

The European Union action in the field of rare diseases

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Abstract

Background: Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10 000). The specificities of rare diseases - limited number of patients and scarcity of relevant knowledge and expertise - single them out as a unique domain of very high European added-value.

Methods: The legal instruments at the disposal of the European Union, in terms of the Article 152 of the Treaties, are very limited. However a combination of instruments using the research and the pharmaceutical legal basis and an intensive and creative use of funding from the Second Health Programme has permitted to create a solid basis that Member States have considered enough to put rare diseases in a privileged position in the health agenda.

Results: The adoption of the Commission Communication, in November 2008, and of the Council Recommendation, in June 2009, and the future adoption of the Directive on Cross-border healthcare, end 2009 or mid 2010, have created an operational framework to act in the field of rare disease with European coordination in several areas (classification and codification, European Reference Networks, orphan drugs, European Committee of Experts, etc.).

Conclusions: Rare diseases is an area with enormous and practical potentialities for European cooperation.

Key words: rare diseases, Europe

Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 per 10 000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. This definition appeared first in EU legislation in Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products [1]. It was extended to the public health field by the Community action programme on rare diseases including genetic diseases, 1 January 1999 to 31 December 2003 [2], and most recently by the Commission Communication COMM(2008) 679 final on Rare Diseases: Europe's challenges [3] of 11 November 2008. It is estimated that between 6.000 and 8.000 distinct rare diseases exist today (currently 5 860 are described in the Orphanet database), affecting between 6% and 8% of the population in total. In other words, between 27 and 36 million people in the European Union are affected by a rare disease.

The specificities of rare diseases - limited number of patients and scarcity of relevant knowledge and expertise - single them out as a unique domain of very high European added-value. There is probably no other area in health where collaboration between 27 different national approaches can be as efficient and effective. Coordination at EU level is probably the best way of pooling the very limited resources available.

The European Union's objective in the field of rare diseases is to bring together the necessary elements for an efficient overall strategy, hence the adoption of Commission Communication COMM(2008) 679 final on 11 November 2008, setting out what the European Commission will do in this field, and the Council Recommendation on an action in the field of rare diseases [4], of 9 June 2009, advising the Member States on what they should do. The complementarity of objectives in both documents results in a clear strategy for European Union intervention in this field aimed at improving patients' access to appropriate and timely diagnoses, information and care. In this area, European action can be more

effective than Member States acting on their own. This involves the following steps:

- **making rare diseases more visible** by developing proper identification and coding of rare diseases, many of which currently go unrecognised, leading to inappropriate treatment for individuals and lack of appropriate resources overall;
- **encouraging Member States to develop national rare diseases plans in their health policies** to ensure equal access to and availability of prevention, diagnosis, treatment and rehabilitation for people with rare diseases. More initiatives in terms of public awareness-raising in the Member States are needed. In addition to targeting public opinion, these efforts should also be directed at healthcare and social services professionals, decision-makers, health and social services managers and the media;
- **providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared** everywhere in Europe. There should also be specific actions in areas such as research, centres of expertise, access to information, incentives for the development of orphan drugs and screening. Cooperation between existing European programmes also needs to be improved.

Rare diseases also differ widely in severity and in expression. Rare diseases patients have a significantly lower life expectancy. Many are complex, degenerative and chronically debilitating, whilst others are compatible with a normal life - if diagnosed in time and managed and/or treated properly. They affect physical capabilities, mental abilities, behaviour and sensorial capacities, and generate disabilities. Several disabilities often co-exist, with many functional consequences (defined as polyhandicap or plurihandicap). These disabilities enhance the feeling of isolation and could be a source of discrimination and reduce any educational, professional and social opportunities.

Under normal market conditions, the pharmaceutical industry is reluctant to invest in medicinal products and devices for rare conditions because of the very limited market for each disease. This explains why Rare Diseases are also called "**orphan diseases**": they are "orphans" of research focus and market interest, as well as of public health policies. Under the responsibility of DG ENTR of the European Commission and the EMEA (European Medicines Agency) the EU implements a policy on Orphan Drugs. The mentioned Orphan Medicinal Product Regulation

(Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products) establishes criteria for orphan designation in the EU and includes a number of incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) for research into, and the development and marketing of medicines to treat, prevent or diagnose Rare Diseases. In 2008 [5], a total of 119 applications were submitted for designation as orphan medicinal products and the Committee for Orphan Medicinal Products (COMP) adopted 86 positive opinions and one negative opinion. As in previous years, cancer treatment was the most-represented therapeutic area for which the COMP adopted positive orphan-designation opinions. Almost two-thirds of designated orphan medicinal products were for conditions affecting children and the COMP took on average 66 days to evaluate applications, the same as in the previous year (Figure 1).

There are specific bottlenecks linked to rarity and the way forward is to increase collaboration at European level to scientifically establish the (added) therapeutic value of Orphan Medicinal Products. In this respect the COMP, which is part of the European Medicines Agency, in cooperation with the future EU Committee of Experts on Rare Diseases, could make a positive contribution to any future collaboration at European level on the scientific assessment of the (added) therapeutic value of such products. This input could be used by National Competent Authorities when appraising Orphan Medicinal Products for pricing and reimbursement purposes. Access to orphan medicines should be ensured and appropriately defined within all Member States. Administrative delays beyond the 180-days legal limit should be prevented. The aim should be to ensure that patients with rare diseases are not disadvantaged in any way compared to patients with more prevalent diseases.

Over the last two decades, collaborative and coordinated research projects supported by successive European Community Framework Programmes for Research and Technological Development have made a substantial contribution to advancing knowledge on rare diseases. In the current framework programme, FP7 [6], rare diseases have been designated a priority for research activities. Research on Rare Diseases has offered us a much better understanding of the mechanism of common conditions like obesity and diabetes, as they represent a model of dysfunction of a biological

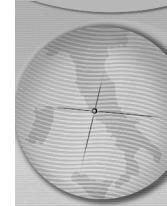
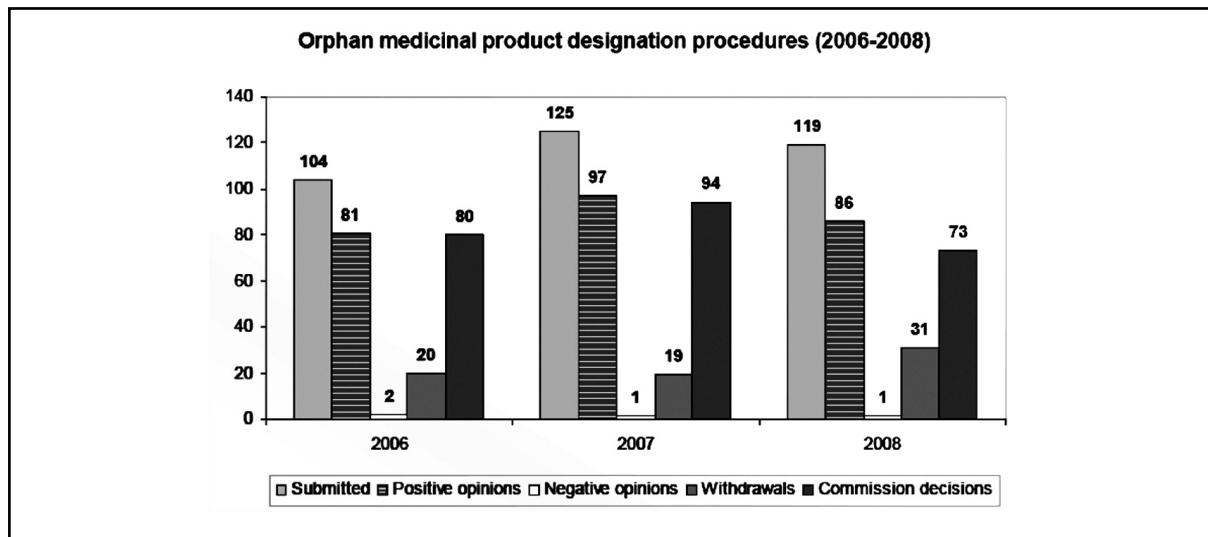


Figure 1. Orphan Medicinal product designation procedures (2006-2008).



pathway. Research on Rare Diseases has been fundamental in identifying the most currently-known human genes and a quarter of the innovative medicinal products that have received market approval in the EU (orphan drugs). The FP5 programme supported 47 research projects on rare diseases (for a total of 64 million euros). There were 59 such projects in the FP6 programme (for a total of 230 million euros). The FP7 will give priority to Europe-wide studies of natural history, pathophysiology and the development of preventive, diagnostic and therapeutic interventions. This sector will include rare Mendelian phenotypes of common diseases and should help to identify and mobilise a critical mass of expertise to (i) shed light on the course and/or mechanisms of rare diseases, or (ii) test diagnostic, preventive and/or therapeutic approaches to alleviating the negative impact of the disease on patients' and their families' quality of life, as appropriate, depending on the level of knowledge concerning the specific disease or group of diseases under study.

In 2005, DG SANCO established the High Level Group on Health Services and Medical Care (HLG) to implement the recommendations of the reflection process on patient mobility and the future adoption of a Directive on Cross-border healthcare [7]. One of its working groups deals with reference networks of centres of expertise, in particular for rare diseases. In the Commission Communication and the Council Recommendation, high importance is given to the creation of European Reference Networks on Rare Diseases. Diagnosis of a rare disease is often delayed, and for the majority of rare diseases no appropriate treatment exists. Sometimes,

knowledge and appropriate treatment of a disease may exist in another Member State but mobility of information is hampered by inefficiency and fragmentation of the limited resources available.

Rare diseases offer a prime example of the benefits of trans-national co-ordination. When diseases are rare, expertise is scarce as well. Certain centres have developed expertise which is widely used by other professionals from their country or even internationally. In some countries these centres are officially recognised, but in most they are only established by reputation. The Commission has decided to prioritise cooperation and knowledge sharing between them as the most efficient approach. Certain principles have been developed regarding European Reference Networks (ERN), including their role in tackling rare diseases or other conditions requiring specialised care, patient volumes and other criteria that such centres should fulfil. ERNs should also serve as research and knowledge networks updating and contributing to the latest scientific results, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. ERNs should also reflect the need for services and expertise to be appropriately distributed across the enlarged European Union. The EU rare diseases Task Force 2006 Report '*Contribution to policy shaping: For a European collaboration on health services and medical rare in the field of rare diseases*' [8] recommends that Member States contribute to the identification of their expert centres and support them financially as much as possible. It also recommends that Member States organise healthcare pathways for their patients through the establishment of

cooperation with all necessary expert centres within the country or from abroad when necessary.

The European Reference Networks will have a strategic role in harmonising care and improving quality of treatment for all patients throughout the European Union. Within ERNs, knowledge and expertise will be shared across different Centres. If necessary at specific moments of the development of a disease, it will be considered as "normal and fair" to travel from one Centre to another within the same network to confirm a diagnosis or seek a second opinion, or for important medical procedures, such as surgical operations, transplantations and other invasive medical interventions. It should not be an administrative, legal and medical battle for a patient to travel abroad for involuntary medical reasons.

Both approaches (transfer of knowledge and patient mobility) are useful. A centrifugal approach to transferring knowledge from the central network to a broader periphery allows more local delivery of care/treatment to patients and the dissemination of information. The benefits are care close to the patient's home/environment and dissemination of knowledge to a wide community. This however does not guarantee that the knowledge is in the hands of experts or that the patient will have access to the latest treatment/technology. A centripetal approach favouring the concentration of patients in one expert centre increases the expertise/standard of care of the centre. The benefits are a high quality of care/treatment for the patients, access to the latest technology and the possibility for patients and their families to feel less isolated. However, it keeps the expertise in the expert's hand and requires patients to travel to the centre.

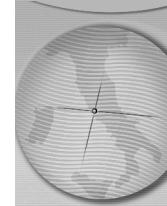
European Reference Networks should initially be evaluated at EU level via an agreed set of criteria (minimum set of standardised criteria and objectives) and then regularly assessed on common indicators using both soft and hard values. Methods and tools should also be developed in order for European reference networks to perform regular self-evaluations.

The EU should cooperate closely with WHO in revising the existing ICD (International Classification of Diseases) to ensure better codification and classification of rare diseases. All rare diseases should be adequately coded and traceable in all health information systems, thus contributing to their adequate recognition in the national health care and reimbursement systems. This has required the creation of a working group

on Classification and Codification of rare diseases, acting as an advisory working group to WHO in the current ICD revision process [9]. Once the ICD-11 becomes available, active cooperation of the EU Statistical Programme will be necessary to ensure that the new version, including new codes for rare diseases, is used for death certificates and in hospital discharge tabulation systems in all Member States. Similar efforts should also be made to ensure proper coding of rare diseases in the SnowMed and MedDRA coding systems. The ICD is always the basis for the Diagnosis Related Groups used to calculate hospital care disease costs.

Adequate information on the epidemiology and prevalence of rare diseases is a necessary basis for efficient action. This type of information is also essential when deciding whether the orphan drugs designation is appropriate. The key element for improving diagnosis and care in the field of rare diseases is to provide and disseminate accurate information in a format adapted to the needs of professionals and affected persons. Since 2000, the Orphanet database [10], with the support of the Health Programme and the Framework Programmes for Research, has been providing information concerning over 5.000 diseases in six languages. It provides a comprehensive encyclopaedia of rare diseases; a directory of professional services in 35 countries; a directory of European centres of expertise; a database of orphan drugs providing information on their stage of development and availability in EU countries; and a range of other services for specific categories of stakeholders, including a facility to retrieve diagnoses through symptoms and signs and a library of recommendations for emergency situations. Orphanet has already established a searchable database of clinical symptoms and provides a valuable resource which constitutes the European and world reference for the identification and epidemiological description of rare diseases. Funding for Orphanet should be confirmed with additional resources to allow the dictionary of rare diseases to be translated into all EU languages and provided in print version to make it accessible across all Member States. A Joint Action is scheduled in the Work Plan for the Implementation of the Health Programme for the year 2010.

The establishment of a dynamic inventory of rare diseases will contribute to tackling one of the main causes of neglect of rare diseases, namely ignorance of which diseases are rare. There is a need for an accurate inventory of rare diseases,



regularly updated and classified by medical speciality, prevalence, mechanism and aetiology, to maximise awareness and provide documentary support to research and data storage in general. This European inventory of rare diseases could also inform and influence health-care spending and planning. It would therefore need to be agreed by Member State Governments, and health, care authorities and be made available to appropriate professionals. The forthcoming EU Committee of Experts on Rare Diseases could be responsible for establishing this inventory. Consideration should be given to Orphanet's fundamental role in developing and hosting this inventory.

This support for a more EU oriented information framework does not make support for existing (or future) specific disease information networks any less essential. Exchanging information via existing European information networks, promoting better classification of particular diseases, developing strategies and mechanisms for exchanging information between stakeholders, defining relevant health indicators, developing comparable epidemiological data at EU level, supporting exchanges of best practices and developing measures for patient groups are all major priorities. Such projects make a key contribution to our overall understanding of rare diseases (e.g. EUROCAT for congenital anomalies [11], ENERCA for rare anaemia disorders [12], Rare Bleeding Disorders Database [13], EuroWilson [14], etc.). Ongoing EU projects have already proven their relevance. This type of project should be supported at both Member State and EU levels.

An excellent example of a type of project that the European Union can support in the field of rare diseases is EUROCAT (Surveillance of Congenital Anomalies in Europe). EUROCAT provides essential epidemiological information on congenital anomalies in Europe based on a common dataset with common coding as specified in the EUROCAT Guide and the EUROCAT Data Management Programme (EDMP) used by member registries for data input/import, validation and annual transmission to the Central Registry. They act as information and resource centres for the population, health professionals and managers regarding clusters or exposures or risk factors of concern. They provide a readily available collaborative network and infrastructure for research into the causes and prevention of congenital anomalies and the treatment and care of affected children, and survey policies and practices with regard to periconceptional folic

acid supplementation.

Community action in the Rare Diseases field is clearly justified by a combination of the subsidiarity principle (*"The Union does not take action (except in the areas which fall within its exclusive competence) unless it is more effective than action taken at national, regional or local level"*) and Article 152, which is the legal basis for EU action in the area of Public Health. The EU has no mandate for the organisation of health care in Member States.

In order to integrate all the necessary initiatives that have to be taken at national and/or regional levels, Member States are invited by the Council Recommendation on a action in the field of rare diseases adopted the 9th June 2009 to establish national or regional action plans or strategies for Rare Diseases before 2013 in order to implement the actions suggested in the Commission Communication and the Council Recommendation. European guidelines for the elaboration of action plans for RD might be useful. In support of this, the project EUROPLAN (European Project for Rare Diseases National Plans Development) [15] has been selected for funding in 2007 in the Public Health Programme. The project will ensure that common policy guidelines are shared everywhere in Europe and will contribute to the development of national programme for Rare Diseases within Member States linking national efforts with a common strategy at European level. EUROPLAN defines a rare diseases plan as *'A national plan/strategy (NP/NS) can be defined as the sum of integrated and comprehensive health policy actions for RD to be developed and implemented at national level. As such a NP/NS should have well specified objectives and actions to be supported by a budget, implemented within a time frame, evaluated with specific indicators'*. Only a limited number of Member States have adopted or will soon adopt a National Plan/Strategy or launch relevant initiatives. While only France has established a comprehensive action plan (2005-2008) [16] and will launch the Second Plan in 2010 and Bulgaria for the period 2009-2013 [17], other Member States have adopted national strategies not explicitly supported by a budget (Portugal, Spain) or national policies in a certain number of areas which can be translated in the form of a plan or strategy very soon (Italy, Sweden, Denmark, United Kingdom, The Netherlands, Czech Republic, Romania, Luxembourg). The development of health indicators is needed to monitor the situation of affected persons in the EU as well as its evolution. Compilation of existing

sources of data should be encouraged, especially those already funded at EU level.

Another key element of the Commission Communication (point 5.8) and in the Council Recommendation (point 17 d) is the statement that neonatal screening for phenylketonuria and congenital hypothyroidism is current practice in Europe and proved highly efficient in preventing disabilities in affected children. As technology evolves, many tests can now be performed for a wide range of rare diseases, especially metabolic disorders and genetic conditions in general. The Council Recommendation refers also to the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences, as a privileged area of cooperation between the Member States. This is the aim of a call for tender launched in July 2009 by the European Commission. The planned output is an extensive report on the practices of NBS (Newborn Screening) for rare disorders implemented in all the Member States including number of centres, estimation of the number of infants screened and the number of disorders included in the NBS as well as reasons for the selection of these disorders. A possible Council Recommendation on NBS for some rare disorders could be submitted to discussion with Member States in some years.

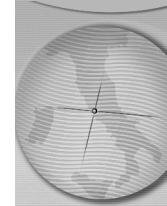
Patient organisations play an active and instrumental role in determining rare diseases research policies and projects. Due to the large number of rare diseases, there are over 1.700 patients' organisations in Europe. Many of them are organised into national alliances of rare diseases, and/or affiliated to EU disease-specific umbrella organisations, such as the European Organisation for Rare Diseases (Eurodis) [18]. Eurodis gathers organisations in 33 countries, permitting a direct dialogue between the European Commission, other stakeholders and the patient community of rare diseases. Patient organisations have proven to be invaluable partners, at the Member States and EU level, to increase the visibility of rare diseases, to gather and disseminate the information required for defining a public policy on rare diseases, to improve access to quality information on rare diseases and orphan drugs, to organise workshops at European and national level, as well as to produce guidelines and pedagogical documents.

These specific initiatives as described above (orphan drugs, codification, European Reference Networks, registries, National Plans, research on rare diseases) aim to improve the chance for patients to get appropriate care and information

on rare diseases and to reverse the current situation of uncertainty and invisibility for people suffering from a rare disease. Health professionals and public health authorities have insufficient knowledge of the majority of rare diseases. This lack of knowledge underlies diagnostic error - a great source of suffering for patients and their families - and delayed care provision, which can sometimes be prejudicial. Proposals are still being developed, but are currently structured around ten specific objectives and actions in the Commission Communication and in the Council Recommendation on an action in the field of rare diseases:

1. To improve information, identification and knowledge on rare diseases
2. To improve prevention, diagnosis and care of patients with Rare Diseases
3. To develop national/regional centres of reference and establish EU reference networks
4. To help ensure equal access to all EU patients to orphan drugs and compassionate use
5. To help to develop specialised and adapted social services for rare diseases patients
6. To accelerate research and developments in the field of Rare Diseases and Orphan Drugs in order to strengthen at European level the limited and scattered expertise on rare diseases
7. To empower patients with Rare Diseases at individual and collective level
8. To support implementation of National Plans for Rare Diseases
9. To develop international cooperation on rare diseases
10. To coordinate relevant policies and initiatives at EU level

In order to implement the Commission Communication and the Council Recommendation intensive work involving all the stakeholders will be required. In this sense a European Union Committee of Experts on Rare Diseases with representation from Member States, Patient's organisations, industry, research and public health projects on rare diseases and other interested parties will be created in 2010. This Committee will assist the Commission in formulating and implementing the Community's activities in the field of rare diseases. It will also foster exchanges of relevant experience, policies and practices between the Member States and the various parties involved. In addition it will assist the Commission in the monitoring, evaluating and disseminating the results of measures taken at Community and national level in the field of rare



diseases, contribute to the implementation of Community actions in the field, in particular by analysing the results and suggesting improvements to the measures taken and deliver

opinions, recommendations or submit reports to the Commission either at the latter's request or on its own initiative.

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