

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



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

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

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

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

Disclaimer:

The findings and conclusions in this report are those of the contributors and validating authorities, who are responsible for the contents; the findings and conclusions do not necessarily represent the views of the European Commission or national health authorities in Europe. Therefore, no statement in this report should be construed as an official position of the European Commission or a national health authority.

Copyright information:

The “2014 Report on the State of the Art of Rare Disease Activities” is copyrighted by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD). This product and its contents may be used and incorporated into other* materials on the condition that the contents are not changed in any way (including covers and front matter) and that no fee is charged by the reproducer of the product or its contents for their use. The product may not be sold for profit or incorporated into any profit-making venture without the expressed written permission of the EUCERD Scientific Secretariat. Specifically:

- 1) When the document is reprinted, it must be reprinted in its entirety without any changes.
- 2) When parts of the documents are used or quoted, the following citation should be used.

*Note: The “2014 Report on the State of the Art of Rare Disease Activities in Europe” contains material copyrighted by others. For material noted as copyrighted by others, the user must obtain permission from the copyright holders identified in the document.

To quote this document:

Rodwell C., Aymé S., eds., “2014 Report on the State of the Art of Rare Disease Activities in Europe”, July 2014.

<http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesIV.pdf>

©European Union, 2014

Cover photo credit: Michel Depardieu ©Inserm

CONTENTS

A. EUROPEAN MEDICINES AGENCY (EMA) ACTIVITIES.....	6
1. EMA activities in the field of orphan medicinal products and therapies for rare diseases.....	6
2. EMA Committee for Orphan Medicinal Products' (COMP) activities	9
3. EMA Committee on Human Medicinal Products (CHMP) activities	10
4. EMA activities in the field of clinical trials	11
5. EMA activities in the field of advanced therapies	12
6. EMA activities in the field of medicinal products for paediatric use.....	14
7. Other EMA activities and initiatives relevant to rare diseases and orphan medicinal products	15
8. International cooperation between regulators in the field of orphan medicinal products	17
B. OTHER EUROPEAN RARE DISEASE ACTIVITIES	20
1. Pharmaceutical Forum (2005-2008)	20
2. E-Rare	20
3. Clinical genetics as a medical speciality	21
4. Resolution on pharmacy prepared medicinal products adopted by the Council of Europe (2011)	21
5. International Rare Disease Events in 2013	22
6. Other European activities in the field of rare diseases in 2013	22
CONTRIBUTIONS, SOURCES, METHODOLOGY AND STRUCTURE	24

ACRONYMS

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

GENERAL INTRODUCTION

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

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

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

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2013

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

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

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

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

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

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

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 Agency¹

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 procedure². 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 advice³ and other assistance to companies for the development of new medicines. It publishes guidelines on quality-, safety- and efficacy-testing requirements. A dedicated SME Office⁴, established in 2005, provides special assistance to small and medium-sized enterprises.

Seven scientific committees⁵, composed of members of all EU and EEA-EFTA states, some including patients' and doctors' representatives, conduct the main scientific work of the Agency: the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO), the Committee for Advanced Therapies (CAT), and the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC started working in 2012 and it is the last Committee being created at the Agency; and is 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 monitoring the effectiveness of those risk management systems.

The Agency works with a network of over 4,500 'European experts'⁶ 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 network⁷ comprising over 40 national competent authorities in 30 EU and EEA-EFTA countries, the European Commission, the European

¹ 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

² 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

³ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800229b9

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cc

⁵ 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

⁶ 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

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 nations⁸. 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 referral⁹ or arbitration procedures relating to medicines that are approved or under consideration by Member States in non-centralised authorisation procedures.

Work programme

The European Medicines Agency's Management Board, at its meeting on 13 December 2012, adopted the Agency's work programme and budget for 2013¹⁰. The Agency's priorities will be to continue to ensure that assessment activities are conducted to the highest scientific levels, to increase efficiency in its activities, and to develop initiatives for greater transparency and communication with stakeholders. Further specific drivers include the continued implementation of the pharmacovigilance legislation and the new falsified-medicines legislation, and the planned revision of the veterinary medicines legislation. In 2013, the Agency expects a stable total number of applications for human medicines, with 100 applications in 2013. These include some 54 applications for new medicinal products (excluding designated orphan medicines), 20 new orphan medicines and 20 generic applications (2012: 52, 13 and 39 respectively). Some 10 applications for new veterinary medicines are expected, with 3 generic applications (2012: 9 and 3 respectively). The work programme is accompanied by a budget of €231.6 million, an increase of 4.1% over 2012, which includes fee revenue of €179.8 million (3.8% increase compared with 2012, this increase is mainly due to inflation) and a European Union (EU) contribution of €39.2 million.

During 2013 the Agency aimed at continuing to foster its approach to communication and transparency in order to strengthen public confidence in the Agency and the EU system of evaluation and supervision of medicines. The publication of the agendas and minutes of all scientific committees' meetings has already been put in place by the Committee for Orphan Medicinal Products since September 2012. Following the successful workshop in November 2012 on access to clinical-trial data and transparency, the Agency started a consultation with stakeholders at the beginning of 2013 in order to publish a policy on the release of data from clinical trials in early 2014. The EMA received more than 1,000 comments during the public consultation on its draft policy on publication and access to clinical-trial data.

In December 2014 the EMA adopted their 2014 work programme¹¹. In 2014, the Agency expects a slight general increase in its assessment activities for human medicines compared with 2013. Activities in the early stages of medicines development remain at a high level; these activities, which provide support to sponsors, include scientific advice on clinical development, orphan designation and support to micro-, small- or medium-sized enterprises. A 16% increase in the number of extensions of indication and variations applications is expected. A 12% decrease in the number of initial marketing-authorisation applications received is forecast, which is mainly due to a lower number of generic applications. The number of applications for new medicines containing a new active substance is expected to be stable. The road will also be cleared for the publication of the minutes of all scientific committees. The revision of the conflict of interests policy is also scheduled.

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 consultation¹² 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,

⁷ 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

⁸ 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

⁹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d0

¹⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/12/WC500136442.pdf

¹¹

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001990.jsp&mid=WC0b01ac058004d5c1

¹² http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf

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 2011¹³ and detailed information on the implementation of the road map was provided in the document 'From vision to reality'¹⁴.

EMA annual reports

The EMA published in 2013 the annual concerning 2012¹⁵. The report highlights the introduction of the new pharmacovigilance legislation which has led to the Pharmacovigilance Risk Assessment Committee (PRAC) and several changes in the structure of the agency. The agency has also endeavoured for an increased levels of transparency in their proceedings. The report has underscored the progress in bringing orphan medicinal products to the market. There was an 18% increase in application for orphan drug designation and a 36% increase in the number of Marketing Authorisation for OMP in 2012 compared to 2011. EMA also reported a 30% increase in the number of applications from micro, small and medium-size enterprises (SMEs), where 68% of the applications submitted by SMEs were for OMP's. According to the report, *"the Agency processed a total of nearly €7.5 million in fee reductions for designated orphan medicinal products"* in 2012. The Agency's Committee for Advanced Therapies received 3 applications for Advanced-therapy medicinal products. They also adopted a draft opinion for Glybera, the first gene-therapy medicine approved in the EU, and a *"second recommendation on certification on the quality data of a tissue-engineered product"*.

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. 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. In a welcome decision by the EMA, these SMEs continued to avail in 2013 the free services of protocol assistance (scientific advice); fee waiver for initial market-authorisation applications, pre-authorisation inspections, post-authorisation applications and annual fee waiver in the first year from marketing authorisation. However, Non-SMEs developing orphan medicinal products had fewer benefits in 2013 in some categories. Fee reductions for non-SME will now include a 40% reduction for non-paediatric protocol assistance (previously 75%) and no fee reductions for initial market-authorisation applications (previously 10%) and pre-authorisation inspections (previously 100%). Protocol assistance for paediatric-related medicines will continue to be free for non-SME. The EMA announced in 2013 greater fee reductions for large companies planning to market orphan drugs for rare diseases in the EU, thus further incentivising development of orphan medicinal products. The changes that will take effect in 2014, will offer reduced regulatory fees for larger companies and not just ones that are micro, small or medium-sized enterprises (SMEs). From 2014, non-SME companies submitting a marketing application for an orphan drug will be eligible for a 75 per cent fee reduction for non-paediatric-related initial and follow-up protocol assistance. Previously this reduction was only 40 per cent for larger firms. The EMA will also introduce a 10 per cent fee reduction for initial marketing-authorisation applications, where currently there is no reduction. There will also be a 100 per cent reduction for pre-authorisation inspections, updating the current situation where no fee reduction is offered. These incentives are intended to encourage more

¹³ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf

¹⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/10/WC500115960.pdf

¹⁵ http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2013/04/WC500142077.pdf

pharma companies to enter the growing rare disease market, which has tended to be off-putting for drug makers due to the limited customer base.

Incentives for SMEs in 2013

The European Medicines Agency (EMA) has continually provided incentives to micro, small and medium size enterprises to support them in the development of orphan medicines.

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 Products¹⁶ (COMP) at the European Medicines Agency (EMA). The COMP is comprised of health professionals representing each of the Member States, three patient representatives, and three other representatives nominated by the EC after recommendation from the EMA. The Committee meets once a month and it is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union. The Commission adopts decisions on designation based on an opinion from the COMP. The EMA maintains a searchable list of opinions on rare disease (orphan) designations¹⁷. The fulfilment of the criteria for designation are reviewed by the COMP at the time of marketing authorisation, recommending to the Commission whether the medicinal product should enter the market as an orphan or a non-orphan product. 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 Commission¹⁸. 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.

The COMP is presently chaired by Bruno Sepodes (Portugal) and co-chaired by Lesley Greene (Patient Representative, UK). 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 implementation¹⁹, the Orphan Regulation has yielded more than 1234 positive opinions for orphan product designation, adopted from 1798 applications reviewed since 2000. To date, the distribution of the prevalence of conditions for which the designations have been adopted shows that the most frequently designated conditions have been those that affect between 1 and 3 in 10 000 patients, that is between approximately 50 000 and 150 000 people (receiving 50% of all orphan designations). Indeed, 48% of the orphan medicinal products having obtained market authorisation in the EU, are for the treatment of diseases affecting less than 1 in 10 000 patients.

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

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,

¹⁶This section reproduces information from <http://www.ema.europa.eu/htms/general/contacts/COMP/COMP.html>

¹⁷http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/orphan_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d12b

¹⁸<http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>

¹⁹Data provided by EMA

http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2014/01/WC500159429.pdf

oligonucleotides): at the end of 2013, the COMP had given more than 80 positive opinions for advanced therapy products out of a total of 1234 opinions for orphan medicinal product designation.

Positive opinions on orphan designations in 2013

The COMP adopted 136 positive opinions on orphan designations in 2013. The European Commission granted 136 orphan designations in 2013. Seven orphan medicinal products received marketing authorisation in 2013 covering 8 conditions (due to variations)²⁰.

EMA's Committee for Orphan Medicinal Products initiative to publish prevalence information (2012)

As part of a general growing trend toward sharing data and resources in the interest of facilitating rare disease and orphan drug information and research, the European Medicines Agency (EMA) has created a table of relevant sources for prevalence data for orphan conditions²¹. The sources included in the document were validated by the Committee for Orphan Medicinal Products (COMP) during the evaluation of orphan designation applications. The table, publicly available, will be updated on a regular basis. While sponsors are still required to submit original, verifiable, current prevalence data with their application for an orphan designation, the table is considered a useful resource for facilitating access to such data. Orphan designated medicinal products are indicated for conditions that affect 5 persons or less per 10 000 of the population in the EU. Determining prevalence can be challenging for stakeholders. The new table lists the sources, such as relevant scientific literature, registries and databases, used to determine prevalence for a condition at the time an orphan designation was sought.

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 use²², 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.

CHMP opinions in 2013 concerning orphan medicinal products

In 2013, the CHMP issued positive opinions for marketing authorisation applications for the following medicinal products with orphan designation: Bosulif for treatment of chronic myeloid leukaemia, Iclusig for the treatment of chronic myeloid leukaemia and the treatment of acute lymphoblastic leukemia, Pomalidomide for

²⁰ Data provided by EMA and

http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2013/03/WC500140633.pdf

²¹

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001576.jsp&mid=WC0b01ac058004d5c1

²² 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

treatment of multiple myeloma, Procysbi for treatment of cystinosis, Orphacol for treatment of inborn errors in primary bile-acid synthesis, Defitelio for treatment of severe hepatic veno-occlusive disease, and Opsumit for treatment of pulmonary arterial hypertension.

CHMP guidelines on the clinical investigation of orphan medicinal products

In 2013 consultations on guidelines for the clinical investigation of medicinal products for Duchenne and Becker muscular dystrophies, and chronic primary immune thrombocytopenia were launched by the CHMP.

4. EMA activities in the field of clinical trials

EudraCT Database

A European database – EudraCT²³ – 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”²⁴, 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)²⁵, 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.

Public access does not currently extend to data concerning trial results. The guideline relating to the posting and publication of result-related information in EudraCT has been published by the European Commission, in accordance with Article 57(2) of Regulation (EC) No 726/2004 and Article 41 of Regulation (EC) No 1901/2006 and their implementing guidelines 2008/C168/02 and 2009/C28/01. This guideline covers the sharing of result-related information in the public domain. Additionally, the technical guidance on the format of the fields provides a visual representation of the clinical trial results data that are required to be captured by EudraCT. At present, no result-related data is uploaded in EudraCT, but this will change with the release of EudraCT v9, later in 2013. After this date, clinical trial result fields identified as public will be available to users of the EU Clinical Trials Register.

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 (ENCePP²⁶).

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.gov²⁷ 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 project²⁸ on the harmonisation of data sets

²³ <https://eudract.ema.europa.eu/>

²⁴ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

²⁵ http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true

²⁶ <http://www.encepp.eu/>

²⁷ <http://clinicaltrials.gov/>

²⁸ <http://www.hl7.org/index.cfm?ref=nav>

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 paper²⁹ 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.

Workshop on clinical trial data and transparency (22 November 2012)

The European Medicines Agency (EMA) announced in 2012 that it will proactively publish clinical trial data and enable access to full data sets by interested parties. As there are a number of practical and policy issues that need addressing before complex data sets can be made available, a workshop was held on 22 November 2012 to discuss topics relating to this evolution. The workshop sought to elicit the views and concerns from a broad range of institutions, groups and individuals in order to help the Agency define the modalities of proactive access to clinical trial data. A report³⁰ was published after the workshops which presents the debate that was at the heart of the clinical-trial transparency event, and also outlines the Agency's action plan with regard to access to clinical-trial data.

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)³¹ – the EMA's sixth scientific committee. Created following new European Union legislation concerning the regulation of advanced-therapy medicinal products (Regulation (EC) 1394/2007³²), 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 has to "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.

As of April 2013, 14 orphan products have been classified as ATMPs since the CAT was created: ATMP classification allows companies to verify whether the product they are developing meets the definition of an advanced therapy product and can benefit from the new regulatory pathway for these products. 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 statement³³ 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,

²⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/06/WC500091530.pdf

³⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/12/WC500135842.pdf

³¹ 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&isenabled=true

³² <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>

³³ http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/04/WC500089472.pdf

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 2010³⁴ 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 tiparvec) 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 system³⁵ 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 668/2009³⁶ "... 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 2010³⁷ with the overarching goal of bringing more advanced therapy products to the market. Measures, some of which are already underway, include "training and early dialogue" with relevant stakeholders and an examination of the existing regulatory framework with an eye to making it "...more accessible for small and medium-sized enterprises, academia, patient groups, hospitals, charity foundations and trusts developing ATMPs".

Procedural advice on the provision of scientific recommendation on classification of advanced-therapy medicines (2013)

The EMA released a reflection paper³⁸ on the classification of advanced-therapy medicines for public consultation in 2013. The paper clarified the legal basis for the classification of medicines as advanced therapies and provides information on how these medicines are classified as gene therapy, somatic-cell therapy, tissue-engineered or combined medicines. The paper additionally discussed the information required

³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20190786>

³⁵ 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

³⁶ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:194:0007:0010:EN:PDF>

³⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/11/WC500099025.pdf

³⁸ [Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation \(EC\) No 1394/2007](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/04/WC500099025.pdf)

for application for classification. In December 2013 the Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with Article 17 of Regulation (EC) No 1394/2007³⁹ was published.

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

Paediatric Committee (PDCO)

The main responsibility of the Paediatric Committee (PDCO) at the EMA, established after the introduction of Regulation (EC) N° 1901/2006⁴¹, is to assess the content of proposed paediatric investigation plans and adopt opinions on them in accordance with Regulation (EC) 1901/2006 as amended. This includes the assessment of applications for paediatric investigation plans with a full or partial waiver and assessment of applications for paediatric investigation plans with deferrals. The PDCO is not responsible for the evaluation of marketing-authorisation applications for medicinal products for paediatric use. This remains fully within the remit of the Committee for Medicinal Products for Human Use (CHMP). However, the CHMP or any other competent authority may request the PDCO to prepare an opinion on the quality, safety and efficacy of a medicinal product for use in the paediatric population if these data have been generated in accordance with an agreed paediatric investigation plan.

The Paediatric Committee (PDCO) has developed an inventory process aiming to identify areas in which further research and development specific to paediatric medicinal products are needed. Such an inventory could assist industry in identifying opportunities, provide a source of information for healthcare professionals and patients, and aid various PDCO assessment processes. The Agency published lists of medicines by therapeutic class progressively during 2012 and 2013. Each list was open for comments for two months after publication. The lists are available in online⁴².

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)⁴³. 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 list⁴⁴ was compiled following a call for expressions of interest in 2010. Some 36 networks and centres have thus far applied for membership. Of these, 18 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)

³⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf

⁴⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf

⁴¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF>

⁴²

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000096.jsp&mid=WC0b01ac05800260a1

⁴³ http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a

⁴⁴ http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500100152

In 2011 the European Medicines Agency made available a database⁴⁵ 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) launched in 2010 the ENCePP E-Register of Studies, a publicly available electronic register developed with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)⁴⁶ allowing users to consult the pharmaco-epidemiological and pharmacovigilance studies that are undertaken by academic centres and other research organisations. The E-Register offers a database resource of information on the safety and effectiveness of medicinal products. An added dividend of the E-Register is the contribution to the reduction of publication bias by *“...handling both positive and negative study results in the same manner and promote exchange of information, thereby facilitating collaboration within the scientific community and preventing unnecessary duplication of research”*. While the registration of a study in E-Register is completely voluntary, studies applying for the ‘ENCePP Studies’ seal that is *“awarded to wholly or partially EU-based, benefit/risk studies that are carried out in compliance with the ENCePP Code of Conduct for independence and transparency and the ENCePP Checklist of Methodological Research Standards”* need to register before they commence.

EMA Public Register for SMEs (2010)

The European Medicines Agency launched in 2010 a public register⁴⁷ 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 paper⁴⁸ 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.

⁴⁵ <http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/>

⁴⁶ <http://www.encepp.eu/encepp/studiesDatabase.jsp>

⁴⁷ <http://fmapps.emea.europa.eu/SME/>

⁴⁸ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf

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

EudraGMP⁴⁹ 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.

Public website for reports of adverse effects (2012)

The European Medicines Agency (EMA) launched in 2012 a public website⁵⁰ housing reports of adverse effects suspected in medicinal products authorised in the European Economic Area (EEA). The reports originate from national medicines regulatory authorities and the pharmaceutical companies that hold marketing authorisations for the medicines and are extracted from EudraVigilance, the European Union medicinal product safety database. The website launch is in compliance with EudraVigilance⁵¹ Access Policy, developed to improve public health by supporting the safety-monitoring of medicines and increasing the EMA’s level of transparency. According to a press release, the new website houses data on some 650 medicinal products, and gathers various incidents on a given product into one report. The information can be viewed by various features, including age, gender, the nature of the adverse effect, and outcome. There is also information provided on how to report a suspected adverse reaction to a medicine. The website is available in all 23 EU languages.

Pilot for electronic application forms for submission of centralised marketing authorisation applications (2012)

The European Medicines Agency (EMA) has launched a four-month pilot phase of electronic application forms for the submission of centralised marketing authorisation applications. The pilot will allow sponsors to use an interactive PDF form for initial marketing authorisation applications for human medicines as well as variation and renewal applications for human and veterinary medicines. The pilot moves forward the EMA's progression toward the standard use of electronic applications.

Public consultation on a revision of the guideline for the evaluation of human anticancer medicines (2012)

The European Medicines Agency has opened a public consultation on the revised guideline on the evaluation of human anticancer medicines. The guideline seeks to provide guidance on all stages of clinical drug development for the treatment of malignancies, including rare cancers and paediatric cancers, all of which are rare. The guideline revision emphasises exploratory studies to properly define the most appropriate target population as well as the role of biomarkers. Also new, the guideline incorporates disease-specific guidance. Comments on the reflection paper were open until 31 May 2012.

Guideline on use of pharmacogenetics in evaluating pharmacokinetics of medicines (2012)

Following a period of public consultation and the consequent adoption by the Committee for Medicinal Products for Human Use, the *Guideline on the Use of Pharmacogenetic Methodologies in the Pharmacokinetic Evaluation of Medicinal Products*⁵² has now been published by the European Medicines Agency. This guideline elaborates requirements and recommendations on when pharmacogenetic studies should be performed; how these studies should be designed and carried out; how the clinical impact of genetic differences between patients should be evaluated; how dosing or treatment recommendations for genetic subpopulations should be studied; consequences for treatment recommendations and labelling; and the impact of interactions between medicines and of impaired or immature organ function. Companies applying for marketing authorisation should follow the guideline from 1 August 2012.

⁴⁹ <http://eudragmp.ema.europa.eu/inspections/displayWelcome.do>

⁵⁰ <http://www.adrreports.eu/index.html>

⁵¹ <http://eudravigilance.ema.europa.eu/human/index.asp>

⁵² http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500121954.pdf

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 are aimed at establishing contacts that facilitate exchange of information and discussion of regulatory issues in order to respond to the globalisation of product development and research.

The COMP has established an active international cooperation. In 2008, the Committee started collaboration with the United States Food and Drug Administration (FDA), allowing applications for orphan-drug designations to be submitted in parallel to the two agencies. The parallel submission process helps rationalise the development of orphan medicines by facilitating access to parallel scientific advice (protocol assistance) from the two regulatory authorities. Based on the success of this collaboration, which led to 62% of applications submitted in parallel in the EU and the FDA in 2012, last year the COMP began to collaborate with the Japanese regulatory authorities. An increase in the number of Japanese orphan-drug designations with prior European designations was observed in 2012. A dialogue with Health Canada has been established and a closer collaboration with this country is anticipated.

EU-USA collaboration in the field of orphan medicinal products⁵³

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 2010⁵⁴. They are now effective for an indefinite period without the need for further renewal.

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

The interaction between the Agency and the FDA has been supported further by the transatlantic administrative simplification action plan^{55,56}. This plan was set up in November 2007 by the European

⁵³Information taken from the page

http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000228.jsp&url=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176e&jsenabled=true#section2 (accessed 22/04/2011).

⁵⁴http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/document_listing/document_listing_000228.jsp&url=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003176e&jsenabled=true#section2

⁵⁵http://ec.europa.eu/health/files/international/doc/eu_fda_action_plan_200806_en.pdf

⁵⁶http://ec.europa.eu/health/files/international/2009_tas_implementation_report.pdf

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.”* 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 in London 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. In 2012 the two regulatory agencies held a second workshop in Washington. The workshop provided information about the EMA and FDA Orphan Drug Designation programs, the FDA Humanitarian Use Device (HUD) Designation program, the FDA Orphan Products Grants program, and European Union (EU) rare disease research programs to over 200 participants from over 11 countries representing pharmaceutical, biotechnology, device companies, academia, drug and device regulators. The workshop was held in partnership with the European Organisation for Rare Diseases (EURORDIS), Genetic Alliance and the National Organization for Rare Disorders (NORD).

The FDA published a report⁵⁷ 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.

In fiscal year 2012, FDA continued to bring innovative drugs to patients in the United States quickly and efficiently, while ensuring that medicines are safe and effective. Of the 35 novel drugs approved in 2012⁵⁸, nine concerned orphan diseases, continuing FDA's commitment to approve drugs for patients with rare conditions. Again, FDA expedited the review and approval of over half of these innovative medicines by using its several review authorities for important new drugs, including Fast Track, Priority Review, and Accelerated Approval.

A workshop on orphan product designation and grants took place on 10 March 2014 at the EMA⁵⁹. Jointly organised by the EMA, the FDA and for the first time the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), this one day workshop was an effort towards bringing more treatments for rare disease patients faster. This one-of-a-kind workshop brought together the regulatory authorities from three large regions with legislation encouraging orphan medicinal product development: the United States, European Union and Japan. The agencies representing these areas,

⁵⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM278358.pdf>

⁵⁸ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM330859.pdf>

⁵⁹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/12/event_detail_000810.jsp&mid=WC0b01ac058004d5c3

with contributions from Canada and Australia, have worked jointly over the years to improve the quality and number of orphan designations as well as encourage parallel submission for orphan medicinal designation. The workshop aimed at enhancing efficiency and avoiding ambiguity between the agencies and sponsors by highlighting 3 areas, the process of granting orphan medicine designation by the FDA, MHLW/PMDA and EMA, the post designation incentive programmes (accessible after receipt of designation) and the grants available through the FDA, European Commission and NIBIO (Japan) intended to boost research and development in the therapeutic management of rare diseases. Finally the sponsors also had a chance to attend 40 minute face-to-face sessions with the 3 agencies to discuss their individual concerns or comments.

Confidentiality agreement with Japan (2012)

The European Medicines Agency and the European Commission announced in 2012 the extension of their confidentiality arrangement with the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency of Japan, established in 2007, for another year⁶⁰. Under the arrangement, advance drafts of legislation and regulatory guidance documents, scientific advice on medicine development, assessments of applications for marketing authorisations and information concerning the safety of marketed medicines may be exchanged between the two agencies. This is welcome news for the rare disease and orphan drug community, which is striving to reduce duplication of effort and encourage cooperation in the field. 22% of current submissions are now made in parallel.

Joint work plan with EUnetHTA (2013)

The EMA has agreed a three-year joint work plan with EUnetHTA⁶¹, which represents health technology assessment (HTA) bodies across Europe in an effort to harness its relationship with national bodies that assess cost-effectiveness of drugs. In this plan enhancement in collaboration was key, so that the work done by the EMA can assess the benefits and risks of a medicine for approval in the EU while at the same time addressing the needs of HTA organisations, which in turn assess the suitability of approved medicines for national reimbursement. However, the need for extended scientific advice and early dialogue between the EMA, HTA bodies and pharma companies was also commented in the plan. Also included in the plan is the exchange of ideas on the development of scientific and methodological guidelines to facilitate clinical-trial design that can generate data relevant to both parties. Additionally, collection of post-authorisation data once the drug is on the market and specific ways to share information on orphan drugs for rare diseases are also part of the plan. This publication is part of a collaborative effort between the EMA and EUnetHTA initiated in 2010 to address the recommendations made by the Pharmaceutical Forum – a group comprising members from Member States, EU institutions, industry, healthcare professionals and patients.

⁶⁰ http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001429.jsp&mid=WC0b01ac058004d5c1

⁶¹ www.eunetha.eu

B. OTHER EUROPEAN RARE DISEASE ACTIVITIES

1. Pharmaceutical Forum (2005-2008)

The Pharmaceutical Forum⁶² 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”⁶³ developed by its members, The High Level Pharmaceutical Forum recommended the following⁶⁴: 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. E-Rare

The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis, few medicinal products and difficult access to care. That is why rare diseases are a prime example of a research area that strongly profits from coordination on a European scale. ERA-Net E-Rare was launched in 2006 and its second phase in 2010 (E-Rare-2, 2010 - 2014, FP7). The major goals of E-Rare are to foster systematic exchange of information and build a transnational research programme on rare diseases. The E-Rare Consortium gathers seventeen research-funding organisations from 13 European and Associated countries (Austria, Belgium, France, Greece, Germany, Hungary, Italy, Israel, Portugal, Romania, Spain, the Netherlands and Turkey) as well as Poland and Latvia, as observers. To continue and expand its activities in accelerating the development of new diagnostics and therapeutics for patients suffering from rare diseases in 2012 E-Rare joined the International Rare Diseases Research Consortium (IRDiRC). As a member of IRDiRC E-Rare strongly promotes transnational funding activities and facilitates the participation of a wide range of different funding organisations which might not have a strong RD research funding priority giving them the opportunity to participate in the shaping of the rare diseases research landscape and policies.

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

⁶² http://ec.europa.eu/pharmaforum/index_en.htm

⁶³ http://ec.europa.eu/pharmaforum/docs/pricing_orphans_en.pdf

⁶⁴ Conclusions and Recommendations of the High Level Pharmaceutical Forum 2005-2008, Recommendation 7.3 on Access to medicines for EU citizens http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf

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

3. 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*⁶⁵. 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.

The EC Regulation No 213/2011⁶⁶ 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.

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

Resolution CM/ResAP(2011)1⁶⁷ 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.

⁶⁵ <http://admin.uems.net/uploadedfiles/1305.pdf>

⁶⁶ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:059:0004:0007:EN:PDF>

⁶⁷ <https://wcd.coe.int/wcd/ViewDoc.jsp?Ref=CM/ResAP%282011%291&Language=lanEnglish&Ver=original&BackColorInternet=DBDCF2&BackColorIntranet=FDC864&BackColorLogged=FDC864>

5. International Rare Disease Events in 2013

Rare Disease Day 2013 (28 February 2013)

The 6th edition of the annual Rare Disease Day 2013, organised by EURORDIS, was held on 28 February 2013. For Rare Disease Day 2013, which had as its theme *Rare Disorders without Borders*, thousands of activities took place in a 73 countries and regions. All around the world, rare disease stakeholders – including patients and patient alliances, health-care professionals, researchers, members of learned societies, policy makers, biopharmaceutical companies, media, and friends, turned out to help raise public and political awareness for the issues the rare disease community faces on a daily basis – a lack of knowledge and information, scarce and scattered resources, and a lack of medicines, treatments and services. New to the movement in 2013 were Bahrain, Iceland, Israel, Lebanon, Macedonia, Palestine, Saudi Arabia and Singapore.

In Brussels, EURORDIS co-hosted with Members of the European Parliament a Policy Discussion Meeting entitled “*Faster Access to Medicines for Rare Disease Patients*”, designed to move forward the process of improving access to treatment in the context of the revision of the EU Transparency Directive. The event was attended by 100 participants, and watched simultaneously by over 200 viewers from 10 countries through livestreaming.

Rare Disease Day was also the occasion to acknowledge the outstanding contributions of members of the rare disease community with the 2013 EURORDIS Awards⁶⁸.

The Internet and social media again proved successful in spreading the Rare Disease Day message and allowing the rare disease community to interact and share. The Rare Disease Day⁶⁹ website received over 20 000 visits on 28 February alone. In the months leading up to Rare Disease Day, visits topped 75 000. Hundreds of photos and videos were uploaded to the website’s *Tell Your Story* section, including scores of images demonstrating the Rare Disease Day call to raise and join hands.

The official Rare Disease Day 2013 video, created to raise awareness for this year’s theme of solidarity, and particularly international cooperation and collaboration, was translated into 15 languages and viewed over 60,000 times. The video was “liked” over 140,000 times on Facebook. Rare Disease Day also garnered plenty of “tweets” via Twitter. With some 28,000 tweets on 28 February (working out to about 17 tweets per minute), social media was a key tool for awareness raising.

From a Rare Disease Day Barbecue in Australia, to a scientific symposium in Bahrain, or a daylong event in Singapore based around the theme *Love is not Rare* the array of events on offer around the world was as diverse and original as the participants themselves. Painting classes, press conferences, policy events, petitions, fun runs, medical conferences were among the events that took place.

6. Other European activities in the field of rare diseases in 2013

ECRIN-ERIC

The European Clinical Research Infrastructures Network (ECRIN⁷⁰) is a non-profit organisation that supports multinational academic clinical research projects in Europe which is “*hampered by the fragmentation of health and legislative systems in Europe*”. ECRIN provides information, consulting and services to investigators and sponsors in the preparation and in the conduct of multinational clinical studies, for any category of clinical research and in any disease area. This is particularly relevant for investigator-initiated or academic clinical trials, and for clinical research on rare diseases where international cooperation is a key success factor. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.

On 29 November 2013, ECRIN was officially awarded the status of European Research Infrastructure Consortium (ERIC), a legal status designed to facilitate the joint establishment and operation of research infrastructures of European interest. Germany, Spain, France, Italy and Portugal are the founding members of ECRIN-ERIC, whose management office is located in the host country (France), in Paris.

In 2013, ECRIN organised a call for applications to allow multinational extension of trials already

⁶⁸ <http://www.eurordis.org/eurordis-awards>

⁶⁹ <http://www.rarediseaseday.org>

⁷⁰ www.ecrin.org

funded in the coordinating country in three specific areas: Nutrition, Medical Devices and Rare Diseases. Trials were proposed by public or private non-profit institutions, and to address important clinical questions. The evaluation process was based on the possible impact on the health of European citizens, the scientific merit and excellence, and the feasibility of each proposed trial. Project selection was carried-out by the ECRIN IA Scientific Board (which also includes patients representatives), supported by external peer-reviewers, each assessing one clinical trial in his/her specific field of competence, and three methodologists, each assessing all the trials pertaining to one of the clinical areas considered by the call. The ECRIN European Correspondents provided the Board with an estimation of the logistical feasibility and cost of the trials. Eight clinical trials, involving a total of 21 European countries, were recommended for free access to ECRIN services : 4 of the trials chosen are in the field of rare disease research.

CONTRIBUTIONS AND SOURCES⁷¹

Input for this volume was received from:

Jordi Llinares-Garcia (*Head of Product Development Scientific Support*)

Stiina Aarum (*Head of Orphan Medicines, ad interim*)

Daria Julkowska (*E-Rare Coordinator*)

This report was compiled by Charlotte Rodwell

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

A full list of the over one hundred contributors to the State of the Art report and its sources can be found here:

http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivities_ContributionsSources.pdf

METHODOLOGY AND STRUCTURE

1. SOURCES

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

- **European Commission websites and documents**

Information and documentation from the European Commission was used in order to establish this report, principally accessed through the rare disease information web pages of the Directorate General Public Health⁷² and Directorate General Research CORDIS website⁷³ as well as the site of the European Medicines Agency⁷⁴, in particular the pages of the COMP⁷⁵ (Committee of Orphan Medicinal Products).

- **OrphaNews Europe**

Data from the OrphaNews Europe⁷⁶ newsletter for the 2013 period was reviewed and analysed in order to identify initiatives, incentives and developments in the field of rare diseases. The data chosen for analysis and inclusion in the report is mainly information concerning actions of the Commission in the field of rare diseases, the development of rare disease focused projects funded by the Commission and other bodies, and developments in the field of rare diseases at MS level (in particular data

⁷¹ 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.

⁷² http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

⁷³ http://cordis.europa.eu/home_fr.html

⁷⁴ www.ema.europa.eu

⁷⁵ 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

⁷⁶ <http://www.orpha.net/actor/cgi-bin/OAhome.php?Ltr=EuropaNews>

concerning the development of national plans and strategies for rare diseases). A similar analysis of the French language newsletter OrphaNews France⁷⁷ (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 EUCERD⁷⁸ (July 2010), 2011 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD⁷⁹, 2012 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD⁸⁰, and the 2013 Report on the State of the Art of Rare Disease Activities in Europe of the EUCERD⁸¹. The methodology for the production of these previous reports is outlined in their respective introductions. In addition, reports from previous workshops of the EUCERD, including the EUCERD Joint Action have been used.

- **Reports of the EUCERD meetings**

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

- **Reports on orphan medicinal products**

The information provided for each Member State concerning the state of affairs in the field of orphan medicinal products has been elaborated, when referenced, from the basis of the 2005 revision of the *Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products*⁸² 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*)⁸³. This report notably provided information for the Member State sections on Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The Office of Health Economics Briefing Document "*Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries (No. 52 October 2009)*" also provided information on orphan medicinal product availability and reimbursement for the Member State sections on France, Germany, Italy, Spain, Sweden, the Netherlands and the United Kingdom. Further detail for Part V was added during the revision of the 2012 edition thanks to the JustPharma report *Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, 2011 Edition*⁸⁴ by Donald Macarthur: this report is referenced in footnotes when used.

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

The site of EURORDIS, the European Organisation for Rare Diseases⁸⁵ was used to provide information on EURORDIS activities and projects and to collect data concerning umbrella patient organisations in each of the European Member States and country-level rare disease events. The websites of national

⁷⁷ <http://www.orpha.net/actor/cgi-bin/OAhome.php>

⁷⁸ <http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf>

⁷⁹ <http://www.eucerd.eu/upload/file/Reports/2011ReportStateofArtRDActivitiesI.pdf> ;

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

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

⁸⁰ <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivitiesI.pdf> ;

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

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

⁸¹ <http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivitiesI.pdf>

⁸² http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf

⁸³ *Politiques relatives aux maladies orphelines et aux médicaments orphelins*

https://kce.fgov.be/sites/default/files/page_documents/d20091027332.pdf

⁸⁴ <http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe->

[%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf](http://www.justpharmareports.com/images/Orphan%20Drugs%20in%20Europe-%20Pricing,%20Reimbursement,%20Funding%20&%20Market%20Access%20Issues,%202011%20Edition.pdf)

⁸⁵ <http://www.EURORDIS.org/secteur.php3>

patient alliances were also consulted for information. In addition to this the Rare Disease Day site⁸⁶, maintained by EURORDIS, also provided information on events at Member State level⁸⁷ concerning Rare Disease Day.

- **Orphanet**

The Orphanet database was consulted to retrieve data on centres of expertise and the number of genes and diseases tested at Member State level, as well as specific information concerning rare disease research projects, registries, clinical trials, patient organisations and rare disease/orphan medicinal product policies outside of Europe for Part I. Orphanet also provides links⁸⁸ to other web-based information services and help-lines which were used to collect information at country-level. The Orphanet Country Coordinators also provided valuable input into the elaboration of information at country level, notably via contributions to OrphaNetWork News. The national Orphanet websites were also consulted to gather national events and initiatives.

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

2. METHODOLOGY

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

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

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

Part I was the final volume of the report to be elaborated: the overview of the state of the art of rare disease activities in Europe is the result of an analysis of the information collected for Parts II, III, IV and V. Part I was

⁸⁶ <http://www.rarediseaseday.org/>

⁸⁷ <http://www.rarediseaseday.org/country/finder>

⁸⁸ http://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=EN

drafted by the Scientific Secretariat of the EUCERD Joint Action and then sent to all EC Expert Group on Rare Diseases Member State representatives for their input concerning their country's activities before publication in June 2014.

3. REPORT STRUCTURE

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

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

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

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

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

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

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

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

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

relevant to rare diseases and orphan medicinal products, EU-USA collaboration in the field of orphan medicinal products and other EC activities and initiatives in the field of orphan medicinal products.

- The sub-section concerning other European rare disease activities provides information on transversal rare disease activities and initiatives at EU level and includes information on the High Level Pharmaceutical Forum, actions undertaken in the scope of recent European Union presidencies, the E-Rare ERA-Net for rare diseases and outcomes of European and International rare disease congresses and conferences in 2013.

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

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

- Definition of a rare disease
- National plan/strategy for rare diseases and related actions
- Centres of expertise⁸⁹
- Registries
- Neonatal screening policy
- Genetic testing⁹⁰
- National alliances of patient organisations and patient representation;
- Sources of information on rare diseases and national help lines
- Guidelines
- Training and education initiatives
- National rare disease events in 2013⁹¹
- Hosted rare disease events in 2013⁹²
- Research activities (National research activities, Participation in European research projects⁹³, Participation in E-Rare, Participation in IRDiRC)
- Orphan medicinal products (Orphan medicinal product committee, Orphan medicinal product incentives, Orphan medicinal product availability⁹⁴, Orphan medicinal product pricing policy, Orphan medicinal product reimbursement policy, Other initiatives to improve access to orphan medicinal products), Other therapies for rare diseases
- Orphan devices
- Specialised social services

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

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

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

⁸⁹ The term “official centre of expertise” used in this report means officially designated via a (ministerial) procedure.

⁹⁰ This section contains data extracted in January 2014 from www.orpha.net of the number of genes for which there is a diagnostic test registered in Orphanet and the estimated number of diseases for which diagnostic tests are registered in Orphanet (the term ‘estimated’ is used as the concept of a single disease is a variable one).

⁹¹ As announced in OrphaNews Europe.

⁹² As announced in OrphaNews Europe.

⁹³ Number of projects (Framework Programme 7 funded, including E-Rare) in which research teams from the country are participating as extracted from www.orpha.net in March 2014.

⁹⁴ 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.

Co-funded by the



Co-funded by
the Health Programme
of the European Union