularly welcome to the fields of rare diseases and orphan medicinal products, which depend upon the coordination and sharing of information and activities.

#### **EMA website update (2011)**

The European Medicines Agency has updated its website in order to allow users of the site to search and share contents more readily. According to a press release, new features include: a 'share' button that allows users to bookmark pages and share them via tools such as email, Facebook or Twitter; a 'search by type' feature: lets users browse the human European public assessment reports for generic, biosimilar or orphan medicines, medicines authorised under exceptional circumstances or medicines granted conditional approval; an improved document searching: allows document library searches by reference number, year of publication or consultation status; an enhanced event searching: permits keyword and year-by-year searches within the calendar of events and meetings; and searching PIPs by condition (allows a search of all opinions and decisions on paediatric investigation plans (PIPs) by a given condition or disease). These updates build upon the EMA's drive towards more openness and transparency.

<sup>70</sup> <http://fmapps.emea.europa.eu/SME/>

<sup>71</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2011/02/WC500101692.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf)

<sup>72</sup> <http://eudragmp.ema.europa.eu/inspections/displayWelcome.do>

### EMA Database of European Experts (2011)

The European Medicines Agency (EMA) has created a database of European experts<sup>73</sup> that furnishes information on declarations of interest. The database, publicly available, coincides with the entry into force of new rules around conflicts of interests of scientific experts nominated by competent authorities for medicines regulation across the European Union and involved in the Agency's activities. In a press release, the database is described as "...a major building block of the Agency's new rules on the handling of conflicts of interests of its scientific experts, which aim at protecting the Agency's scientific opinion-making processes from the influence of any improper interests". Conflicts of interests are classified into three categories: "direct", "indirect" and "no interests" and experts provide a signed declaration of interests form detailing any direct or indirect financial or other interests that could affect their impartiality.

## 8. International cooperation between regulators in the field of orphan medicinal products

The European Medicines Agency has been supporting the development of international collaboration between regulators. In the field of orphan medicinal products the Agency has established regular contacts with the Office for Orphan Products Development of the FDA (OOPD FDA) and the Japanese authorities (PMDA and MHLW). These contacts area aimed at establishing contacts that facilitate exchange of information and discussion of regulatory issues in order to respond to the globalization of product development and research.

### EU-USA collaboration in the field of orphan medicinal products<sup>74</sup>

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 medicinal product 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<sup>75</sup>. 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*

<sup>73</sup>[http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fabout\\_us%2Flanding%2Fexperts.jsp&murl=menus%2Fabout\\_us%2Fabout\\_us.jsp&mid=WC0b01ac058043244a&searchTab=&authorityId=&alreadyLoaded=true&isNewQuery=true&startLetter=View+all&selectedCountry=&jenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fabout_us%2Flanding%2Fexperts.jsp&murl=menus%2Fabout_us%2Fabout_us.jsp&mid=WC0b01ac058043244a&searchTab=&authorityId=&alreadyLoaded=true&isNewQuery=true&startLetter=View+all&selectedCountry=&jenabled=true)

<sup>74</sup>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&jenabled=true#section2](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&jenabled=true#section2) (accessed 22/04/2011).

<sup>75</sup>[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&jenabled=true#section2](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&jenabled=true#section2)

*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 be 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<sup>76,77</sup>. 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 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.

As a result of the aforementioned initiatives, currently more than 80% of the applications for orphan designation use the EMA/FDA common application form which is facilitating parallel submission and decreasing the administrative burden for sponsors.

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.

In 2011 the FDA and the EMA hosted the first joint workshop on applications for orphan designation, marking the first occasion in which sponsors have been able to discuss in real time applications for designation with both Regulatory Authorities.

The FDA published a report<sup>78</sup> of their activity in the realm of innovative medicines in 2011. Orphan drugs come out well making up almost a third of the 35 innovative medicinal products that were approved by the FDA in fiscal year 2011. Moreover, the FDA approved nearly half (16) of the innovative drugs under the agency's "priority review" programme. This scheme accelerates the approval process for drugs that may offer major advances in treatment. The FDA defines innovative medicines as "new molecular entities", novel chemical structures, including biological products, which have never been approved before to treat any disease, and often represent the most innovative drugs entering the market. Ten of the innovative products approved in fiscal year 2011 have orphan indications.

<sup>76</sup> [http://ec.europa.eu/health/files/international/doc/eu\\_fda\\_action\\_plan\\_200806\\_en.pdf](http://ec.europa.eu/health/files/international/doc/eu_fda_action_plan_200806_en.pdf)

<sup>77</sup> [http://ec.europa.eu/health/files/international/2009\\_tas\\_implementation\\_report.pdf](http://ec.europa.eu/health/files/international/2009_tas_implementation_report.pdf)

<sup>78</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM278358.pdf>



## B. OTHER EUROPEAN RARE DISEASE ACTIVITIES

### 1. Pharmaceutical Forum (2005-2008)

The Pharmaceutical Forum<sup>79</sup> 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”<sup>80</sup> developed by its members, The High Level Pharmaceutical Forum recommended the following<sup>81</sup>: 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

#### Hungarian presidency of the European Union (January – June 2011)

On 26 February 2011 experts came together in Budapest to commemorate Rare Disease Day 2011 at an informal event of the EU supported by the Hungarian presidency<sup>82</sup>, organised by HUFERDIS president Gabor Pogany. The event was attended by a range of stakeholders from Hungary and Europe and gave insights into actions at Hungarian and European level in the field of rare diseases. During the day Dr. Ildikó Horváth, Head of Department for Health Politics, State Secretariat for Healthcare, Ministry of National Resources, and her colleague Ildiko Szy presented more than 20 professional clinical guidelines for rare diseases.

### 3. E-Rare

E-Rare, the ERA-NET for rare diseases, is an initiative launched within the European Commission's Framework Programmes for research<sup>83</sup>. E-Rare launched two Joint Transnational Calls in the first phase of the project (2006-2010). The aim of the first call was to enable scientists in different countries to build an effective collaboration on a common research project based on complementarities and sharing of expertise. Six E-Rare

<sup>79</sup> [http://ec.europa.eu/pharmaforum/index\\_en.htm](http://ec.europa.eu/pharmaforum/index_en.htm)

<sup>80</sup> [http://ec.europa.eu/pharmaforum/docs/pricing\\_orphans\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/pricing_orphans_en.pdf)

<sup>81</sup> 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](http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf)

<sup>82</sup> <http://sites.rirosz.hu/rbv/ritka-nap-2011/programme-in-english>

<sup>83</sup> For more information on the E-Rare ERA-NET, see part III of this report on European Commission activities.

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 2<sup>nd</sup> 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 2<sup>nd</sup> 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<sup>84</sup>.

The latest 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. The selected<sup>85</sup> projects 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. Thirteen consortia were funded with a budget of around €9 million foreseen. The rare disease areas of the chosen projects include haematology, metabolic diseases, neurology, dermatology, and congenital malformations. Therapeutic approaches include pluripotent stem cells, gene therapy vectors and customised animal models.

In late 2011 E-Rare ERA-NET on rare diseases launched its 4th Joint Transnational Call issued a call entitled “European Research Projects on Rare Diseases driven by Young Investigators”<sup>86</sup>. The aim is to provide to young, independent investigators the opportunity of building transnational collaborations in the field of rare disease research. The transnational project should be based on complementarities and sharing of expertise, demonstrating a clear added value of the cooperation and impact of the expected results on patients affected by rare diseases. Eligible under this call will be young investigators who have been awarded their first PhD/MD or equivalent of doctoral degree since at least 2 and up to 10 years.

E-Rare issued its very first newsletter<sup>87</sup> and made over its website in 2011.

#### 4. Clinical genetics as a medical speciality

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*<sup>88</sup>. 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.

<sup>84</sup> <http://www.e-rare.eu/images/stories/e-rarejtc2009fundedprojects.pdf>

<sup>85</sup> <http://ns356946.ovh.net/~erare2/content/funded-projects-joint-transnational-call-2011>

<sup>86</sup> <http://www.e-rare.eu/content/joint-call-european-research-projects-rare-diseases-driven-young-investigators-jtc-2012>

<sup>87</sup> <http://www.e-rare.eu/newsletter/subscriptions>

<sup>88</sup> <http://admin.uems.net/uploadedfiles/1305.pdf>

The EC Regulation No 213/2011<sup>89</sup> amending Annexes II and V to Directive 2005/36/EC of the European Parliament and of the Council on the recognition of professional qualifications entered into force on 4 March 2011. Published in the *Official Journal of the European Union*, the amendment states that:

(7) Medical genetics is a specialty that responds to the rapid development of knowledge in the field of genetics and its implication in numerous specialised fields, such as oncology, foetal medicine, paediatrics, chronic diseases. Medical genetics plays a growing role in screening and in the prevention of numerous pathologies. Specialist medical training in medical genetics is not listed in point 5.1.3 of Annex V to Directive 2005/36/EC. However, it has developed into a separate and distinct specialist medical training in more than two fifths of the Member States, which justifies its inclusion into point 5.1.3 of Annex V to Directive 2005/36/EC.

(8) In order to ensure a sufficiently high level of specialist medical training, the minimum period of training required for the medical specialty of medical genetics to be automatically recognised should be four years.

Recognition of the speciality is critical both for the training of professionals and the organisation of related services.

## 5. Resolution on pharmacy prepared medicinal products adopted by the Council of Europe (2011)

Resolution CM/ResAP(2011)1<sup>90</sup> on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients was adopted by the Committee of Ministers of the Council of Europe on 19 January 2011. Special needs can arise from factors such as patient age, medical condition (such as rare diseases), individual disposition or environmental factors. The resolutions help to harmonise the preparation of medicinal products in community and hospital pharmacies throughout Europe and address the added value of pharmacy preparations; the responsibilities of health-care professionals; the preparation process; the product dossier; labelling; the reconstitution of medicinal products in health-care establishments; and authorisation for pharmacies or licences for companies making preparations for pharmacies.

## 6. International Rare Disease Events in 2011

### Rare Disease Day 2011 (28 February 2011)

The Fourth edition of the annual Rare Disease Day 2011, organised by EURORDIS, was held on 28 February 2011. Rare Disease Day 2011 included 55 countries (up from 46 in 2010, 30 in 2009 and 18 the first year) with newcomers including Armenia, Iran, Mexico, Morocco, Nepal, Panama, Peru, Thailand, the United Arab Emirates, and Uruguay. EURORDIS has partnerships with 22 national alliances and added Cyprus and Switzerland as new alliances joining the celebrations.

The official Rare Disease Day (RDD) website<sup>91</sup>, maintained by EURORDIS, received almost 50,000 visits from some 150 countries between 1 January and 3 March 2011. On 28 February the site logged some 10,000 visits. The number of RDD friends leapt to 292 from 187 last year, including patients, patient organisations, caregivers, healthcare professionals, researchers, members of the biopharmaceutical industry and public authorities. Scores of testimonials addressing the subject of this year's theme "Rare but Equal" were posted on the RDD website. RDD was also active on the major social networking sites with over 14,000 fans on Facebook, 1,446 followers on Twitter, 432 photos posted on Flickr, and a hundred videos on YouTube.

One of the most significant benefits of the awareness-raising day is the momentum the event provides for advancing the national plans that countries are urged to create following the *Council Recommendation on an Action in the Field of Rare Diseases*. Indeed, France took the occasion of RDD to unveil its second plan, and

<sup>89</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:059:0004:0007:EN:PDF>

<sup>90</sup> <https://wcd.coe.int/wcd/ViewDoc.jsp?Ref=CM/ResAP%282011%291&Language=lanEnglish&Ver=original&BackColorInternet=DBDCF2&BackColorIntranet=FDC864&BackColorLogged=FDC864>

<sup>91</sup> <http://www.rarediseaseday.org/>

frameworks for strategies were evoked in Croatia, Hungary, and Ireland. Belgium chose the occasion to hold a symposium for the drafting of a national plan, and in Switzerland, a member of the Health Commission proposed a vote for a strategy. Across the Atlantic, meanwhile, the U.S. Senate unanimously adopted a resolution officially designating 28 February, 2011 as Rare Disease Day in all states. The icing on the cake of recognition came from the Vatican when Pope Benedict XVI included a personal message to rare disease patients and families including a wish that advances in research will help patients.

Significant publications released in honour of RDD included the release of the Eurobarometer survey *European Awareness of Rare Diseases Report*. At the national level, the Rare Disease UK group released a major report outlining recommendations for a strategy for rare diseases. Luxembourg released a study undertaken by the Rare Disease Working Group entitled *Rare diseases: A National Survey on the Situation of Persons with Rare Diseases in Luxembourg*. RDD 2011 also marked the relaunch of the Orphanet site in Portuguese.

This year's RDD also caused a stir in the press – including a 20 page supplement in the UK newspaper *The Independent*. Other leading country dailies and press agencies lending awareness for the rare disease cause on RDD include *Les Echos* (France), *El Pais* (Spain), *Romania Libera* (Romania), the *Emirates News Agency*, and the *Cyprus Mail*, for example. There were also publications and websites launched presenting the patient experience and perspective in Canada, Denmark, Georgia, Panama, and Russia.

At the EU level, the *European Symposium- Rare but Equal- Addressing Health Inequalities for Rare Disease Patients in Europe* was organised by EURORDIS with the support of DG SANCO. Amongst the 86 participants were four representatives from the European Commission along with Member of Parliament Antonia Parvanova, shadow rapporteur on the recently adopted EU Directive on Cross-Border Healthcare and Patient Mobility. The symposium provided a venue for discussing the issue of health inequalities as well as strategies to remedy the inequalities rare disease patients endure. The Cross-Border Healthcare Directive was cited as a mechanism for levelling the field. The European Commission confirmed that diminishing rare disease health inequalities is a priority. Stefan Schreck, DG SANCO, Head of Unit for Health Information, evoked the EUCERD as an engine to facilitating better rare disease healthcare based upon the principles of equity and solidarity.

The EUCERD fully endorses the International Rare Disease Day campaign to raise awareness for the health inequities in the field – and particularly supports the promotion of rare diseases in the Third EU Public Health Programme (2014 to 2020) - and will continue working hard to level the playing field for all the rare disease stakeholders out there.

### **Final Europlan conference (Rome, 25 February 2011)**

On 25 February 2011 the final conference of the Europlan project was held<sup>92</sup>. Europlan, a three-year DG Sanco-funded project coordinated by the Italian National Centre for Rare Diseases (Istituto Superiore di Sanita) launched in April 2008, as an instrument to help the European Union Member States (MS) define a strategic plan for rare diseases following the adoption of a Council Recommendation on an Action in the Field of Rare Diseases that calls on the MS to elaborate and adopt a rare disease plan or strategy by the end of 2013.

At the final Europlan meeting, it was observed that one of the strongest elements of the Europlan project was its role in adding the European dimension to individual national strategies. This point is critical to the field of rare diseases, which relies on coordination and collaboration at the European and international levels. The 2011 Eurobarometer survey results demonstrate that there is support for European cooperation. Commission representatives cited the E-Rare project as an effective strategy for the funding of collaborative research.

A Round Table meeting reviewed some of the overall results of the Europlan project such as its role in harmonising concepts and terminology between the MS and in helping to raise awareness at the MS level for key EU documents in the field of rare diseases and orphan medicinal products. During this session, the need for integrating the elements of the national rare disease plans into the national health care systems was discussed. The importance of mapping existing resources - which Orphanet, the pan-European information portal for rare diseases and orphan medicinal products, is doing – was also evoked. Other elements identified include the need for inclusivity – i.e., involving all the various stakeholders in the development of a national plan; the need for the national protocols for diagnostics and care of a disease to include the provisions for patient coverage for testing and care; and the healthcare pathways – the multidisciplinary algorithms of care structured to support the implementation of clinical guidelines and protocols.

Discussion of the status of particular countries was also raised. While Bulgaria has a concrete plan, accessing funding remains problematic, especially in the area of diagnostics. Croatia hopes to put forward a

<sup>92</sup> <http://www.europlanproject.eu/ContenutoPage/127/en-GB/final-meeting/proceedings.aspx>

plan in 2012. Denmark is in a period of regression, illustrated by the country's information centre exclusively for rare diseases that has been extended to encompass all diseases. Greece has a plan on paper, but it is not yet legally recognised and the country has no national committee to implement it. There are also significant problems with access to orphan medicinal products in Greece. Starting a process to develop a plan in a country with 21 autonomous regions is a priority Italy – but the country's organisation presents a daunting challenge. Italy also reports a long time for orphan medicinal product approvals to be processed. The Netherlands is a country with a solid general health plan, which could explain why the Minister of Health is not in favour of developing a plan specifically for rare diseases. Furthermore, the country's Steering Committee for Orphan Drugs is to be shelved at the end of 2011. In Poland, the process of elaborating a plan has not yet begun, but awareness is increasing. Poland needs to focus on all elements of rare disease strategising – not just the orphan medicinal products. Spain does have a plan, but it has neither a budget nor a time-table. The UK seems to be moving forward, thanks in large part to the steam of the Rare Disease UK and similar patient-driven efforts.

With several plans existing only on paper, other countries reporting a regression, and other MS lacking resources, the dream that each MS will have a specific strategy to care for its rare disease patients, and which includes cooperation between the EU countries to share resources, is a fragile one. This is a critical time for each stakeholder to continue acting as a catalyst to push change forward. The recent adoption of the Cross Border Health Care Directive increases the need for concerted effort, with each EU country identifying its pockets of expertise and making them known, within the context of acknowledging and respecting the individual dynamic of each country, particularly its size and resources. Analysis of the results of this first Europlan project can help refine the second leg of the plan, which is being funded via the upcoming DG Sanco three-year EUCERD Joint Action (*Support to the implementation of national plans/strategies on rare diseases and related measures to implement Council Recommendation and Commission Communication on rare diseases*). The second phase of Europlan will continue to offer support and guidance to countries that have delineated a strategy and will aid countries that have not developed a plan to move forward, taking into account the specifics of each country in terms of size, prioritisation of measures and health care systems. There will also be an emphasis on the exchange of expertise between countries, as well as identifying outcome indicators that can be monitored. Around twenty national conferences are being planned for the second phase of Europlan within the EUCERD Joint Action.

#### **EUCERD/EMA workshop on a public-private partnership model for rare disease registries (London, 4 October 2011)**

On 4 October, stakeholders gathered at the Canary Wharf, London-based European Medicines Agency for a brainstorming session on how to best design, manage and share rare disease registries in a way that will be purposeful and satisfying for all players<sup>93</sup>. Experts from academia, the biopharmaceutical industry, patient organisations, and regulatory agencies all lent their expertise to the event, which culminated in a consensus towards disease-based registries that could ultimately be shared amongst all relevant public and private partners. This consensus, shifting from the drug- or patient-based designs to a larger-encompassing disease-based model, moves forward the challenge of how to coordinate, manage and share the goldmine of data that the disease registries potentially yield.

Well constructed and managed rare disease registries can significantly speed up clinical research in the fields of rare diseases and orphan medicinal products, further the understanding of many elements including prevalence, natural history, and treatment outcome for rare diseases, provide regulatory bodies – including pricing and reimbursement agencies - with crucial data, serve as a resource for trial recruitment, and help patient organisations to coordinate efforts and share information.

The EUCERD/EMA workshop, organised in the context of the ongoing scientific activities of the EU Committee of Experts on Rare Diseases (EUCERD) dedicated to registries in the field of rare diseases, builds upon the Rare Diseases Task Force (RDTF) report, Patient registries in the field of rare diseases<sup>94</sup>, based on outcomes of the 2008 RDTF workshop on this field, updated in 2011, as well as the tender report on the *Creation of a mechanism for the exchange of knowledge between Member States and European authorities on the clinical added-value of orphan drugs (CAVOD)* and the Orphanet Report Series Disease registries in Europe<sup>95</sup>.

Future meetings already being planned will tackle the complex questions of how to protect important privacy rights for industry, academic and patient registry partners, how to manage post-marketing

<sup>93</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/EUCERDWorkshopRegistries2011.pdf>

<sup>94</sup> <http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf>

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authorisation data for orphan medicinal products, how to coordinate at an international level, and harmonisation between registries. The EpiRare project (European Platform for Rare Disease Registries) launched in April 2011, seeks to gather more information on the needs of stakeholders, while the International Rare Diseases Research Consortium brings to the table the international perspective, expectations and experience.

**European Agency for Health and Consumers Rare Disease media event (Luxembourg, 25-26 October 2011)**

The European Agency for Health and Consumers (EAHC) organised a media initiative<sup>96</sup> focused on exploring what is being done at the European level to improve the situation for rare disease patients and their families. The two-day event featured a busy agenda of presentations from some of the main rare disease players in Europe, including pan-European information portal Orphanet and rare disease patient umbrella group EURORDIS, as well as a number of projects focusing on individual groups of diseases, and powerful testimonies from patients and their families. The event brought a fresh reminder of the situation millions of rare disease patients grapple with as the momentum for each of the European Union Member States to develop a specific strategy for meeting the needs of its rare disease patients, as put forward in the European Council Recommendation on an action in the field of rare diseases continues. The conference included presentations of some of the activities and initiatives that are funded at the European-level and described how they are contributing to improving the lives of rare disease patients and moving forward the search to better understand and treat this large group of heterogeneous diseases. A ten-minute video, narrated by Commissioner for Health and Consumers Mr John Dalli served to illustrate on a concrete level some of the complex issues rare disease patients and their families face.

**Rare 2011 (Montpellier, 4 November 2011)**

On 4 November 2011, the European Committee of Experts on Rare Diseases (EUCERD) organised, in collaboration with EuroBioMed, the first European day of the French 'Rare2011' conference in Montpellier, France<sup>97</sup>. The day consisted of three sessions highlighting priority topics in the field of rare diseases which call for collaboration at European level: Ensuring Visibility of Rare Diseases in Health Information Systems, Partnering to Optimise the Use of Patient Data to Improve Clinical Research and Healthcare, and Improving Access to Expertise and Quality Care. A wide range of stakeholders including researchers, policy makers, members of the industry and patient representatives were present at this event, of which the proceedings are detailed in this present document.

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<sup>96</sup> [http://ec.europa.eu/eahc/health/Rare\\_Diseases\\_conference\\_2011.html](http://ec.europa.eu/eahc/health/Rare_Diseases_conference_2011.html)

<sup>97</sup> <http://www.orpha.net/nestasso/EUCERD/upload/file/Rare2011.pdf>

## LIST OF CONTRIBUTIONS<sup>98</sup>

### Contributions from the European Medicines Agency<sup>99</sup>:

#### European Medicines Agency

Jordi Llinares-Garcia (*Head of Orphan Medicines*)

#### This report was compiled by Charlotte Rodwell

(*Scientific Secretariat of the European Union Committee of Experts on Rare Diseases, INSERM US14, France*)

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<sup>98</sup> The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

<sup>99</sup> Disclaimer: the EMA is not responsible for the completeness and correctness of the information included in this report.

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<sup>100</sup> All websites and documents were last accessed in May 2012.



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- Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare  
[http://ec.europa.eu/health/ph\\_information/dissemination/documents/com2009\\_380\\_en.pdf](http://ec.europa.eu/health/ph_information/dissemination/documents/com2009_380_en.pdf)

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- EU Programme of Community Action in the Field of Health 2003-2008  
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- DG Sanco Work Plan 2011  
[http://ec.europa.eu/health/programme/docs/wp2011\\_en](http://ec.europa.eu/health/programme/docs/wp2011_en)

- DG Sanco Work Plan 2012  
[http://ec.europa.eu/health/programme/docs/wp2012\\_en.pdf](http://ec.europa.eu/health/programme/docs/wp2012_en.pdf)
- DG Research and Innovation FP7 Calls  
[http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.FP7ActivityCallsPage&id\\_activity=1](http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.FP7ActivityCallsPage&id_activity=1)
- EMA Work Programme 2011  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Work\\_programme/2011/02/WC500102044.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2011/02/WC500102044.pdf)
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## KEY DOCUMENTS

### DG Enterprise and Industry

- Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision)  
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- Final Conclusions and Recommendations of the High Level Pharmaceutical Forum (2<sup>nd</sup> October 2008)  
[http://ec.europa.eu/pharmaforum/docs/final\\_conclusions\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf)
- Initial investigation to assess the feasibility of coordinated system to access orphan medicines (Gesundheit Österreich GmbH, May 2011)  
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### DG Health and Consumers

- RDTF Report – Overview of Current Centres of Reference on rare diseases in the EU - 12 September 2005  
<http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf>
- RDTF Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and Recommendations of the Rare Diseases Task Force – 1 September 2006  
<http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>
- RDTF Report – State of the Art and Future Directions – 11 March 2008  
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- RDTF Report: Health Indicators for Rare Diseases: State of the art and future directions – June 2008  
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<http://www.eucerd.eu/upload/file/Publication/RDTFOD2007.pdf>
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- EUCERD Report: Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for rare diseases - May 2011  
<http://www.eucerd.eu/upload/file/Reports/ERN2011Analysis.pdf>

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- COMP Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009)  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2010/07/WC500095341.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf)

#### DG Research and Innovation

- International Rare Disease Research Consortium (IRDiRC) First Workshop Summary Report  
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- International Rare Disease Research Consortium (IRDiRC) Second Workshop Summary Report  
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#### OTHER DOCUMENTS

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- Orphanet Report Series: Prevalence by decreasing prevalence or number of published cases  
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- Orphanet Report Series: Patient registries in Europe  
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- Orphanet Report Series: List of orphan drugs in Europe  
[http://www.orpha.net/orphacom/cahiers/docs/GB/list\\_of\\_orphan\\_drugs\\_in\\_europe.pdf](http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf)
- Orphanet Report Series: European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases and European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases  
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- EURORDIS report: Rare Diseases: Understanding this Public Health Priority" (November 2005)  
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- EURORDIS report: Results of the 4<sup>th</sup> EURORDIS Survey on Orphan Drug Availability in Europe (2007)  
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## 2. INTERNATIONAL SOURCES

#### WEBSITES

- International Rare Disease Research Consortium (IRDiRC)  
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- Topic Advisory Group for Rare Diseases – Revision of the WHO ICD  
<http://www.who.int/classifications/icd/TAGs/en/index.html>

#### REPORTS/ ARTICLES USED FOR THE UPDATE OF THIS REPORT

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