EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C2 - Health information

PUBLIC CONSULTATION

RARE DISEASES: EUROPE'S CHALLENGES

This document does not represent an official position of the European Commission. It is a tool to explore the views of interested parties on a preliminary proposal. The suggestions contained in this document do not prejudge the existence, the form or the content of any future proposal by the European Commission.

Responses to this consultation do not need to be limited to the questions presented in this text.

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1. THE ISSUE

Rare diseases (RD) are life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Most of them are genetic diseases, the others being rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases among other categories. They call for a global approach based on special and combined efforts to prevent significant morbidity or avoidable premature mortality, and to improve quality of life or socio-economic potential of affected persons.

- A **Community action programme on RD**, **including genetic diseases**, was adopted for the period 1 January 1999 to 31 December 2003[1]. This programme defined a prevalence as low if a disease affects **less than 5 per 10 000 persons** in the European Union.

- While this prevalence rate of 5 per 10 000 seems low, it translates into approximately **246 000 persons per disease in the EU with 27 Member States (MS)**.

- On the basis of present scientific knowledge, **between 5 000 and 8 000 distinct RD** affect up to 6% of the total EU population at one point in life. In other words, **around 15 million** people in the European Union (with 27 MS) are affected or will be affected by a RD.

- According to available sources in medical literature[2], less than 100 RD have a prevalence near the threshold of 5 per 10 000, such as Brugada Syndrome, Guillain-Barré Syndrome, Scleroderma or neural tube defects. Most RD are very rare, affecting one in 100 000 people or less such as haemophilias, Ewing Sarcoma, Duchenne muscular dystrophy or Von Hippel-Lindau disease. Thousands of RD affect only a few patients in Europe such as Pompe disease, Alternating hemiplegia or Ondine Syndrome. Patients with **very rare diseases** and their families are particularly isolated and vulnerable.

- There is also a great diversity in the **age at which the first symptoms occur**: half of RD can appear at birth or during childhood (such as Williams's syndrome, Prader-Willi syndrome, retinoblastoma). The other half of RD can appear in adulthood (such as Huntington disease, Creutzfeld Jacob disease, Amyotrophic Lateral sclerosis).

- Most RD are **genetic diseases,** but they can also result from **environmental** exposures during pregnancy or later in life, often in combination with genetic susceptibility. Some are rare forms or rare complications of common diseases.

- **RD also differ widely in severity and in expression**. The life expectancy of RD patients is significantly reduced. 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.

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[1] Decision No 1295/1999/EC of the European Parliament and of the Council of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003).
[2] Prevalence of rare diseases: A bibliographic survey July 2007 - Orphanet

- **Relatively common conditions can hide underlying RD**, e.g. autism (major symptom in Rett Syndrome, Fragile X, Angelman, Adult Phenylketonuria, Sanfilippo disease, *etc*.) or epilepsy (Tuberous sclerosis, Shokeir Syndrome, Dravet Syndrome, *etc*.). Many conditions classified in the past as mental deficiency, cerebral palsy, autism or psychosis, are manifestations of RD still to be characterised. Many types of cancers, including all cancers affecting children, are RD, as well as most congenital malformations.

- **Research** on RD has proved to be very useful to better understand the mechanism of common conditions like obesity and diabetes, as they represent a model of dysfunction of a biological pathway. Research on RD has been fundamental to the identification of most human genes identified so far and to a quarter of the innovative medicinal products that received market approval in the EU (**orphan drugs**). However, research on RD is not only scarce, but also scattered in different laboratories throughout the EU. Under normal market conditions, the pharmaceutical industry is reluctant to invest into medicinal products and medical devices for rare conditions because of the very limited market for each disease. This explains why RD are also called "**orphan diseases**": they are "orphan" of research focus and market interest, as well as of public health policies.

- Although RD heavily contribute to morbidity and mortality, they are invisible in health care information systems due to the lack of appropriate **coding and classification** systems.

- The **lack of specific health policies for RD** and the scarcity of the expertise, translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, sometimes birth of affected siblings, inadequate or even harmful treatments and loss of confidence in the health care system. Although some RD are compatible with normal life if diagnosed on time and properly managed.

- The focus on RD is a **relatively new phenomenon** in most EU MS. Until recently, public health authorities and policy makers largely ignored these challenges due to the splintering of policy debates across many different RD rather than the recognition of common issues for all RD.

- The national healthcare services for diagnosis, treatment and rehabilitation of people with RD differ significantly with respect to their availability and quality. Citizens from MS and/or regions inside the MS have **unequal access** to expert services and to orphan drugs. A few MS have successfully addressed some of the issues raised by the rarity of the diseases, while others have not yet considered possible solutions

2. SCOPE FOR EUROPEAN ACTION

- The **legitimacy of Community action in the RD field** clearly appears when combining the principle of subsidiarity (*"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"*) with the legal basis for EU action in the area of Public Health, Article 152, which states: *"A high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities. Community action, which shall complement national policies, shall be directed towards improving public health, preventing human illnesses and diseases, and obviating sources of danger to human health"*.

- Community strategy on RD is also linked to implementation of **European values**, such as the fight against discrimination, including those based on disabilities, and the protection of human rights.

- The specificities of RD - 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 public health where the collaboration between the 27 different national approaches can be as efficient and effective as RD. This is well recognised and acknowledged by both national and European decision makers, and by all concerned parties.(overstatement) The need to pool together the very limited resources could be better addressed in a coordinated way at EU level.

- **Research** on RD requires collaboration between teams of different disciplines and access to data and biological material gathered at EU level to ensure adequate sample size. **Collaborative research projects and coordination** projects are particularly relevant in this field as well as the establishment of shared **infrastructures**: registries, databases, repositories and technical platforms.

- Patients with a Rare Disease should have the **right to equal prevention, diagnosis and treatment like any other patients**. The development of a European **collaboration for the delivery of health care** and medical services to RD patients will have a major potential for bringing benefits to European citizens by:

    - overcoming the limited experience of professionals confronted with rare conditions;
    - improving access for EU citizens to treatment requiring a particular concentration/pooling of resources (infrastructure and knowledge) or expertise;
    - offering to patients the highest possible chance of success through sharing of expertise and resources;
    - cost-effective use of resources by concentrating them where appropriate;
    - helping to share knowledge and provide training for health professionals;
    - acting as benchmarks to help develop and spread best practices throughout Europe;
    - helping countries with insufficient resources from their health care sector to provide a full range of highly specialised services of the highest quality.

- Over 2 000 of RD can be diagnosed through a **biological test**. Given this large number 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 biological testing.

- The access to information is an absolute right. The release of **accurate information** on each of the thousands of RD, adapted to the needs of the health professionals and of the patients and their family, is a challenge which can only be addressed at EU level, even if translations in national languages and adaptation to national health care frameworks is needed.

- Many RD are very rare. **Isolated families** should be more informed on the appropriate services available. This can only be better implemented at European level through appropriate tools such as Internet services and help lines.

3. PREVIOUS AND ONGOING ACTIVITIES IN RD FIELDS

Based on Article 152, a **Community action programme on RD**, including genetic diseases, was adopted for the period 1 January 1999 to 31 December 2003. The aim of the programme

was to contribute, in co-ordination with other Community measures, to ensure a high level of health protection in relation to RD. As a first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases.

RD are now one of the priorities in the **EU Public Health Programme 2003-2008**[3]. According to the DG SANCO Work Plans for the implementation of the Public Health Programme, the main lines of action defined by DG SANCO have been:

- The support to RD information networks and the support to best practices development; Regarding RD projects and as a general criterion, DG SANCO prioritises generalist networks, which centralise information on as many RD as possible - not just a specific single disease - to improve information, monitoring and surveillance.

- The creation of a European consultative structure, the Rare Disease Task Force (supported by a Scientific Secretariat)[4], as the European reference for the exchange of best practice;

- The coordination of action efforts in the Public Health Programme with research efforts in the FP6 and FP7 Programmes.

RD will continue to be a priority for action in the new Public Health Programme (2008-2013). The Common Position adopted by the Council on 22 March 2007 with a view to the adoption of **a Decision of the European Parliament and of the Council establishing a second programme of Community action in the field of health (2007-2013)**[5] establishes in point 2.2.2. of the Annex: *'Promote action on the prevention of major diseases of particular significance in view of the overall burden of diseases in the Community, and on rare diseases, where Community action by tackling their determinants can provide significant added value to national efforts'.*

The Commission Staff Working Document accompanying the **White Paper 'Together for Health: A Strategic approach for the EU 2008-2013'** [6] also identifies RD as a priority.

Under the responsibility of DG ENTR and the EMEA (the European Medicines Agency) the EC implements a **policy** on Orphan Drugs. 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 products[7]) 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 RD. The EU pharmaceutical legislation has completed the policy in 2003 with a compulsory EU centralised procedure for market authorisation for all orphan drugs.

In 2000, a Committee for Orphan Medicinal Products (COMP)[8] was established within EMEA to review applications from persons or companies seeking **"orphan medicinal product designation"** for products they intend to develop for the diagnosis, prevention or treatment of RD.

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[3] Decision No 1786/2002/EC of the European Parliament and of the Council of 23 September2002 adopting a programme of Community action in the field of public health (2003-2008)
[4] See http://ec.europa.eu/health/ph_threats/non_com/rare_5_en.htm
[5] Amended proposal for a Decision of the European Parliament and of the Council establishing a second Programme of Community action in the field of Health and consumer protection (2007-2013) COM(2006) 234 final
[6] See http://ec.europa.eu/health/ph_overview/strategy/health_strategy_en.htm
[7] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
[8] See http://www.emea.europa.eu/htms/general/contacts/COMP/COMP.html

For seven years the European Commission, the EMEA and the MS have provided incentives to the pharmaceutical industry for the research, development and marketing of such orphan medicinal products in the fields of cancer, metabolic disorders, immunology, cardiovascular and respiratory disorders among other diseases. Under normal market conditions, no such medications would have been developed. The Commission is required to publish a detailed inventory of all these incentives. Two reports were published so far, in 2002 and 2006. The last report, published by DG ENTR on 26 June 2006, underlines that **the EU policy for orphan drugs is a success** and one of the most successful EU policies overall. In the period between April 2000 and August 2007, the EMEA has received more than 740 applications for orphan designation. As of July 2007, more than 40 **different new orphan medicinal products** have received a marketing authorisation for the treatment of more than 40 different life-threatening or chronically debilitating RD. In addition, more than 500 further medicines have already been designated by the COMP as orphan medicinal products, but are still undergoing clinical tests. The report[9] also details the national incentives put in place so far. The situation is highly diverse from one MS to another, some focussing to supporting further research (such as Spain or Germany for instance), others focussing on health care delivery and expert centres (Scandinavian countries, Denmark, Italy). Only one country has a comprehensive approach to the issue of RD through a national action plan (France for the period 2005-2008). However, **MS do not yet ensure full access to each authorised orphan drug approved**.

Rare disease research projects are supported through the **European Community Framework Programmes for Research and Technological Development**[10]. In the current framework programme, the FP7, the Health Theme, one of ten themes proposed under the "Cooperation" specific programme, is designed to support transnational cooperation in different forms across the Union and beyond, to improve the health of European citizens, increase the competitiveness and boost the innovative capacity of European health-related industries and businesses, while addressing global health issues. Emphasis will be put on translational research (translation of basic discoveries into clinical applications including scientific validation of experimental results), the development and validation of new therapies, methods for health promotion and prevention, including promotion of child health, healthy ageing, diagnostic tools and medical technologies, as well as sustainable and efficient healthcare systems. More specifically, the focus for rare disease research in FP7 is on Europe-wide studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions.

An FP6-supported **ERA-NET** project is dedicated to RD (E-Rare)[11] for the development of joint and trans-national activities (survey on national programmes, identification of gaps and overlaps among national research programs and activities on RD). E-Rare foresees to set up sustained and long lasting **cooperation between MS partners**, to coordinate national research programmes in order to overcome the fragmentation of research on RD and promote interdisciplinary approaches, to harmonize and develop synergies among the national and/or regional research programs of the participating countries, to develop common research policy on RD and to sustain a favourable competitive position with regard to research on RD in other regions of the globe such as North America and Asia.

DG SANCO has established the High Level Group on Health Services and Medical Care (HLG) as a means of taking forward the recommendations made by the reflection process on patient mobility. One of the Working Groups of this High Level Group deals with **reference networks of centres of expertise for RD**. In 2006, the RD Task Force submitted a report '*Contribution to*

[9] See http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006_08.pdf.
[10] See http://cordis.europa.eu/fp7/home_en.html
[11] See http://www.e-rare.eu/cgi-bin/index.php

policy shaping: For a European collaboration on health services and medical rare in the field of RD' [12] to the HLG, updating the information about reference networks in Europe. The report details the use of the concept of reference networks for RD in Europe as well as their respective functions. The Work Plans 2006 and 2007 for the implementation of the EU public health programme have introduced, as a priority in the area of RD, the development of European Reference Networks for RD. According to this priority some pilot Projects have been selected for funding[13] (in Cystic Fibrosis, Rare bleeding disorders, Alpha 1 antitrypsin deficiency, Porphyries, Dysmorphology, Paediatric Hodking's Lymphoma, Histocytosis, and Paediatric Neurological diseases).

In this sense, Article 16 of the **Proposal for a Directive of the European Parliament and of the Council on Health Services**[14] establishes*: 'Member States shall, in close cooperation with the Commission, facilitate development of the European reference networks to provide high quality and cost-effective healthcare to patients with conditions requiring a particular concentration of resources or expertise.'*

EMPOWERMENT OF PATIENTS

The World Bank defines empowerment as "*the process of increasing capacity of individuals or groups to make choices and to transform those choices into desired actions and outcomes*". The World Health Organization (WHO) has described empowerment as a "*prerequisite for health"* and "*a proactive partnership and patient self-care strategy to improve health outcomes and quality of life among the chronically ill"*. Defined as such, empowerment is a necessity for the patients with RD, which are chronic, difficult to manage, so rare that coordinated efforts are imperative to make progress, and largely disregarded by the research/medical community and policy makers. RD patients and their supporting organisations are amongst the most empowered groups in the health sector, mainly as a result of their own fight for recognition and for improved care. In the area of research in RD, they have led the way for a new era by bridging the gap largely ignored by on the one hand public research which overlooked their demands and expectations, and on the other market-driven research which confines research projects to those profitable enough to justify private investments. Patient organisations now play an active and instrumental role in determining RD research policies and projects. Due to the large number of RD, there are over 1 700 patients' organisations in Europe. Many of them are organised into national alliances of RD, and/or affiliated to EU disease-specific umbrella organisations, and/or to EU umbrella organisations dedicated to RD such as the European Organisation for Rare Diseases (Eurordis)[15]. Eurordis gathers organisations in 33 countries, permitting a direct dialogue between the European Commission, other stakeholders and the patient community of RD.

4. OBJECTIVES

The objective of this document is to sum up the **necessary elements for an efficient policy** addressing the important issue of Rare Diseases in Europe. The strategic objective of the EC(?) intervention in this field is aimed at improving the chance for patients to get appropriate and timely diagnosis, information and care. This will in turn contribute to the overarching goal - an

[12] See http://ec.europa.eu/health/ph_threats/non_com/rare_8_en.htm
[13] The 2007 projects are selected for funding and should receive co-financing under condition that the negotiation procedures with the European Commission are successful and that the grant agreement is signed.
[14] See http://ec.europa.eu/health/ph_overview/co_operation/mobility/patient_mobility_en.htm
[15] See http://www.eurordis.org

improvement in health outcomes, and therefore a growth in Healthy Life Years, a key Lisbon Strategy indicator[16].

This requires:

- **strengthening the cooperation between EU programmes**: those programmes include the EU Public Health Programmes, the Framework Programmes for Research and Technological Development, the Orphan Drugs strategy, the paediatric drug regulation[17], the advanced therapies strategy, the future Health Services Directive[18], the EU Statistical Programme[19] and any other existing or future EU initiative

- **encouraging EU - 27 in developing national health policies** to ensure equal access and availability of prevention, diagnosis, treatment and rehabilitation for people with RD. More initiatives in terms of public awareness-raising in the MS are needed. In addition to targeting public opinion, these efforts should also be directed at professionals in healthcare and social services, decision-makers, managers of health and social services and media. This could be achieved n particular through an annual awareness campaign.

- ensuring that **common policy guidelines are developed and shared** everywhere in Europe: specific actions – in areas such as research, centres of reference, access to information, incentives for the development of orphan drugs and screening, – shall be part of an overall common strategy on RD. The Communication is also expected to reinforce cooperation between MS, within a Community framework.

These general aims will be reached through specific objectives and actions

4.1. To improve identification and knowledge of RD

- **Common definition of RD in the EU:** The existing definition of RD in the EU was adopted by the Community action programme on RD 1999-2003 as those diseases presenting a prevalence **less than 5 per 10,000** persons in the European Union. The same definition is used by EMEA for the designation of orphan drugs (Regulation) and by several MS which have taken specific initiatives such as France, Germany, Italy, The Netherlands and Spain. However the UK, Sweden and Denmark use different definitions. Even if the current definition is considered too wide by some stakeholders, the EU is in favour of maintaining the current definition.

Question 1: Is the current EU definition of a rare disease satisfactory?

- **Better codification and classification of RD**: The EU should cooperate closely with WHO in the process of revising the existing ICD (International Classification of Diseases) in order to ensure that RD can be adequately coded to be traceable in all health information systems. This requires the support of a working group on Classification and Codification of RD, acting as Advisory Working Group to the WHO in the ICD revision process[20]. An active cooperation of the EU Statistical Programme should also be necessary as soon as the new ICD-11 is available in order to ensure the use of the new ICD version including new

[16] See http://ec.europa.eu/health/ph_information/indicators/lifeyears_en.htm
[17] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
[18] See http://ec.europa.eu/health/ph_overview/co_operation/mobility/news_en.htm
[19] Decision No. 2367/2002/EC of the European Parliament and of the Council of 16 December 2002 on the Community Statistical Programme 2003 to 2007 as amended by Decision No 787/2004/EC
[20] See http://www.who.int/classifications/icd/en/index.html

codes for RD in the death certificates and in the hospital discharges tabulation systems in all MS. A similar effort should be made to ensure proper coding of RD in the SnowMed and in the MedDRA coding systems.

Question2: Do you agree that there is a pressing need to improve coding and classification in this area?

- **Establishment of an inventory of RD**: among the causes of neglecting the issue of RD is the ignorance of which diseases are rare. It is necessary to provide the community with an accurate inventory of RD, regularly updated, classified by medical specialty, by prevalence, by mechanism, by aetiology, so as to maximise awareness and to provide documentary support to research and data storage in general. The European Commission should provide financial support for this activity through the Public Health Programme.

Question 3: Can a European inventory of rare diseases help your national/regional system to better deal with RD?

4.2. To improve prevention, diagnosis and care of patients with RD

- **Dissemination of appropriate information:** The key element for improving diagnosis and care in the field of RD is to provide accurate information in a format adapted to the needs of professionals and of affected persons. Since 2000, the Orphanet[21] database for RD has been providing information about over 5 000 diseases in six languages. It provides a comprehensive encyclopaedia of RD; a directory of professional services in 35 countries; a directory of European centres of reference; 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. The European Commission, through the Public Health Programme and the FP7, should provide further financial support for this activity.

- **Support to information networks:** A priority for action is to guarantee the exchange of information via existing European information networks, to promote better classification, to develop strategies and mechanisms for exchanging information between stakeholders, to define relevant health indicators, to develop comparable epidemiological data at EU level, to support an exchange of best practices and develop measures for patient groups. Ongoing projects have already proven their relevance. The support of this type of projects should be pursued both at MS and EU level. Support to specific international consensus conferences also appears to be very relevant. The European Commission through the Public Health Programme and the FP7 should provide financial support for this activity.

- **Development of national/regional centres of reference and establish EU reference networks**: When diseases are rare, the expertise is scarce as well. Some centres of expertise (also called centres of reference) have developed an 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 countries they are only established by reputation. The EC has decided to prioritise cooperation and knowledge sharing between them as the most efficient approach. Some principles have been developed regarding European Reference Networks (ERN), including their role in tackling RD or other conditions requiring

[21] See http://www.orpha.net/

specialised care, patient volumes and some other criteria that such centres should fulfil. ERN should also serve as research and knowledge networks updating and contributing to the latest scientific results, treating patients from other MS and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERN should also reflect the need for services and for expertise to be appropriately distributed across the enlarged European Union. The EU RD Task Force 2006 Report '*Contribution to policy shaping: For a European collaboration on health services and medical rare in the field of RD'*[22] recommends that MS contribute to the identification of their expert centres and support them financially as much as possible. It recommends also that MS organise healthcare pathways for their patients through the establishment of cooperation with all necessary expert centres within the country or from abroad when necessary. It recommends that relevant EU programmes continue to financially support reference networks of centres of expertise in the field of RD until an evaluation of the output of the networking process is available for further action.

Question 4: Should the European Reference Networks privilege the transfer of knowledge? The mobility of patients? Both? How?

- **Development of e-Health in the field of RD:** Electronic services developed by Orphanet and by other EU funded projects, are a clear demonstration of how e-technologies can contribute to putting patients in contact with other patients, 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. **On-line and electronic tools** are very efficient and should be a strong part of the EU strategy on RD. **They** can save life of persons with RD in **emergency situations**. The European Commission should provide financial support for this activity through the Public Health Programme and the FP and MS.

Question 5: Should on-line and electronic tools be implemented in this area?

- **Availability and accessibility of accurate diagnostic tests, including genetic tests**: Many RD 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. This results in exchange of patient material and testing across national borders. Transborder flow is clearly a mechanism that will fill a significant gap in the availability of tests for RD. There is a need to enable and facilitate this exchange through clearly stated, transparent, **EU agreed standards and procedures**. There is a need for bridging regulatory differences among countries in confidentiality practices, reimbursement, sample transport and storage and certification of laboratories. Laboratories should be encouraged to participate in **proficiency testing**, with special attention to result in reporting. Provision of pre- and post-test genetic counselling should be ensured. This requires support at the appropriate level (depending on the number of tests per year) to **reference laboratories**. Different stakeholders (the European Commission[23], the Council of Europe and in particular the OECD[24]) have put efforts in the quality assurance policy of laboratories in the past two years.

[22] See http://ec.europa.eu/health/ph_threats/non_com/docs/contribution_policy.pdf
[23] See http://www.eurogentest.org/
[24] See OECD Guidelines for Quality Assurance in Molecular Genetic Testing (http://en.eurogentest.org/files/public/QAGuidelineseng.pdf)

Question 6: What can be done to further improve access to quality testing for RD?

- **Evaluation of population screening (including neonatal screening) strategies for RD:** Neonatal screening for PKU 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 RD, especially metabolic disorders and genetic conditions in general. This should not be a reason to introduce them into population screening policies without careful assessment against the criteria established by WHO in 1965 (to be verified), as screening can be harmful to the screened persons and consumes major public resources. Currently there is little agreement on which diseases justify a systematic screening approach according to WHO criteria. The organisation of population or targeted screening is conditioned by many issues such as the quality and reliability of the test, the availability of an effective treatment/intervention for those screened, the prevalence of the disease and its severity and the choice/value that society attributes to the screening. It is recommended to encourage cooperation in this area to generate the evidence on which decisions should be based at MS level.

Question 7: Do you see a major need in having an EU level assessment of potential population screening for RD?

- **Primary preventive measures when possible:** There are very few RD for which a primary prevention is possible. Environmental factors are important in the causation of a wider range of rare congenital malformations, as well as childhood cancers. What is needed to prevent these RD is special targeting of the preconception period and pregnancy in public health measures aimed at major health determinants – nutrition, obesity, alcohol, smoking, recreational drugs and environmental pollution. Vaccination against diseases such as rubella (for prevention of congenital rubella syndrome) must take into account the consequences of migration between countries with different vaccination policies. In addition, attention must be paid to women before conception and in early pregnancy in the management of chronic diseases such as diabetes, epilepsy and infertility. Among the possible interventions is raising folic acid intake of women before the time they conceived as to prevent neural tube defects (e.g. spina bifida) and other malformations. Many studies provide evidence that adequate folic acid intake, during the peri-conceptional period, can prevent more than half of the neural tube defects. Action in this field should be the topic for a debate at EU level aiming to determine for which RD primary preventive measures may be successful.

- **Best practices on RD care**: Identifying and describing best practices is essential to share information and data on effective strategies to address RD and, therefore, to improve information and knowledge for the development of the best practices related to the RD care. Sharing best practices will allow EU MS to draw from the experience that has been built up so as to make possible the building of networks between the different care suppliers involved in the field of each RD. Benchmarking at the MS level will increase the chances of achieving success in addressing RD.

- **Equal access to orphan drugs:** Despite the successful incentives for orphan drugs development and registration, access of citizens to life-saving treatment is limited by two factors. First, some companies do not provide their marketing approved products in all MS, due to the constraints of registration at MS level. Second, administrative delays (far beyond

the 180 days legal limit) in the availability of authorised orphan drugs have been reported[25]. This results in large differences between MS in the number of available drugs. Solutions to this situation should be found. The Commission should present a report to the Council and the Parliament identifying these bottlenecks (delays, marketing, access, reimbursement, prices, etc.) every two years, proposing the necessary legislative modifications in order to guarantee **equal access** to orphan drugs throughout the EU. Hospital orphan drugs need to be funded at a level administered higher than the local hospital to ensure capacity to provide these drugs to patients.

Question 8: Do you envisage the solution to the orphan drugs accessibility problem on a national scale or on an EU scale?

- **Orphan Medical devices and orphan diagnostics**: The Orphan Medicinal Product regulation does not cover the field of medical devices and diagnostics. However, the problem of the limited size of the market is a disincentive to the development of products for RD patients. Initiatives to develop incentives for industry in the field of medical devices and diagnostics for RD should be explored on the model of what has been done for orphan medicinal products.

Question 9: Should the EU have an orphan regulation on medical devices and diagnostics?

- **Health Technology Assessment of Orphan Drugs**: Health technology assessment of orphan drugs which has to be established before deciding on price and reimbursement is another factor that is starting to play a determinant role in delaying access for patients or even preventing them to benefit from treatments. Methods used for assessing the cost effectiveness of drugs for common conditions do not apply to orphan drugs and there is most of the time no comparator and scarce data. In addition an ethical approach to this issue can not be based only on economic criteria, the economic evaluation being only an element of the decision-making process which should take into account the choices and preferences of the community. A coordinated approach to this issue by MS is necessary. In addition research into relevant evaluation methods should be encouraged, taking into account the patient perspective.

- **Coordinated compassionate use programme**: A better system for the provision of medicines to patients in need before approval and/or reimbursement (so-called compassionate use) of new drugs is needed. The supply of therapies for compassionate use should be a shared responsibility between the clinician, the developer of the product and the authorities. It should be reminded that a number of orphan drugs are developed by Small and Medium-sized Enterprises which cannot support long-term compassionate use programmes without public intervention and financial support. This issue should be subject to coordination between MS with the support of the EC. The Article 83 of Regulation (EC) 726/2004 establishes the possibility for member states to use its responsibility for compassionate use and establishes that the EMEA (European Medicines Agency) can issue an opinion on the conditions of use and distribution of a medical product when compassionate use is envisaged.

- **Specialised social services** are important to improve the quality of life of people living with a RD. Amongst different social services, the following ones have been identified as being particularly useful to enhance quality of life of both patients and their care givers, who are

[25] EURORDIS survey on OD availability and COMP's reports.

often family members: **Respite care services**: they allow both care givers and patients to organise their lives and to have some periods of rest; **Information services and help lines**: they increase the chances for patients and carers to access relevant information on the rare disease they live with and have to manage daily; **Therapeutic recreation programmes for children and young adults**: they allow patients to have another perspective for life than being sick; **Financial support**: it will help fighting pauperisation so that working carers who juggle paid employment with unpaid caring are recognised; **Psychological support**. The European Commission should provide financial support for this activity through the Public Health Programme and the Disabity Action Plans.

Question 10: What kind of specialised social and educational services for RD patients and their families should be recommended at EU level and at national level?

4.3. To accelerate research and developments in the field of RD and OD

- **Supporting databases, registries, repositories and biobanks**: Registries and databases constitute key instruments to develop clinical research in the field of RD. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research. Registries of patients treated with orphan drugs are particularly relevant as they allow gathering the evidence on the effectiveness of the treatment and on its possible side effects, knowing that marketing authorisation is usually granted at a time when evidence is still limited although already convincing. Collaborative efforts to establish data collection and maintain them should be supported, providing that these resources are accessible upon agreed rules. Many research and public health networks financially supported by DG RTD and by DG SANCO have put in place such shared infrastructures, which proved to be very efficient tools to improve knowledge and organise clinical trials. A specialised network, such as EuroBioBank[26], represents an invaluable European resource which requires long term funding and EU based approach in order to be fully developed and its use optimised. This type of initiative should be supported at MS and EU level and long-term funding should be made available for these infrastructures, providing that their utility is established. The same applies to repositories of biological samples and biobanks. A specific need in RD biobanking is to allow collection and storage of material from patients with very RD, even in the absence of an on-going research protocol. Areas to be supported by the MS and the European Commission are: quality standards, including development of strategies and tools for periodical monitoring of the quality of databases and for database cleaning; minimum common set of data to be collected for epidemiological and public health purposes; attention to user-friendliness, transparency and connectivity of databases; intellectual property, communication between databases/registries (genetic, more generically diagnostic, clinical, surveillance-driven, etc). Importance should be given to linking international (European) databases to national and/or regional databases, when existing.

Question 11: What model of governance and of funding scheme would be appropriate for registries, databases and biobanks?

- **Biomarkers**: Biological markers (biomarkers) are “objectively measurable indicators of biological processes”. They can be used to diagnose the disease and evaluate its progression and the response to therapeutic interventions. A great number of currently used diagnostic tests (tumour markers, fragments of DNA sequences causing or associated to a disease) fall

[26] See http://www.eurobiobank.org

under the definition of biomarkers. Functional and radiology assessments can also be considered biomarkers. In evaluating disease progression and potential new treatments, biomarkers may be used as surrogates for natural endpoints such as survival or irreversible morbidity, endpoints which require long periods of observation and large patient populations. This is particularly true for rare diseases, due to the small numbers of affected people for each disease. Marketing authorisations have already been granted on the basis of biomarkers as endpoints to judge on the efficacy of the drug. Impulse to the field of biomarker discovery has been given by new molecular biology techniques (e.g. genomics, proteomics, combinatorial chemistry), which allow identifying large numbers of potential biomarkers at one time. It is important that the EU support new techniques for biomarker discovery, including radiodiagnostic and functional techniques. Even more crucial is the support of studies and activities bringing potential biomarkers to their validation and clinical use. This process is long, costly and, at present, not efficient. In the field of RD, this process could profit from funding activities assessing validity of specific biomarkers (or clusters of biomarkers) on as large as possible numbers of patients (reference networks) and from increasing partnership between pharmaceutical industry and academia, so to assure completion of the "bench-to-bedside" track.

- **Data protection**: All these infrastructures should be implemented following the EU Regulations and agreements concerning data confidentiality and the protection of patient's privacy. Special attention has to be drawn to the EC **Data Protection Directive**[27]. The IDA (Interchange Data among Administrations)[28] initiative should be considered in the interest of the activities on RD in order to facilitate the creation of European registries on certain RD of high public health relevance.

- **Networks of research for RD**: coordinated research projects at EU level are key elements for success. Coordinated networks should be supported both at MS and EU level, and RD should remain a priority in future DG RTD programmes. Furthermore, some new areas as social research on RD should be introduced.

- **Coordination between MS funding agencies**: The EU FP6-supported ERA-NET project which is currently coordinating the funding policies for RD of seven countries is an example of a successful solution to the fragmentation of research efforts. This approach should be pursued and additional MS invited to join this initiative.

- **Intensifying Research**: For most severe RD 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 public support of early phases of clinical development and the lack of interest 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 discouraged the pharmaceutical industry from developing drugs for RD, despite the huge medical need. Although orphan drug regulations have certainly facilitated the development of treatments for RD, major difficulties still persist and additional initiatives are needed. Since the identification of therapeutic targets largely depends on the genetic and molecular characterization of the diseases and on the elucidation of biological mechanisms, it is crucial to intensify pathophysiological and clinical research on RD. With advances in research, sequencing of the human genome, and development of high-throughput genomic and post-

[27] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
[28] See http://europa.eu.int/idabc/

genomic tools, we may expect that the mechanisms underlying many rare genetic disorders will be unravelled in the next few years. For these disorders, therapeutic research needs to be promoted, including innovative biotechnological research (monoclonal antibodies, cell and gene therapy, and enzyme replacement therapy) as well as classical therapeutic research based on the search for active chemical compounds. Indeed, even in the field of rare genetic disorders, selection of chemical compounds acting on identified biological targets represents an important objective for drug discovery. Since in most cases pharmaceutical industries will not undertake this primary step, it is important to develop a public-sector interest in doing so. Academic research in preclinical development should be supported by the EU. Links with the European high throughput platforms which are currently set up and the use of shared European libraries of molecules should also be encouraged. Studies at the interface between pharmaceutical companies and public-sector organisations have to be promoted through a public-private partnership leading to the evaluation of these drug candidates in the field of RD. At European level, the challenge could be addressed by the establishment and funding of a public-private forum for RD, that would enable the development of promising preclinical and clinical multi-centre projects through provision of the necessary expertise and funding. Independent academic clinical trials should be supported at national level on the model of what as been done so far in Italy, France and Spain and these efforts should be coordinated to ensure enough patient participation.

Question 12: How do you see the role of partners (industry and charities) in an EU action on rare diseases? What model would be the most appropriate?

4.4. To empower patients with RD at individual and collective level

- **Common approach to the empowerment of patient organisations**: Patient organisations have proven to be invaluable partners, at the MS and EU level, to increase the visibility of rare diseases, to gather and disseminate the information required for defining a public policy on RD, to improve access to quality information on RD and orphan drugs, to organise workshops at European and national level, as well as to produce guidelines and pedagogical documents. The collective empowerment of patients and patient organisations will need support for activities such as: capacity-building, training and networking of activities between patient groups at regional, national and European levels, exchange of information, experience, and best practices on services to patients, and creation of "support patient communities" for very rare, isolated patients and families. The Public Health Programme and the FP7 should integrate such support as a priority for action.

4.5 To coordinate policies and initiatives at MS level and EU level

- **Adoption of National/regional Plans for RD**: In order to integrate all the necessary initiatives that have to be taken at national and/or regional levels, MS are invited to establish national or regional action plans for RD. Only a limited number of MS have adopted or will soon adopt a National Plan or launch relevant initiatives. While only France has established a comprehensive action plan (2005-2008)[29], other MS have national policies in a limited number of areas (Italy, Sweden, Denmark, United Kingdom) or are in the process to establish policies (Bulgaria, Portugal, Spain, Romania, Luxembourg). Other MS have a targeted policy only in the area of research (Germany, The Netherlands). The EU should strongly recommend the adoption of national/regional plans in line with the recommendation of the present Communication and their coordination when established. European guidelines

[29] See http://www.orpha.net/actor/EuropaNews/2006/doc/French_National_Plan.pdf

for the elaboration of action plans for RD might be useful. This will support the EU policy on "equitable access to health services as well as their cost and quality". The Public Health Programme has integrated such support as a priority for action.

Question 13: Do you agree with the idea of having action plans? If yes should it be at national or regional level in your country?

- **Development of health indicators in the field of RD**: The development of health indicators is needed to monitor the situation of affected persons in the EU and its evolution. Compilation of existing sources of data should be encouraged, especially those already funded at EU level. A set of realistic and meaningful indicators should be defined in the area of orphan drugs availability and accessibility, in the area of centres of expertise/reference, in the policy field at MS and EU levels.

- **Organisation of European Conferences on RD**: European Conferences on RD have been organised in the past every two years (Copenhagen 2001, Paris 2003, Luxembourg 2005[30] and Lisbon 2007[31]). They proved invaluable in providing a forum of exchange between stakeholders and in being a powerful communication instrument to ensure media visibility for RD. They should serve as a platform for patients, health care professionals and policy-makers to review policies, strategies and examples of successful action, voice their needs, promote patient-centred policies at national and European levels and confirm the vitality of the rare disease community in Europe. The conference should be organised in conjunction with the EU Advisory Committee on RD.

- **Creation of the EU Advisory Committee on RD**: The EU Advisory Committee on RD will accomplish the tasks currently performed by the EU Rare Disease Task Force. The Committee needs to be assisted by a Scientific Secretariat set up to contribute to the development of public health action in the field of RD and being competent to advise the Commission on: (i) the organisation of services on RD based on National Plans (subsidiarity); (ii) clinical tests and screenings; (iii) the labelling of reference networks for RD and quality control; (iv) the development of best practice guidelines; (vi) the periodic epidemiological report on the situation of RD in the EU; (vii) the EU registries/networks/ad hoc surveys; (viii) the support for policy developments at EU level; (ix) to set up a common framework in the field of public health for RD, and (x) to produce an electronic newsletter on RD. The composition of this EU Advisory Committee on RD will preserve the role of the ongoing and past projects in the area of RD supported by the Public Health Programme but should integrate a wide representation of FP RD projects, of the most relevant patient's organisations and a high level representation of the Public Health authorities of MS. To ensure the action capacity of this committee, a specific budget should be fixed in the EU Budget during the coming years.

- **Rare Diseases in the EU budget**: Currently all initiatives financially supported by the EC are funded on a short-term contract basis. Although regular assessment of the effectiveness of the projects and of their relevance in relation with EU policy is acknowledge, the fact that their renewal is difficult and sometimes impossible with the current rules, is perceived as a serious obstacle to the development of shared common infrastructures. Another main cornerstone of the future EU Programme of Public Health (2014-2020) in the area of RD should be the creation of a Rare Diseases Fund in order to ensure the EU activity of the European Reference Networks for RD, the Information services, the genetic and laboratory

[30] See http://ec.europa.eu/health/ph_threats/non_com/ev_pre2005_en.htm
[31] See http://www.rare-diseases.eu/home_en.php

accreditation for RD, the sustainability of the European repository platform for RD registers and databases, and any other RD activity needing sustainable, long-term support as it will be defined in the Implementation Reports, from the Commission to the Council and the European Parliament, on the present Communication.

- **Establishment of a Community Agency for RD**: A European Agency would address the need to establish a permanent, sustainable instrument for the long-term implementation of RD policies at Community level. According to the definition, "*A Community agency is a body governed by European public law. It is distinct from the Community Institutions and has its own legal personality. It is set up by an act of secondary legislation in order to accomplish a very specific technical, scientific or managerial task*". An EU Agency dedicated to RD can be an excellent instrument to ensure the permanence and coherence of relevant strategies at EU level in different areas such as patient registries, biobanks, clinical trials, information on RD, networks of centres of reference, consensus clinical care recommendations and quality assessment. On the basis of the work of DG SANCO and the advice from the European Advisory Committee on RD, the EC should launch a feasibility study in 2009 for the creation of a European Agency on RD. This agency could be the cornerstone of the future EU Programme of Public Health (2014-2020) in the area of RD.

Question 14: Do you consider it necessary to establish a new European Agency on RD and to launch a feasibility study in 2009?

- **Regular report on the situation of RD in the EU**: Every three years The Commission should produce an **Implementation report** on the Communication addressed to the Council, the Parliament, the Social and Economic Committee and the Committee of the Regions on the situation and epidemiology of RD in the EU and about the state of implementation of the Commission Communication in RD.

5. NEXT STEPS

Responses to this consultation, focussed around the specific questions identified in the text above, should be sent to the Commission by 14 February 2008, by email to **sanco-rarediseases-consultation@ec.europa.eu**, or by post to:

European Commission
Health and Consumer Protection Directorate-General
Rare Diseases consultation
HTC 01/198
11, Rue Eugène Ruppert
L-2557 Luxembourg

All contributions received will be published, unless specifically indicated otherwise. Following this consultation, the Commission intends to bring forward appropriate proposals in 2008.