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**COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN
PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL
COMMITTEE AND THE COMMITTEE OF THE REGIONS**

on Rare Diseases: Europe's challenges

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1. INTRODUCTION

Rare diseases are diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect not more than 5 per 10 000 persons in the European Union. This still nevertheless means that between 5 000 and 8 000 different rare diseases affect or will affect an estimated 29 million people in the European Union.

The specificities of rare diseases - limited number of patients and scarcity of relevant knowledge and expertise - single them out as a distinctive domain of very high European added-value. European cooperation can help to ensure that scarce knowledge can be shared and resources combined as efficiently as possible, in order to tackle rare diseases effectively across the EU as a whole.

The Commission has already taken specific steps in many areas to address the issues of rare diseases. Building on those achievements, this Communication on Europe's Challenges in the field of Rare Diseases aims to be an integrated approach document, giving clear direction to present and future Community activities in the field of rare diseases in order to further improve the access and equity to prevention, diagnosis and treatment for patients suffering from a rare disease throughout the European Union.

2. THE ISSUE

Most rare diseases are genetic diseases, the others being rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases among other categories. Research on rare diseases has proved to be very useful to better understand the mechanism of common conditions such as obesity and diabetes, as they often represent a model of dysfunction of a single biological pathway. However, research on rare diseases is not only scarce, but also scattered in different laboratories throughout the EU.

The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, inadequate or even harmful treatments and loss of confidence in the health care system, despite the fact that some rare diseases are compatible with a normal life if diagnosed on time and properly managed. Misdiagnosis and non-diagnosis are the main hurdles to improving life-quality for thousands of rare disease patients.

The national healthcare services for diagnosis, treatment and rehabilitation of people with rare diseases differ significantly depending on their availability and quality. Depending on the Member State and/or region where they live, EU citizens have unequal access to expert services and available care options. A few Member States have successfully addressed some of the issues raised by the rarity of the diseases, while others have not yet considered possible solutions.

Under the responsibility of the Commission and the EMEA (the European Medicines Agency) a policy is already implemented in the field of Orphan Drugs. These drugs are called "orphans" because the pharmaceutical industry has little interest, under normal market conditions, in developing and marketing products intended for only a small number of patients suffering from very rare conditions. The Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products¹) was proposed to set up the criteria for orphan designation in the EU and describes the incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation) to encourage the research, development and marketing of medicines to treat, prevent or diagnose rare diseases. The EU policy for orphan drugs is a success. However, Member States do not yet ensure full access to each authorised orphan drug approved.

3. OBJECTIVES

The Community's role in the area of health under Article 152 of the Treaty is to encourage cooperation between the Member States and if necessary to lend support to their action. 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. The objective of this Communication is to set out an overall Community strategy for support to Member States in ensuring effective and efficient recognition, prevention, diagnosis, treatment, care, and research for rare diseases in Europe.

This will in turn contribute to the overarching goal - an improvement in health outcomes, and therefore a growth in Healthy Life Years, a key Lisbon Strategy indicator². For this purpose this Communication will orient the operational actions in three main fields of work.

3.1. Improving Recognition and Visibility on Rare Diseases

The key to improving overall strategies for rare diseases is to ensure that they are recognised, so that all the other linked actions can follow appropriately. To improve diagnosis and care in the field of rare diseases, appropriate identification needs to be accompanied by accurate information, provided and disseminated in inventory and repertory formats adapted to the needs of professionals and of affected persons. This will contribute to tackling some of the main causes of neglecting the issue of rare diseases. The Commission therefore aims to put in place a thorough coding and classification system at European level, which will provide the framework for better sharing knowledge and understanding rare diseases as a scientific and public health issue across the EU.

3.2. Supporting Policies on Rare Diseases in the Member States

Efficient and effective action for rare diseases depends on a coherent overall strategy for rare diseases mobilising scarce and scattered resources in an integrated and well-recognised way, and integrated into a common European effort. That common European effort itself also depends on a common approach to work on rare diseases

¹ Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

² See http://ec.europa.eu/health/ph_information/indicators/lifeyears_en.htm.

across the EU, in order to establish a shared basis for collaboration and to help improve patients' access to care and information.

The Commission therefore proposes that Member States base themselves on common approach for addressing rare diseases, based on existing best practice, through the adoption of a Council Recommendation. The Commission's proposal for a Council Recommendation accompanying this Communication recommends that Member States put in place strategies organised around:

- putting in place inter-sectoral action national plans for rare diseases;
- adequate mechanisms for definition, codification and inventory of rare diseases and production of good practice guidelines, in order to provide a framework for recognition of rare diseases and sharing of knowledge and expertise;
- fostering research on rare diseases, including cross-border cooperation and collaboration to maximise the potential of scientific resources across the EU;
- ensuring access to high-quality healthcare, in particular through identifying national and regional centres of expertise and foster their participation in European Reference Networks;
- ensuring mechanisms to gather national expertise on rare diseases and pool it together with European counterparts;
- taking action to ensure empowerment and involvement of patients and patients' organisations;
- and ensuring that these actions include appropriate provisions to ensure their sustainability over time.

3.3. Developing European cooperation, coordination, and regulation for rare diseases

Community action will help Member States to achieve efficiency in bringing together and organise the scarce resources in the area of rare diseases, and can help patients and professionals to collaborate across Member States in order to share and coordinate expertise and information. The Community should aim at coordinating better the policies and initiatives at EU-level, and to strengthen the cooperation between EU programmes, in order to maximise further the resources available for rare diseases at Community level.

4. OPERATIONAL ACTIONS TO IMPROVE RECOGNITION AND VISIBILITY OF RARE DISEASES

4.1. Definition of rare diseases

The existing definition of rare diseases in the EU was adopted by the Community action programme on rare diseases 1999-2003 as those diseases presenting a prevalence not more than 5 per 10 000 persons in the European Union. The same definition is set out in Regulation (EC) 141/2000 and, accordingly used by the European Commission for the designation of orphan drugs. The EU will maintain the current definition. A more refined definition taking into account both prevalence and incidence will be developed using the Health Programme resources and taking into account the international dimension of the problem.

4.2. Classification and codification of rare diseases

The international reference for classification of diseases and conditions is the International Classification of Diseases (ICD), coordinated by the World Health Organisation (WHO³). The Commission will lead work with regard to rare diseases within the process of revising the existing ICD (International Classification of Diseases) in order to ensure a better codification and classification of rare diseases. For this purpose a working group on Classification and Codification of rare diseases⁴ will be created by the Commission. This working group could be appointed as Advisory Working Group by the WHO in the current ICD revision process.

4.3. Dissemination of knowledge and information on rare diseases

One 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 of affected persons. The establishment of an EU dynamic inventory of rare diseases will contribute to tackle some of the main causes of neglecting the issue of rare diseases including the ignorance of which diseases are rare. The Commission will ensure that this information continues to be available at European level, building in particular on the Orphanet⁵ database, supported through Community programmes.

4.4. Disease information networks

Priorities for action regarding the existing (or future) specific disease information networks are:

- to guarantee the exchange of information via existing European information networks;
- to promote better classification of particular diseases;
- to develop strategies and mechanisms for exchanging information between stakeholders;
- to develop comparable epidemiological data at EU level;
- and to support an exchange of best practices and develop measures for patient groups.

5. OPERATIONAL ACTIONS TO DEVELOP EUROPEAN COOPERATION AND IMPROVE ACCESS TO HIGH-QUALITY HEALTHCARE FOR RARE DISEASES

5.1. Improving universal access to high-quality healthcare for rare diseases, in particular through development of national/regional centres of expertise and establishing EU reference networks

Member States share a common commitment to ensuring universal access to high-quality healthcare on the basis of equity and solidarity⁶. But when diseases are rare, expertise is scarce as well. Some centres of expertise (also called centres of reference or excellence in a few Member States) have developed an expertise which is widely

³ See <http://www.who.int/classifications/icd/en/>.

⁴ See <http://www.who.int/classifications/icd/en/index.html>.

⁵ See <http://www.orpha.net/>.

⁶ Council Conclusions on Common values and principles in European Union Health Systems, OJ 2006/C 146/01.

used by other professionals from⁷ their country or even internationally, and which can help to ensure access to appropriate healthcare for patients with rare diseases. The EU rare diseases Task Force 2006 Report to the High Level Group '*Contribution to policy shaping: For a European collaboration on health services and medical care in the field of RD*'⁸ recommends that Member States contribute to the identification of their expert centres and support them financially.

The High Level Group on health services and medical care has been working on the concept of European reference networks since 2004⁹. On the basis of the work of the High Level Group, Article 15 of the proposal of Directive of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare (COM(2008)414) provides for the development of European reference networks (ERNs) to be facilitated by the Member States. The ERN for Rare Diseases will have a strategic role in the improvement of quality treatment for all patients throughout the European Union as called by the patients' organisations¹⁰.

5.2. Access to specialised social services

Centres of expertise may also have an essential role in developing or facilitating specialised social services which will improve the quality of life of people living with a rare disease. Help Lines, Respite care services and Therapeutic Recreation Programmes, have been supported¹¹ and need to be sustainable to pursue their goals: awareness-raising, exchange of best practices and standards, pooling resources using Health Programme and the Disability Action Plans.

5.3. Access to Orphan Drugs

There are specific bottlenecks in access to orphan drugs through the decision making process for pricing and reimbursement linked to rarity. The way forward is to increase collaboration at the European level for the scientific assessment of the (added) therapeutic value of Orphan Medicinal Products.

The Commission will set up a working party to exchange knowledge between Member States and European authorities on the scientific assessment of the clinical added value of orphan medicines. These collaborations could lead to non-binding common clinical added value assessment reports with improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities¹².

Furthermore, the involvement of the EMEA and existing international Health Technology Assessment networks as the Health Technology Assessment

⁷ See the report of the Rare Diseases Task Force "Overview of current Centres of Reference on rare diseases in the EU (2005)" http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm.

⁸ http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm

⁹ See the report of the high level group on health services and medical care on European Reference networks http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm.

¹⁰ See Report of the European Workshop on Centres of Expertise and Reference Networks for Rare Disease, Prague, July 2007; http://www.eurordis.org/IMG/pdf/EU_workshop_report_3.pdf

¹¹ similar to those identified thanks to the EU-funded RAPSODY project

http://ec.europa.eu/health/ph_projects/2005/action1/action1_2005_19_en.htm

¹² This as stipulated in the document "Improving access to orphan medicines for all affected EU citizens", adopted by the High level Pharmaceutical Forum.

International (HTAi)¹³, the European Network for Health Technology Assessment (EUnetHTA)¹⁴ or the Medicines Evaluation Committee (MEDEV)¹⁵ should be considered.

5.4. Compassionate use programmes

A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs is needed.

Under the existing pharmaceutical legislation, the EMEA may issue opinions on the use of the product under compassionate use to ensure a common approach across the Community.

The Commission will invite the EMEA to revise their existing guideline with a view to providing patient access to treatment.

5.5. Medical devices

The Orphan Medicinal Product regulation does not cover the field of medical devices. The limited size of the market and the limited potential return on investment is a disincentive. The Commission will assess whether there is a need for measures to overcome this situation, possibly in the context of the forthcoming revision of the Medical Devices Directives.

5.6. Incentives for Orphan Drug development

Pharmaceutical companies invest heavily over a long period of time to discover, develop and bring to market treatments for rare diseases. They need to be able to show a return on investment. However, the ideal is that they are also able to reinvest that return on investment into discovering more treatments. With more than 45 treatments authorised in the EU – and some for the same conditions – there are still many conditions with no treatment. Exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State awareness with these products should be encouraged in accordance with Article 9 of Regulation (EC) No 141/2000.

5.7. e-Health

eHealth can contribute in a number of different ways to this area, in particular through:

- Electronic online-services developed by Orphanet and by other EU funded projects, are a clear demonstration of how Information and Communication Technology (ICT) can contribute to putting patients in contact with other patients and developing patient communities, to sharing databases between research groups, to collecting data for clinical research, to registering patients willing to participate in clinical research, and to submitting cases to experts which improve the quality of diagnoses and treatment;
- Telemedicine, the provision of healthcare services at a distance through ICT, is another useful tool. It can, for instance, enable to bring highly specialised

¹³ <http://www.htai.org/>

¹⁴ <http://www.eunethta.net/>

¹⁵ <http://www.esip.org/publications/pb51.pdf>

expertise on rare diseases to ordinary clinics and practices, such as a second opinion from a centre of excellence¹⁶;

- Research funded under FP7¹⁷ in the area of computer assisted modelling of physiological and pathological processes is a promising approach to help understanding better the underlying factors of rare diseases, predicting outcomes and possibly finding new treatment solutions.

5.8. Screening practices

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, including those by robots, at low cost for a wide range of rare diseases, especially metabolic disorders and genetic conditions in general. It is recommended to encourage cooperation in this area to generate evidence on which decisions should be based at Member States level. An evaluation of current population screening (including neonatal screening) strategies for rare diseases and of potential new ones, will be conducted by the Commission at EU level to provide Member States with the evidence (including ethical aspects) on which to base their political decision. The Commission will consider such support as a priority for action.

5.9. Quality management of diagnostic laboratories

Many rare diseases can now be diagnosed using a biological test which is often a genetic test. These tests are major elements of an appropriate patient's management as they allow an early diagnosis, sometimes a familial cascade screening or a prenatal test. Given the large number of tests and the need to design and validate a specific set of diagnostic assays for each, no single country can be self-sufficient in the provision of testing and in an efficient external quality assessment of the provided tests. There is a need to enable and facilitate the exchange of expertise through clearly stated, transparent, EU agreed standards and procedures.

This could be achieved through the establishment of European reference networks of expert diagnostic laboratories (e.g. EuroGenTest¹⁸). These laboratories will be encouraged to participate in proficiency testing with special attention to result in reporting and in the provision of pre- and post-test genetic counselling¹⁹.

¹⁶ Draft Communication on Telemedicine for the benefit of patients, healthcare systems and society.

¹⁷ http://ec.europa.eu/information_society/activities/health/research/fp7vph/index_en.htm

¹⁸ See <http://www.eurogentest.org/>.

¹⁹ Helping people faced with a diagnosis of genetic disease to understand both the factual information about the disease and the effect it will have on their lives, so that they can reach their own decisions about the future.

5.10. Primary prevention

There are very few rare diseases for which a primary prevention is possible. Still, primary preventive measures for rare diseases will be taken when possible (e.g. prevention of neural tube defects by Folic Acid supplementation). Action in this field should be the topic for a debate at EU level led by the Commission aiming to determine for which rare diseases primary preventive measures may be successful.

5.11. Registries and databases

Registries and databases constitute key instruments to increase knowledge on rare diseases and develop clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research. Collaborative efforts to establish data collection and maintain them will be considered, provided that these resources are open and accessible. A key issue will also be to ensure the long-term sustainability of such systems, rather than having them funded on the basis of inherently precarious project funding. This idea was also elaborated in the document "Improving access to orphan medicines for all affected EU citizens", adopted by the High level Pharmaceutical Forum.

5.12. Research and Development

For most severe rare diseases that would potentially be treatable, there is simply no current specific treatment. The development of therapies faces three hurdles: the lack of understanding of underlying pathophysiological mechanisms, the lack of support of early phases of clinical development and the lack of opportunity/cost perception from the pharmaceutical industry. Indeed, the high cost of drug development, together with the estimated low return on investment (due to very small patient populations), has usually discouraged the pharmaceutical industry from developing drugs for rare diseases, despite the huge medical need.

A process of early dialogue regarding medicines under development should be established between these companies and authorities funding medicines²⁰. This will give the sponsoring company more certainty on its potential future return and will give authorities more knowledge and trust in the value of medicines it will be requested to assess and fund.

Rare diseases research projects have been supported for more than two decades through the European Community Framework Programmes for Research, Technological Development and Demonstration Activities. In the current Framework Programme, the FP7²¹, the Health Theme of the "Cooperation" Specific Programme, is designed to support multinational collaborative research in different forms. The main focus of the Health theme in the rare diseases area are Europe-wide studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions.

The EU Advisory Committee on Rare Diseases (EUACRD, see point 7) and the Committee for Orphan Medicinal Products (COMP) in the European Medicines Agency (EMA) will address to the Commission an annual joint recommendation on

²⁰ This as stipulated in the document "Improving access to orphan medicines for all affected EU citizens", adopted by the High level Pharmaceutical Forum.

²¹ See http://cordis.europa.eu/fp7/home_en.html.

specific points for the calls for proposals in the implementation of the framework programmes.

Coordination projects aimed at an optimal use of the limited resources dedicated to research on rare diseases should be encouraged. As an example, the EU FP6-supported ERANet project (E-Rare)²² currently coordinating the research funding policies for rare diseases of seven countries contributes to tackling the fragmentation of research efforts. Such approaches should be given due consideration.

6. INTERNATIONAL COOPERATION

The Commission policy on rare diseases should aim at fostering cooperation on rare diseases at an international level with all interested countries and in close collaboration with the World Health Organisation. International cooperation is already an integral part of the Framework Programmes for Research.

7. GOVERNANCE AND MONITORING

The Commission should be assisted by an EU Advisory Committee on Rare Diseases (EUACRD) to advise on implementation of this Communication. The Committee will be chaired by the European Commission and will be assisted by a Scientific Secretariat, supported through the Health Programme. This committee will replace the current EU Rare Diseases Task Force.

The organisation of a European Rare Diseases day (29 February, a rare day) and European conferences to raise awareness of professionals and of the general public will also be encouraged.

The Commission will produce an implementation report on this Communication - addressed to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the basis of the information provided by Member States, not later than five years after the date of adoption of this Communication. This report should be addressed at the same time as the implementation report to be produced on the Council Recommendation on rare diseases.

8. CONCLUSION

Although each rare disease only affects a relatively small number of patients and families, taken as a whole they represent a serious health burden for the EU. Moreover, the need to bring together expertise and make efficient use of the limited available resources means that rare diseases is an area where European cooperation can add particular value to the actions of the Member States. The Commission has already taken individual initiatives in the past, such as the rare diseases programme, the regulation on orphan medicinal products, and the attention to rare diseases within the Framework Programmes for research, technological development and demonstration activities. But more action is needed to ensure that these individual strands of work are sustained and brought together into a coherent overall strategy for rare diseases, both at Community level and within Member States, in order to maximise the potential for cooperation overall.

²² See <http://www.e-rare.eu/cgi-bin/index.php>.

With this Communication and the accompanying proposal for a Council Recommendation, the Commission aims to put in place that overall strategy for rare diseases. This offers the potential to maximise the scope for cooperation and mutual support in this challenging area across Europe as a whole. It will support Member States in putting in place their own national and regional strategies for rare diseases. And by doing so, it will provide the patients and families affected by rare diseases with a tangible benefit from European integration in their daily lives.