

# **EURORDIS Contribution to the Public Consultation**

## **“Rare Diseases: Europe’s Challenges”**

### **February 2008**

EURORDIS - the European Organisation for Rare Diseases – represents 310 rare disease organisations from 34 different countries, 23 of which are EU member states, and thereby reflects the voice of an estimated 30 million patients affected by rare diseases in the European Union.

EURORDIS would like to express its satisfaction for the European Commission’s initiative, which represents an important step forward for the rare diseases community, boosting policies and actions aimed at creating a more appropriate public health framework. Rare diseases are a new public health concept to address the expectations of millions of people struggling with unmet medical needs. In this area, every new policy or action has a strong and structuring impact, and a high return. It is now widely acknowledged that, because of the rarity of these conditions, the added value of Community action in this field is very high. The Public Consultation document “Rare Diseases: Europe’s Challenges”, represents a major achievement in the fight of rare diseases patients, families and their representatives to gain social recognition and create new solutions.

In response to the Consultation, EURORDIS is pleased to send its contribution, which includes a core contribution, and four specific inputs on a number of issues for which a particular expertise has been developed within EURORDIS membership, through the implementation of EU funded projects, long-lasting involvement and development of ad-hoc task forces. Therefore, EURORDIS Contribution is articulated as follows:

- Core Contribution:
  1. Additional elements for a comprehensive approach:
    - 1.1 International dimension
    - 1.2 Education and training
    - 1.3 Discrimination based on genetic information.
  2. Positions on the following issues:
    - 2.1 Empowerment of patients
    - 2.2 Establishment of a European Agency for Rare Diseases;
    - 2.3 Definition and figures;
    - 2.4 Creation of an “Orphan Drugs Emergency fund”.
- Specific Contribution: “Centralised Procedure for the scientific assessment of the Therapeutic added value of Orphan Drugs”.
- Specific Contribution: “Centres of Expertise and European Reference Networks for Rare Diseases”.
- Specific Contribution: “Research Priorities for Rare Diseases”.
- Specific Contribution: “Specialised Services for People Living with Rare Diseases”.

## EURORDIS Core Contribution

EURORDIS wishes to add three issues that are missing in the Commission's document "Rare Diseases: Europe's Challenges" and which we believe are significant for a comprehensive approach to rare diseases: the international dimension, education and training and discrimination based on genetic information. Then, EURORDIS wishes to explicate views and positions from the rare diseases patients' perspective on a number of important issues addressed in the Commission's document: empowerment of patients; establishment of a European institution dedicated to rare diseases in order to address the need for sustainability; definition and figures; creation of an "Orphan Drugs Emergency fund".

### **1. Additional elements of reflection to be addressed within a comprehensive European approach to rare diseases:**

#### **1.1 International cooperation on rare diseases**

EURORDIS believes that the forthcoming Commission's Communication should include a reference to the **need to engage a cooperation process beyond the European Union.**

The Communication should be an opportunity also to foster cooperation on rare diseases at an international level: not only between developed rich countries - such as the US, Canada, Japan, Singapore, Australia - especially in the field of research and orphan drug development, but also through a North-South cooperation axe - in particular with non-EU Eastern European countries, the Mediterranean region, and the ACP countries having developed tight links with EU Member States - especially in the field of access to information, knowledge sharing on healthcare, as well as for the networking of patients and health professionals.

#### **1.2 Education and Training at different levels:**

The need for **education and training at different levels of society** is a crucial element to improve the quality of life of people living with rare diseases. Adequate education and training is mainly necessary in the following areas:

- Education at school of children born with rare diseases. This is a prerequisite for future inclusion in the society and access to employment;
- Education and permanent training of health care professionals;

- Education of the general public to raise awareness about rare diseases and reduce discrimination, “fear” and exclusion of patients.

It is fundamental to **share best practices** for integrating children at school, training professionals and the general public. EURORDIS believes that recommendations from the Commission in this field would be very appropriate and useful.

### 1.3 Genetic discrimination of patients

The issue of discrimination is of fundamental importance for patients who also endure, in addition to their disease and lifelong treatment, the aggravating consequences of exclusion in many aspects of their life. This is why EURORDIS wishes to add the following text to the paragraph on discrimination:

Discrimination, with its deeply aggravating consequences for disabled citizens, is to be addressed at EU level:

- by fighting exclusion from healthcare, as well as social exclusion linked to the rarity and lack of awareness;
- by ensuring appropriate compensation of inequalities and disabilities through financial, material and human support, in order to re-establish equality between citizens”;
- by eradicating the “genetic discrimination” preventing access to school, university, work place, insurance coverage and loans. There is a need for a European reflection on genetic discrimination that may lead to a legislative text, as in the US with the Genetic Non-discrimination Act. The Council of Europe has developed a document on genetic discrimination that could be transposed into the EU legislative frame or serve as a basis for reflection in this field.

In fact, recent scientific advances have led to a better understanding of our genetic code. At the same time, the potential misuse of this information may increase the genetic discrimination and raises serious legal issues. As in the US, European patients wish to make genetic discrimination illegal and provide individuals with reasonable protections against improper use of their genetic information. In the US, a Genetic Non-discrimination Act was passed in 2007, aimed at protecting individuals against discrimination based on their genetic information, for example concerning health insurance, loans or employment opportunities. These protections are intended to encourage citizens to take advantage of genetic testing as part of their medical care, without fearing potentially adverse consequences.

## 2. Rare diseases patients’ perspective on the following issues:

### 2.1 Patients’ empowerment

EURORDIS believes that in the document as it stands there is a **lack of “patients’ language”** as used by patients’ representatives to communicate both

internally and externally, with patients' wording. Therefore, in addition to the excellent definition by the WHO, EURORDIS wishes to include the following concepts:

Patient groups address two primary needs of the community of people living with rare diseases:

- **Direct personal support for individuals** living with the disease;
- **Collective work to improve conditions for the community** as a whole and to create a better world for tomorrow's generation of rare diseases patients.

The inadequate scientific knowledge of rare diseases and the scarce attention drawn to these conditions by competent National authorities, as well as by the pharmaceutical industry, has led to the creation of associations of patients and parents. Though easily overlooked, rare diseases patients do attract some public attention through their associations, which raise public awareness and co-produce a knowledge base, together with health professionals. Living too often in a context of human isolation, rare disease patients and their families are known to be very pro-active and as knowledgeable about their affliction as health professionals - and sometimes more.

The Public Health Programme should support the work of the organisations set up by patients, allowing them to act on the course of their existence, individually or collectively, and to participate into the decision making process when they are directly involved, as full actors of the health system. **The PHP should also support initiatives aimed at fostering networking and collaboration between patients' organisations and other stakeholders.**

Empowerment, as defined above, necessitates the support of activities such as exchange of information and best practices, networking around common themes, capacity-building and training for patients and their representatives, elaboration of common positions, outreach to RD patients organisations and "very isolated patients and families", etc. **In the specific field of rare diseases, where the EU added-value is particularly high, the associative platforms gathering many diseases in many Member States are indispensable interlocutors for EU decision-makers.** They provide an invaluable mediation service between policy and citizens, to be supported through core funding from the EU Public Health Programme.

**Empowerment of patients can also be improved through Specialised Social Services for rare diseases patients:** information services and help lines, a unique EU-wide number for rare diseases, improvement in the e-health dimension of the online communities of patients (discussion lists, blogs, wikis, etc).

## **2.2 Need for long-term support to activities on rare diseases (need for sustainability)**

Improving care and developing research for millions of European citizens living with rare diseases does require **long-term coordination and support**. So far,

several European services and infrastructures have been established, such as information databases accessible on the internet, DNA and tissue bank networks, disease specific networks, clinical databases and registries. In spite of remarkable achievements, long term **continuity** of these services and infrastructures is not guaranteed. In fact, the current system based on calls for proposals with projects that cannot be funded for more than 5 to 9 years, definitely does not respond to the **need for sustainability**. Especially in an area with such a strong European added-value, the national level does not have the means to ensure the continuity of essential projects and activities for rare diseases - in both areas of research and services – initiated at Community level.

Furthermore, there is also a need for new infrastructures to be developed in all the EU Member States and for all rare diseases. This trend is destined to intensify as a result of enhanced Community research on rare diseases and increased development of orphan drugs, combined with the elaboration of new National Plans on Rare Diseases.

**A feasibility study should be launched in 2009 and a Report should be delivered in 2011 on the creation of a European Institute dedicated to Rare Diseases**, eventually in the juridical form of an EU Agency. The architecture, scope and concrete activities of this Agency should be defined in the Report through a critical analysis of existing institutes in other fields that could serve as a model and by exploring which issues would mostly benefit from support and coordination by a body of this kind at European level. At present, issues such as research infrastructures, funding of European Networks of Centres of Expertise and quality assessment of gene testing, are areas that would certainly benefit from a coordinated action performed by a dedicated Institute on Rare Diseases.

EURORDIS would very much welcome the idea of a **European Agency to address these issues within the remit of a single structure which would ensure the required sustainability and long-term support of key activities for rare diseases patients and their families.**

This Agency should interact with the rare diseases Community at large, not just with the authorities and professional community, but also with patient organisations recognising their key role in promoting collaboration and knowledge sharing. The Agency should not only coordinate, but also catalyse cooperation and development.

## **2.3 Definition and number of people affected by rare diseases in Europe**

EURORDIS supports the following formulation on the number of patients affected by rare diseases patients in the European Union: “On the basis of present scientific knowledge, between 5000 and 8000 distinct rare diseases affect up to 6% of the total EU population **at one point in life**. In other words, around 30 million people in the EU (with 27 Members) **are affected or will be affected** by a rare disease”<sup>1</sup>.

---

<sup>1</sup> At a given point in time, 3.5% of the population IS living with a RD, this equals to around 17 million people at one point in time.

The current EU definition of a rare disease (a disease which affects less than 5 in 10.000 citizens) is the one used in the major European Community piece of legislation in this area, namely the Regulation on Orphan Medicinal Products. Not only the decision on the definition of rare diseases has already been made in the EU through, amongst others, this Regulation, but the current definition also correspond to a double reality: first, the fact that under normal market conditions, the medicines to diagnose, treat or cure diseases which affect less than 5 out of 10.000 citizens are *de facto* not commercially sustainable in the absence of financial incentives and second, the observation that this definition does correspond to the actual healthcare organisation. This definition exists and is deemed effective in the US since 25 years.

The wish of certain stakeholders to define rare diseases in a more restrictive way is only driven by the aim to reduce the reimbursement of currently marketed Orphan Drugs. As patients' representative and advocate at European level, EURORDIS would not accept this reversal of the current situation which would lead to a worsening for patients.

On the issue of figures and number of citizens affected by a rare disease at a certain point in life, we believe that it is important to explain that any of the figures currently used in this area have been obtained through well-accepted estimations, in the absence of precise data on rare diseases. These figures are subject to revision when more reliable data will be demonstrated through published consensus studies, as the prevalence of rare diseases is still controversial and open to discussion. It is also important to underline that the lack of accurate epidemiological data on rare diseases does represent one of the main challenges in the field to be addressed through additional accurate epidemiological analysis.

EURORDIS believes that at present **there is no new element to justify a change in the definition or in the rare diseases figures**, especially because there is no international scientific consensus on these issues. Furthermore, to change definition and figures in the absence of consensual scientific publications, would create confusion, disrupting the coherence with all the other European reference documents and also with the ones used in the US by the NIH, FDA, NORD and other bodies.

## 2.4 Orphan Drugs Emergency Fund

EURORDIS does support the creation of a European Fund for emergency purposes, to **bridge the gap between the centralised procedure of marketing authorisation and real access to the new orphan drugs at national level**. This "OD Emergency Fund" would cover orphan drugs access, during the period before price and reimbursement are decided in the Member states. During that period, patients normally do not benefit from the drug, and many die just before the drug is made available in their country. This is a particularly unbearable situation for patients and families. With this Fund, access to OD would be improved, while putting pressure on the most reluctant Member States which are currently not providing fair access to orphan drugs.



This system would require neither new experts (as soon as the CHMP has given its positive opinion for compassionate use or Marketing Authorisation, the Fund can cover the emergency use), nor an additional heavy bureaucracy but would also substantially help SMEs developing these OD to survive through the process. This Orphan Drugs Emergency Fund could be administratively managed by the EU Forum on RD.

Concerning access to Orphan Drugs, EURORDIS has been advocating in favour of the establishment of a common scientific evaluation system for the Therapeutic Added Value (TAV) of OD at EU level<sup>2</sup> that would be integrated into the national decision-making process and would help negotiate an ex-factory reference price. There is no contradiction between this proposal and the eventual creation of the Emergency Fund as there would always be a need for the decision on the TAV and its consequences on the price and reimbursement negotiations.

---

<sup>2</sup> See EURORDIS specific contribution on the Therapeutic Added Value of Orphan Drugs.

**EURORDIS Specific Contribution:  
“Centres of Expertise and European Reference Networks  
for Rare Diseases”**

On the issue of Centres of Expertise and European Reference Networks, EURORDIS has launched its reflection process at the Annual Membership Meeting in Berlin (April 2006, 180 participants from 20 countries). This reflection has been enriched and deepened through different steps in the last couple of years:

- through the achievements of the relevant Work packages (WP5 – WP8) of the Rare Disease Patient Solidarity Project (RAPSODY), funded by DG SANCO; 270 patient representatives, health care professionals and decision makers have participated in one-day national workshops in 11 EU Member states following the same methodology and agenda; 80 representatives from 11 countries participated in a two-days European Workshop of synthesis in Prague in July 2007; the final synthesis was presented at the European Conference on Rare Diseases 2007, in Lisbon;
- through EURORDIS participation in and dialogue with the EU High Level Group on Health Services and Medical Care - Working Group on European Reference Network, in 2006 and 2007;
- through the expertise built, shared and disseminated at the DG SANCO Rare Diseases Task Force;
- through the internal consultation process on which EURORDIS has based its contribution regarding Community action on health services, in November 2006.

This process has led EURORDIS to express the **utter need for Centres of Expertise and European Reference Networks for Rare Diseases**, given the overall lack of expertise and the necessity of gathering the scarce knowledge for the benefit of a maximal number of rare disease patients. It is utopia to believe that each of the 5 to 8 thousands rare diseases could benefit from a specific Centre of Expertise in every EU Member State. The establishment of European Reference Networks is the appropriate way to exploit limited human, medical and scientific resources through a consistent and efficient approach that would equitably benefit EU citizens wherever they live.



Therefore, both the Centres of Expertise and/or Centres of reference (according to the national policy set up in the concerned Member States) - physical structures for the management and care of rare diseases patients at Member states level - and the European Reference Networks - as the “networking of knowledge and expertise” through either physical or virtual expertise and/or reference centres and teams of experts at the EU level - are fundamental to address the issue of rare diseases at European and national levels.

It also has to be underlined that the Community added-value of establishing European Reference Networks is particularly high for rare diseases, given the direct consequences of rarity, which implies both limited number of patients and scarcity of expertise at national level, thus maximising the cost-effectiveness of rational quality healthcare provision and of common European research infrastructures such as registries, databases and biobanks.

***Summary:***

- Rare diseases patients do want Centres of Expertise (CoE) and European Reference Networks (ERN) to address their disease. These structures do correspond to the needs expressed by patients.

- Rare diseases patients do not have exceptional demands: they ask for a better flow of scarce information and for a better organisation of patient-centred care. This care must consist of both medical and social aspects, which need to be integrated at all levels. This care has to be improved for all patients throughout the EU, thus addressing the concern for equity expressed by rare diseases patients. Best practices recommendations, standards and guidelines for diagnosis, treatment, care and social support must be shared; reference diagnostic and therapeutic protocols must be disseminated through Centres and Networks.

- On mobility, patients support the idea that knowledge should travel, including data, samples, expertise and healthcare professionals. Nevertheless, patients should be supported when they feel the need to travel, at specific moments of the development of their disease.

- Patients believe that Centres of Expertise and EU Reference Networks should play a role in research efforts at European and international levels, linking excellence of care to excellence of research in the “same place” where both patients and expertise are gathered, thus allowing multi-centred clinical studies.

- Sustainability, long-term funding: CoE and ERN are perceived to be cost effective but still they do need proper funding to be sustained in the long run. Patients have repeatedly expressed the necessity for appropriate long-term public funding.

The RAPSODY EU-funded project launched a dialogue between patients, health care professionals and both national and European policy makers, with the aim at addressing the needs and expectations primarily of patients and families, but also of the other stakeholders on Centres of Expertise and European Reference Networks for rare diseases. The present document is based on the main outcomes of the RAPSODY project and aims at pointing out the following thirteen elements as being fundamental in the current reflection on Centres of Expertise and European Reference Networks.

### **1. Pre-conditions:**

Two essential pre-conditions are required for a Rare Disease Centre of Expertise:

- **Professional qualifications** - stemming from both clinical and scientific experience - that have to be documented by publications, grants, pre-existing certification or accreditation;
- Serious **commitment to cooperate** and share information.

The general “atmosphere and attitude” has also been underlined as an important element of success for a Centre of Expertise: trust - rather than competition - among experts is deemed necessary to ensure effective cooperation.

### **2. Multidisciplinarity:**

Different stakeholders do recognise that only a **multidisciplinary approach** can be effective in providing adequate care to rare diseases patients. It is important to underline that “**care**” **includes both medical and social aspects** for the management of rare diseases patients. Rare diseases are complex and involve different medical specialties, as well as a wide range of paramedical healthcare professionals, working in close collaboration with social workers. Patients and families expect that Centres and Networks have to successfully meet the challenge of organising care through a multidisciplinary approach.

### **3. Different levels of coordination:**

The importance of a good coordination between professionals has been stressed repeatedly, in particular:

- Coordination within and between centres of expertise, within European Reference Networks, and between centres of expertise and primary care centres;
- Coordination between care and research activities;
- Coordination with the aim at circulating information and organising continuum of activities by placing the patient at the centre of the system and making better use of existing expertise and resources;

- Coordination between various services in order to improve quality of care by reducing the psychological burden of patients (feeling lost in the system, lack of support, language barriers, administrative obstacles, etc).

#### **4. Importance of a global and comprehensive approach:**

There is a **need to integrate medical and social aspects, at all levels** (primary care centres, centres of expertise and European Reference Networks). It has been recognised that social support is often underestimated and that there is a need to develop a common European approach to social services when they are specific for rare disease patients. Among the specific administrative tasks of the European networks, there must be the support in favour of patient mobility for cross-border care when necessary, especially concerning the reimbursement issue, which may prove insurmountable for some patients and families.

#### **5. Capacity to pool patients:**

A **critical mass of patients** is a necessary condition for improving scientific and medical knowledge on a disease: there has to be enough patients enrolled in clinical trials and this can only be possible, in the case of rare diseases, through European Reference Networks given the scarce number of patients within a single country.

#### **6. Main expectations:**

- The European Reference Networks will have a strategic role in the **harmonisation of care and the improvement of quality treatment** for all patients throughout the European Union: within the Reference Networks, the level of knowledge and expertise will be shared in different Centres. If needed at specific moments of the development of the disease, it will be considered as **“normal and fair” to travel from one Centre to another** within the same Network for confirming a diagnosis, seeking a second opinion or for important medical intervention (surgical operation, transplantation and other invasive medical interventions). It should not be an administrative, legal and medical fight for a patient to travel abroad for unwished medical reasons.
- The EU Networks will have a major impact on the development of **best practices recommendations, standards and guidelines** for diagnosis, treatment, care and social support of rare disease patients at international level. In fact, specific expertise will be further developed and identified, thus allowing confirmed recommendations to be based on “demonstrated experiences” within the Networks;
- The dissemination of European **reference diagnostic and therapeutic protocols, ensuring equity** at EU level by reducing the impact of the “post code lottery” and therefore increasing trust in local services;

- The provision of expert opinion, confirmation of diagnostic and therapeutic options.

## 7. Research activities at European and International level:

All interested parties consider that Centres of Expertise and European Reference Networks do **facilitate international research** by performing the following tasks:

- To link excellence of care with excellence of research, in the same “place” where patients are gathered and where multidisciplinary expertise on the disease can be found;
- To allow multi-centre clinical studies as well as partnership with pharmaceutical companies;
- To provide **shared research resources**: databases, biological resources (DNA, RNA, tissues, cells), registries (harmonisation of standard operating procedures), international epidemiological surveillance and pharmacovigilance;
- To facilitate participation in **EU-funded research projects**.

## 8. Perform education and training:

Centres of Expertise and European Reference Networks are expected to be instrumental in promoting education and training activities such as:

- **Information and communication** outreach activities towards the public, but also the primary health care professionals in order to improve referrals and follow up;
- **Training activities for health professionals**, including staff exchanges, meetings and conferences to exchange best practices, harmonise processes and disseminate standards and guidelines

## 9. Empowerment of patients:

Empowering activities for patients and their representatives have to be performed at different levels through **information, education and training**. They will help patients and families building their capacity to manage the medical and social aspects of their disease, enhance their autonomy, increase their compliance and generally improve their quality of life.

## 10. Collaboration with patient organisations:

Centres and European Reference Networks must cooperate closely with patients' representatives in the following ways:

- Patient organisations must be **actively involved in the management and evaluation** of both Centres of Expertise and European Reference Networks as experts for the production of information documents, guidelines for diagnostic and care, the choice of the research tools and clinical trials to be performed within the networks;

- Centres and EU Networks must facilitate the creation of patient groups when they do not exist;
- They shall improve relations and exchanges between healthcare professionals and scientists on the one hand, and patients on the other hand;
- Broad links between European Reference Networks, research networks, information networks and patient organisations should be fostered.

## 11. Evaluation:

European Reference Networks should be initially evaluated at EU level via an **agreed set of criteria** (minimum set of standardised criteria and objectives) and then regularly assessed on common indicators through both soft values and hard values. European Reference Networks could therefore play an active role in the evaluation of national centres of expertise and/or reference (according to the national policy set up in the concerned Member States). There is also a need to **develop methods and tools for European reference networks to perform regular self-evaluation**.

### Proposed set of soft values for the evaluation of Centres of Expertise and /or Reference

- Cooperation with patient organisations
- Patient-oriented approach e.g. coordination, information to patients
- Improved outcomes
- Improved atmosphere
- Improved quality of life
- Avoiding unnecessary complications
- Awareness and knowledge dissemination
- Information provision to local centres

### Proposed set of hard values for the evaluation of Centres of Expertise and/or Reference

- Time to get the diagnose
- Waiting time for medical consultations and tests
- Genetic consultation
- Multidisciplinary approach
- Cooperation with other centres and EU networks
- Guidelines and recommendations
- Quality control
- International and national networking
- Economic assessment

## 12. Funding, sustainability and governance:

European Reference Networks are perceived to be cost-effective. They need proper funding for their specific European and international activities. The funding should be a **long-term public funding in order to ensure their sustainability**. EU Networks should be encouraged to establish good governance structures (leadership, regulation, steering committee) and share coordination practice. They should be able to disclose their procedures and outcomes.

## 13. Flexibility:

It has been underlined that flexibility is required in relation to the geographical coverage of the Networks, as well as to the selection of type of centres belonging to the Networks. There should not be any obligation for a Network to have centres in all member states. The European Reference Networks should be able to identify the Centres of Expertise together with the national health authorities and the patients groups.

## Conclusions:

- EURORDIS firmly believes that the establishment of Centres of Expertise and European Reference Networks will play a **key role for improving the lives of people living with a rare disease**, by facilitating the communication between various health care professionals involved in daily care management, improving and harmonising the organisation and provision of high quality care, reducing the time to obtain accurate diagnosis, agreeing treatment and care guidelines, providing expert advice and ensuring that patients have access to the best adequate technologies and treatment at specialised centres and/or through European Reference Networks. *“Expertise should travel rather than patients”* who should travel in another Member State only when they consider it necessary.
- EURORDIS encourages the **mobility of knowledge**, which includes mobility of health professionals, as well as data, samples and expertise. Travelling abroad is not enjoyable for patients and their care-givers, often family members. **Patient mobility has to be supported and facilitated even if limited to key moments** of the development of the disease when patients and families mostly feel the need for a second opinion before important decisions and major therapeutic choices.
- EURORDIS also wishes to express its **appreciation for the inclusive process** that has been established by the European Commission for the EU-wide reflection on Centres of Expertise and European Reference Networks, with all relevant stakeholders.

**EURORDIS Specific Contribution:  
“Centralised procedure for the scientific assessment of the  
Therapeutic Added Value of Orphan Drugs”**

On the issue of the scientific assessment of the Therapeutic Added Value of Orphan Drugs, EURORDIS has gained expertise and knowledge mainly through the participation of patients' representatives members of EURORDIS into regulatory bodies for Orphan Drugs development at EU level, through the EURORDIS Surveys on Orphan Drugs Availability and Pricing and through intense dialogue with all concerned parties such as patients, experts, industry, National Competent Authorities (NCAs), payers, etc.

***Summary:***

Patients do not have real and equitable access to Orphan Drugs.

In order to improve access to Orphan Drugs, the scientific assessment of the Therapeutic Added Value (TAV) of Orphan Drugs should be achieved through a European centralised procedure, at the EMEA, where the relevant expertise and knowledge are gathered.

To this end, a dedicated Working Party within the COMP would be in the best position to deliver an expert opinion on the scientific assessment of the TAV.

## **1. The issue**

Following the recognition that there is a need for specific medicinal products for rare diseases patients based on research and evidence based medicines, the EU has established a regulatory framework aimed at enhancing the development of Orphan Medicinal Products.

In the Regulation on Orphan Medicinal Products 141/2000 of the European Parliament and the Council (16 December 1999), whereas (1) and (2), it is stipulated that “Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients. (...) But “the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions”. “Some conditions occur so infrequently that the cost of developing and bringing to the market a

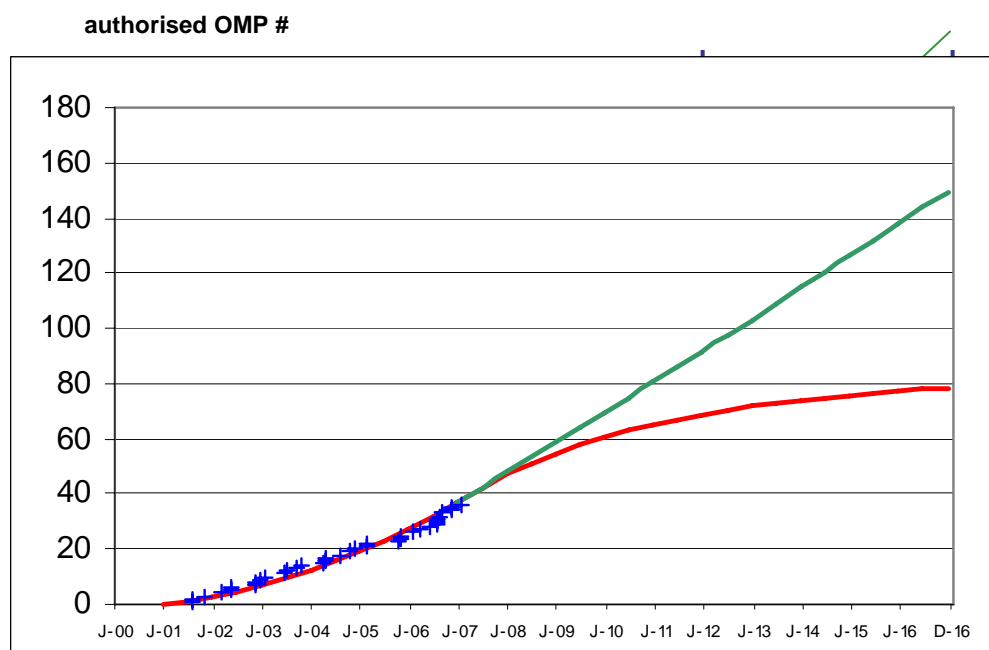
medicinal product to diagnose, prevent or treat these conditions would not be recovered by the expected sales”.

**Article 1 of the Regulation:** Purpose. “The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and **placing on the market** of designated orphan medicinal products”.

**Article 9 of the Regulation:** Other incentives. Incentives are foreseen in this article to support research into, development and **availability** of Orphan Drugs

The Orphan Drugs Regulation can be considered a success as it has allowed, up to January 2008, the designation of 521 Orphan Drugs, among which 52 have been granted a Marketing Authorisation. The time of development between the designation and the Marketing Authorisation, as well as the success ratio of around 17% is similar to the one observed in the US in the last 25 years. Based on the 25 years of experience in the US with the Orphan Drugs Act (March 2007: 1749 designations and 315 Marketing Authorisations) and on the 7 years of European experience with the EU Regulation on Orphan Drugs, EURORDIS has developed a mathematic model to forecast the number of new Orphan Drugs to be potentially approved in the coming years: in 5 years (2012), it is anticipated that around 100 Orphan Drugs will be approved. This means an average of 10 to 12 new drugs per year.

## 5 year forecast for possible approved orphan drugs (source: Eurordis)





The issue that EURORDIS wishes to address in this specific contribution is based on the following unsatisfactory observation: “**Patients do not have real and equitable access to the Orphan Drugs they need**”. This regrettable situation represents a major issue for rare diseases patients and their families.

- Orphan drugs are not available to patients and their doctors within the legal timeframe of 180 days maximum across the different EU Member States and this poses a **legal issue**.
- Orphan drugs are made available to patients in a worst time frame and conditions of access than other drugs, although they are intended for rare conditions where there is unmet medical needs, either with no satisfactory method of treatments or a significant benefit over existing therapeutic interventions. This poses an **ethical issue and a political issue**.

In fact, despite the overall success of the strategy on Orphan Drugs and the encouraging results, the main problem lies in the access to these drugs. The conclusions of the 4<sup>th</sup> EURORDIS Survey on Orphan Drug Availability in Europe<sup>3</sup> clearly show that the **EU legal timeframe** established by the Orphan Drugs Regulation **is not respected** (legal timeframe established by the Council Directive of 21 December 1988 on “Transparency of measures regulating the pricing of Medicinal Products for Human Use and their inclusion in the scope of national health insurance systems”).

#### **EURORDIS Survey on Orphan Drugs availability:**

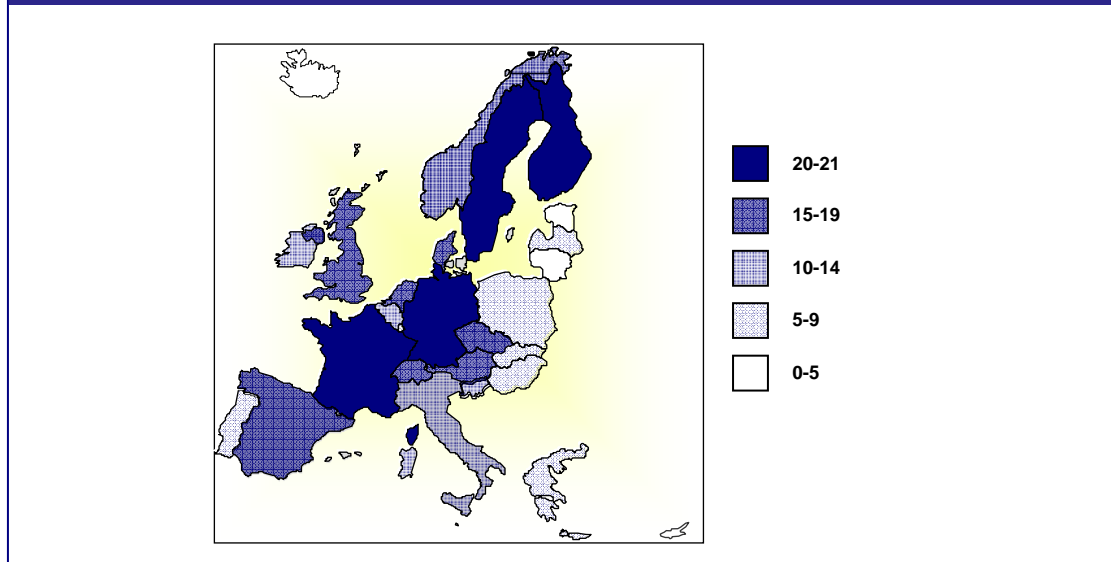
Geographical coverage: the Survey has been conducted in 28 countries: the 25 EU Member States before the last enlargement as well as in Iceland, Norway and Switzerland.

Sources of information: Marketing Authorisation holders, COMP members, NCAs direct contacts and members of MEDEV, and patients groups.

The figures of the 2007 Survey are the ones observed for the access to the 22 Orphan Drugs authorised before 1<sup>st</sup> January 2006, namely minimum 1 year after the Marketing Authorisation has been granted. According to the EU law, all these 22 products should be accessible in every Member State. The Survey shows that there are **major differences between Member States** in the availability of Orphan Drugs, from “0 to 5” available Orphan Drugs up to “20 to 21”, with poor scores also in the “old” EU Member States, such as Ireland, Portugal, Belgium and Greece.

<sup>3</sup> EURORDIS has done four surveys every other year since 2001 (2001, 2003, 2005 and in 2007). The link to the 2007 Survey is : <http://www.eurordis.org/IMG/pdf/2007ODsurvey-eurordis.pdf>

## Availability in 2007 at national level of the 22 first ODs authorised at EU level before 1st January 2006



When looking at the situation of the availability in 2007 of the 12 Orphan Drugs approved before 2004, one can observe that these 12 Orphan Drugs are accessible in almost all EU Member States.

Therefore, **time is the major factor influencing the availability of Orphan Drugs and not the Therapeutic Added Value (TAV) of these products.** As patient representative, EURORDIS does not consider acceptable that the availability of Orphan Drugs is not linked to the TAV of the product – or to its potential value in the therapeutic strategy for the disease but to the time taken by either the pharmaceutical companies to perform the appropriate measures or by the NCA to decide on price and reimbursement.

Furthermore, if one compares the ex factory price for each Orphan Drug in each Member States to its European mean, one finds out that the variations are nowadays surprisingly limited (from – 6% to + 10%). These variations have been reduced, showing that the **clear and solid trend is a *de facto* convergence towards an EU ex factory price.** From the reactions that EURORDIS could gather, this also reflects the wish of most EU pharmaceutical companies.

Another interesting observation is the fact that **the lowest price obtained by the NCA, is not in the Member State where the decision was made last.** Therefore, this shows that the strategy consisting in deferring the decision on price and reimbursement does not reduce the economic burden on healthcare systems, in addition to not being based on the real value of the product. When human lives are at

stake, this kind of argument and strategy – which is furthermore contradicted by the results – is not receivable.

If one then compares the price paid for Orphan Drugs to the GDP of different Member States, it appears that the financial commitment varies from 1 to 10; **the ones making the highest financial commitment are not necessarily the richest EU countries.** These countries are: Austria, Czech Republic, Slovenia and Slovakia.

## **2. The reasons: why are Orphan Drugs not available to patients in the EU?**

In the life cycle of Orphan Drugs in the EU, everything is centralised:

- Orphan Drug Designation (COMP / EMEA)
- Protocol Assistance (SAWP / EMEA)
- Marketing Authorisation Application (CHMP / EMEA)
- Significant Benefit (COMP / EMEA)
- Paediatric Investigation Plan (PCDO / EMEA)
- Main incentive: 10 or 12 years of EU Market Exclusivity
- 5 Year Review of Market Exclusivity (COMP / EMEA)

The majority of Marketing Authorisations for Orphan Drugs are conditional Marketing Authorisation or Marketing Authorisation under exceptional circumstances, usually at the end of Phase II. Therefore, there are **lots of post-marketing obligations**, such as additional studies and follow-up. The CHMP will evaluate these studies after the Marketing Authorisation has been granted and this means that **important scientific data will exist within the centralised system even after Marketing Authorisation.**

Orphan Drugs have an additional specificity compared to other medicinal products, which is the **Significant Benefit (SB)**: if some therapeutic alternatives already exist, the new Orphan Drug shall “do better” in terms of efficacy, safety or contribution to patient care. This **SB assessment is made through EU centralised procedure** by the COMP, based on data provided for the Marketing Authorisation Application. These information are the same ones needed for the scientific evaluation of the Therapeutic Added Value (TAV) and therefore are gathered at European level, within the EMEA.

In the case of Paediatric Drugs, the **Paediatric Investigation Plan (PIP)** is also a “**European level tool**”. It is worthy to remind that 54% of Orphan Drugs are either exclusively intended for a paediatric population or for both paediatric and adult



populations. Therefore, the majority of Orphan Drugs may be subject to a PIP within the Paediatric Committee at the EMEA.

**To summarise: the whole process of scientific evaluation which leads to a decision bearing an economic impact - namely the granting of market exclusivity of 10 or 12 years - is indeed a process taking place at European level, prevailing on the Member States.**

**EURORDIS wishes to underline that there is a fundamental disruption between on the one hand, the scientific evaluation and the major economic decisions - Orphan Drugs Designation and Market Exclusivity - which both belong to the European level and, on the other hand, the evaluation of the TAV and other pharmaco-economic aspects, which belong to the national level, leading to pricing and reimbursement decisions.**

This disruption creates some major difficulties, both at Member State and company levels:

- For Member States: there is not the same level of expertise within the 27 Member States, because Orphan Drugs are intended for rare conditions, some being extremely rare, and it is not surprising that there is a lack of medical expertise to perform a scientific assessment of the TAV, especially in medium-sized and small countries. This is why it has been decided that for designation and Marketing Authorisation decisions, the scarce existing expertise shall be brought together in one place at European level, within the EMEA.
- For companies: the vast majority of companies developing Orphan Drugs are small companies. For these companies it is difficult to follow 27 different procedures in 21 languages, for extremely small markets, often only a few patients. This does *de facto* delay placing on the market by marketing holders mostly in medium-sized and small countries. The observation of reality shows that 6 to 7 countries (making up to 50% of the EU population) are fast served, while the others will have authorised Orphan Drugs placed on their market little by little, at an average “speed” of 3 new countries per year.

## Reality of placing OMPs on the European market

- **The smaller the country, the less attractive it is :**
  - Drugs available in 7 countries: 50% of the global population
  - Drugs available in 14 countries: 75% of the global population
  - Drugs available in 21 countries: 90% of the global population
  - Drugs available in 28 countries: 100% of the global population
- **A dynamic process: the older the M.A., the higher the # of countries**
  - Overall: 6 countries fast served, then 3 new countries/year  
(# countries =  $5.7 + 0.24 \text{ months}$ ;  $p < 0.02$ )

Furthermore, **diverging requirements** between Member States, such as additional comparative studies, observational studies, registries, new health or quality of life measures, **are not always feasible and increase the overall costs** of Orphan Drugs Development.

### 3. The rationale

The specificity of Orphan Drugs is linked to the rarity of patients (small populations), the scarce expertise (need to pool expertise together) and the overall rarity of the knowledge base. In this context, clinical trials needed for the development of Orphan Drugs always take place at European or even international level and their scientific assessment is performed through the EU centralised procedure.

**The development of Orphan Drugs does not stop at Marketing Authorisation:**

Because 50% of Orphan Drugs get the Marketing Authorisation at early stage, mostly at the end of phase II, there are many **post marketing obligations** and the assessment of post marketing studies is performed by the CHMP at EU level. These new data are reflected in the revised EPARs. Concerning the PIP, as recalled above, they are also assessed at EU level by the Paediatric Drugs Committee, at the EMEA.

In parallel, the National Competent Authorities (NCAs) are often also asking for additional data, such as **observational studies and registries**, to answer some of their concerns. The national level has diverging requirements concerning these additional post-marketing studies and data. EURORDIS strongly believes that these data should usefully be managed at European level, in a centralised coordinated way, to avoid duplication of efforts and increased costs, as well as unjustified and unacceptable delays for patient access to Orphan Drugs.

Orphan Drugs are mainly developed by small or medium-sized companies and are very innovative pharmaceutical products, mostly derived from biotechnology. The price and added-value of these products should only be compared to other highly innovative biopharmaceuticals. The conclusion of this comparison is that the **TAV of Orphan Drugs is superior to the TAV of other medicinal products approved during the same period**, as shown in the slide below.

### Example: France Health Technology Agency's (HAS) assessment of Orphan Drugs (July 2007)

- **28/28 : favourable opinions**
- **Assessment of added value (ASMR level) => Improvement over existing therapies**

Improvement	Orphan drugs	<i>All drugs (2006)</i>
Major	3 = 11%	2%
Important	10 = 36%	12%
Moderate	5 = 18%	18%
Minor	4 = 14%	14%
No improvement	1 = 4%	46%

#### 4. The proposal

To address the overall situation as described above and the disastrous consequences it has on patient's access to Orphan Drugs, EURORDIS proposes that the **scientific assessment of the TAV of Orphan Drugs is performed through an EU centralised procedure**, in the same way in which both the designation as Orphan Drug (at COMP) and the decision for Marketing Authorisation (at CHMP) take place at European level.

**The assessment of the TAV of Orphan Drugs (TAVOD) should be performed where the expertise is gathered, and this is not at national level, but within the EMEA.**

**A Working Party of the COMP within the European Agency would be in the best position to deliver an expert opinion on the scientific assessment of the TAV, which would support and speed-up decisions on pricing and reimbursement at national level.**

The proposed **TAVOD Working Party**<sup>4</sup> - composed of COMP members, NCAs representatives, payers and patient representatives - would perform a **common scientific assessment of the TAV for each Orphan Drug and deliver an “opinion document”**. In this way Member States would pool their scarce scientific expertise to assess the TAV and would also recognise the value of this common assessment and opinion document. This system would avoid duplication of procedures at national level.

**Pricing and reimbursement (P&R) decisions will be facilitated and accelerated**, improving the overall coherence, with the following advantages for all parties involved:

- P&R decisions will remain at national level, within NCAs.
- P&R decisions will be based on the Common assessment report of the Therapeutic Added Value of orphan drugs, therefore reducing diverging decisions, helping convergence throughout the EU and optimising resources.
- P&R decisions will be regularly revised on the basis of revised EPARs and European assessment report of therapeutic added value, as well as according to post-marketing studies and observational studies.

The opinion documents can evolve progressively, according to post-marketing obligation and further data produced through registries and observational studies.

The TAVOD Working Party will regularly re-assess the TAV thereby helping to define the most appropriate role of each Orphan Drugs in the therapeutic strategy in real life setting.

---

<sup>4</sup> Committee for the assessment of the Therapeutic Added Value of Orphan Drugs

## Conclusions:

### 1. Orphan drugs are specific and different from other drugs

Because of their rarity:

- The clinical development of orphan drugs is specific because of the hurdles of clinical trials with small, very small and extremely small populations of patients, scarce scientific expertise, limited knowledge on the diseases (e.g. issues natural history, relevant endpoints, etc)...
- Orphan Drugs have a specific profile at marketing authorisation: mostly conditional approval, end of phase II, lots of post-marketing obligations...
- There are also specificities related to Orphan Drugs for placing on the market: small production, stocks, packaging, leaflets for very small quantities, etc.

Because of their specific status in the EU:

- Orphan drugs are, by nature, specific and different within the European market given the Market Exclusivity (10 years + 2 years if paediatric studies)
- Specificity of Significant Benefit
- Specificity of the scientific and economic model: mostly innovative, mostly SMEs, often biotechnology companies.

### 2. The lack of access to Orphan Drugs is critical and requires coordinated action

The Orphan Drugs Regulation adopted by EU policy makers and Member States aims at improving the conditions of an underprivileged category of the EU population. The following pieces of legislation, strategies and policies confirm this orientation. However experience shows that rare disease patients do not have timely and equitable access to Orphan Drugs. They do not access them within the legal timeframe, have different access according to the country where they live and irrelevantly of the national GDP. Furthermore, delays of access are not linked to the real value of the drug and Member States are not really saving any money in the long term by delaying their decision on P&R.

The situation is worsening:

- Affecting patients and population health outcomes
- Undermining the EU competitiveness
- Affecting EU capacity to provide an environment supportive of innovation



**3. A specific EU approach for orphan drugs is feasible**

- EUnetHTA has developed « core principles » in its WP5 for common scientific HTA;
- The MEDEV is supportive and encourages collaboration at EU level;
- Many representatives of NCAs have experienced the limits of the current situation and are calling for collaboration at EU level;
- 10 to 12 new orphan drugs are approved each year in EU

**4. Orphan Drugs can be a model for future products with very small markets or highly innovative**

The adoption in 2007 of the EU Regulation on Advanced Therapy Medicinal Products (gene therapy, cell therapy, tissue engineering), will generate the same kind of issues and will have its own specificities requiring collaboration at EU level to have a common ground for scientific HTA and common rationale for pricing.

The implementation from 2007 of the EU Regulation on Medicinal Products for Paediatric Use may also generate the same needs.

## **EURORDIS Specific Contribution: “Research Priorities for Rare Diseases”**

This Specific Contribution to the Public Consultation “Rare Diseases: Europe’s Challenges” aims to address specifically the needs for research in rare diseases. It is based on the latest debates taking place at the EU level on rare diseases and research and, in particular, on the outcomes of the EURORDIS European Workshop on “Gaining Access to Rare Disease Research Resources”, held in Paris in May 2007; on the conclusions of a workshop on rare diseases and research organised by the European Commission on 14 June 2007; and on the outcomes of the European Conference entitled “Rare Diseases Research: Building on Success”, which took place in Brussels on 13 September 2007, and was also organised by the European Commission, DG Research.

This document also takes on board EURORDIS’ advocacy carried out in 2006 in view of the adoption of the 7th Framework Programme on Research and Technological Development, as well as the experience gained through the participation of EURORDIS as an Observer in the E-Rare project, an Era-net gathering public partners funding rare disease research in their own countries; this paper doesn’t represent their views.

This document was finalised through consultation with the patient organisation representatives involved in the EURORDIS Research Task Force and the EURORDIS European Public Affairs Committee, representing a broad range of rare diseases and EU Member States.

### **Summary:**

Rare diseases are characterised by low prevalence, great number and heterogeneity. These features make rare diseases research a very specific area which:

- Needs be developed at the **European level**, rather than in isolation within single laboratories scattered throughout the EU.
- Justifies a **concerted action** between different national and European financing and management policies, in order to optimise the use of funding, infrastructures and technological platforms.
- Requires a **multidisciplinary approach**, the coordination of teams of researchers specialised in different fields and a global vision of all research fields and rapid reactivity to the development of knowledge and technological tools.
- Requires a greater role played by patients, as the ultimate beneficiaries of research on their diseases and as repository of an expertise which can be instrumental to research. It demands a **patient-centred approach**, research tools which implement patient-driven governance, and research projects centred on patient quality of life.

- It requires the establishment of centralised European funding mechanisms ensuring the **long-term sustainability** of common EU research infrastructures and research projects with long-term aims.

National governments should line up in developing a European policy for research on rare diseases based on a strategic coordinated vision and reflect it in the elaboration of National Plans on Rare Diseases.

Specifically, EURORDIS identified six following strategic areas which deserve the attention of policy-makers and need to be further developed as a matter of priority:

1. Descriptive and analytical **epidemiology, natural history of the disease and clinical nosology**.
2. **Genetic and molecular characterisation** for more than 4000 diseases for which it remains to be done.
3. **Pathophysiological mechanisms**, largely unknown for rare diseases, should be studied once genetic mutations are identified to allow the development of novel therapeutic strategies.
4. **Improvement of the diagnostic performances** in terms of reliability and accessibility to reduce the costs and human consequences associated with diagnostic delays.
5. **Development of therapeutics** for patients living with a rare disease, in particular for children: devices to alleviate disabilities linked with the disease; orphan medicinal products and advanced therapy medicinal products.
6. Research in the **social and human sciences** (sociology, economy, history of sciences, psychology) in the field of rare diseases.

## 1. Specificities of Rare Diseases

### 1.1. The European dimension

Due to the great number of rare diseases, their low prevalence (less than 1/2000) and their heterogeneity, rare diseases represent **by definition an area of research that has great potential for development at the European level, rather than in isolation within single laboratories scattered throughout the EU.**

Although it is not practicable to develop projects for each of the 5000-7000 rare diseases estimated to exist, it is important to establish both horizontal cross-cutting platforms and vertical disease-specific projects, based on excellence, to be used as models for other rare or common diseases. It is therefore crucial to create European structures of excellence through networking and cooperation between expert centres. It is necessary to integrate European research teams in a pan-European space and develop a truly European environment. However, it should not be neglected that gaps between medical research infrastructures exist within EU Member States and should be overcome.

Another specificity of research in rare diseases lies in the fact that, in general, competent European research groups (including SMEs) working on the same topic

are few and can only be supported through instruments, such as smaller size international projects. Nevertheless, in few cases, huge networks of excellence and large integrated projects could be built up. Thus an optimisation of the research potential on rare diseases in Europe, unlike other domains, can only be achieved through **a large spectrum of funding instruments**.

### 1.2. A multi-disciplinary approach

Research on rare diseases has proven to be very difficult as it often implies a **multi-disciplinary approach**, associating teams of researchers specialised in different fields, clinicians, patient organisations and also psychology and social scientists. The advancement status of research on rare diseases varies greatly according to the different pathologies. It is therefore **fundamental to keep a global vision of all research fields in order to ensure rapid reactivity to the development of knowledge and technological tools**. Greater awareness on the need to use a multidisciplinary approach should be raised among experts at national level.

Also, research on rare diseases requires the optimal use of technological platforms, such as sequencing platforms, facilities for transgenic animals and imaging, etc. The organisation and financing of such technological platforms go well beyond the framework of research on rare diseases. It is important to ensure their functioning and viability in the long run, as technological platforms represent a strategic investment for the whole of R&D in Europe and are fundamental to achieve concrete advances in the future.

### 1.3. Patient empowerment in research on rare diseases

**Patients are the ultimate beneficiaries of research on their diseases. They should play a more active role in research.**

Patient and patient representatives have developed an **expertise** which can be instrumental to research, such as the knowledge on the natural history of their rare disease, on the dissemination of information at different levels, on the constitution of cohorts and on the organisation of campaigns for the donation of biological samples.

Furthermore, patient organisations can be **active partners** in research networks:

- To encourage patient-oriented research aiming at improving quality of life and life expectancy, thus reducing financial and social burdens;
- To ensure rapid dissemination of results to patients, health professionals and scientific community;
- To make innovative research goals clear to all EU citizens.

Rare disease organisations also undertake research activities such as the initiation of research projects, co-fund databases, sponsor and support research fellowships, research prizes etc.

Actions to be undertaken:

- **Support the development of more research projects centred on patient quality of life and on a patient-centred approach;**
- **Foster the participation of patient groups to EC funded research projects,** by simplifying the procedure for getting support during the preparatory phase,

ideally implementing a two step approach: expression of interest first, and full application when pre-selected;

- **Train patient representatives on specific research topics** such as: patient registries and databases, clinical trials, etc. In particular, patient organisations should be provided with the appropriate tools to create greater awareness on research and drug development among patients.
- Support the **development of research tools which implement patient-driven governance and the sharing of results with patients**, e.g. databases linking genotypes and phenotypes that can be operated or supervised by patient groups with the support of specialists.
- Involve patients' representatives at each step of clinical trial protocol development to ensure literacy of patient information notice, informed consent form, case record forms or self-administered questionnaires, report summary for patients, etc.
- Involve patients' representatives in research steering and evaluation committees.

#### 1.4. Sustainability of research on rare diseases

At present, research infrastructures and research projects financially supported by the EC are funded on a short-term contract basis. This hampers the development of shared common infrastructures, long-lasting projects and a sustained approach. At the same time, important European investments to create new infrastructures are lost once these structures, despite their importance, have to stop their activities because of the lack of new investors.

A strong commitment of the EC and its Member States is therefore necessary to **overcome the current European system based on calls for proposals for projects, by addressing the need for long-term sustainable projects**, in particular research infrastructures, common to all diseases and all EU countries, such as biobanks, databases and registries. Because of the rarity of the diseases and thus their limited commercial interest, it is very unlikely that private sponsor would take over the long term funding of rare disease research infrastructures created thanks to EU financial support. Similarly, we also observe that single Member States still prefer to concentrate their investments in national infrastructures rather than supporting the long-term joint activity of European networks of infrastructures.

Action to be undertaken:

- **Establishment of funding mechanisms ensuring the long-term sustainability of common EU research infrastructures**, such as biobanks, databases and registries and healthcare infrastructures such as Centres of Expertise, as well as European Reference Networks for Rare Diseases;
- **Longer term support to research projects with long-term aims** (e.g. projects on the natural history of the disease, lifelong follow-up of new therapeutic interventions);
- Training and education for young researchers, with the aim to recruit new talents and to ensure the continuity to future research on rare diseases;
- At country level, **provisions and concrete solutions in the forthcoming National Plans for Rare Diseases to address the issue of financial**

**sustainability for initiatives in the field of research on rare diseases.** In addition, in order to avoid any useless duplication, national initiatives in favour of rare diseases should be coordinated and information exchanged at the EU level.

- Support to alternative funding mechanisms, such as public-private partnerships, to establish networks between different stakeholders;
- EC structural support to new EU Member States to upgrade their medical research infrastructures.

### **1.5. The need for concerted action**

In conclusion, the specificities of research on rare diseases justify a **concerted action between different national and European financing and management policies, in order to optimise the use of funding, infrastructures and technological platforms.** Therefore the impact on European competitiveness, employment and research-driven SMEs will be significant.

Such a concerted action would help achieve the following objectives:

- the development of a European policy for research on rare diseases based on a global vision and a strategic coordinated reflection;
- new programmes of multidisciplinary research and new teams involved in research on rare diseases;
- the concerted work of different departments and institutions involved in research so as to coordinate relevant activities and programmes and to avoid duplications;
- high reactivity towards new scientific and technological developments;
- a sufficient visibility with patients, researchers and health professionals;
- the attraction of young researchers towards this field of research;
- the industrial developments of results from research in the fields of diagnostics and therapeutics;
- the dissemination of new knowledge acquired from research through training and information offers for the scientific community, health professionals and patients.

It is therefore necessary that **national governments line up in recognising the role of research on rare diseases, the need for a sustainable support and the necessity to cooperate with European partners.**

This should be **reflected in the European guidelines for the elaboration of National Plans on Rare Diseases and in each of the National Plans** which will be adopted.

## **2. Six strategic orientations for research on rare diseases**

While keeping in mind the specificities of research for rare diseases, as identified above, it is necessary to focus on the strategic orientations for this research that emerged over the last years. EURORDIS identified the six following strategic areas which deserve the attention of policy-makers as a matter of priority.

## **2.1. Descriptive and analytical epidemiology, natural history of the disease and clinical nosology.**

This field of research needs further development, as it constitutes the **prerequisite of any therapeutic advance and of any new public health decision**. It includes different aspects:

- The collection of information on rare diseases in terms of incidence, prevalence and distribution;
- The definition of new nosological entities through in-depth analysis, at clinical/genetic level, of apparently homogeneous diseases. Advantage should be taken of the huge source of information represented by patient organisations;
- The study of the natural history of the disease, its risk factors, its severity and associated complications;
- The identification of factors that could explain various phenotypes, including the studies of genotype/phenotype correlation.

Actions to be undertaken:

- **The development of multidisciplinary networks associating clinicians, geneticians, epidemiologists, patients, relying on the centres of reference that are currently being established in EU Member States;**
- The constitution of cohorts and observatories;
- **The development of tools needed to implement these studies**, in particular data management tools for shared databases linked to biobanks.

## **2.2. Genetic and molecular characterisation**

Around 1200 genetic anomalies responsible for rare diseases have been identified. There are probably **more than 4000 diseases for which the genetic characterisation remains to be done**. It is of fundamental importance to pursue the efforts in this field, in order to allow the development of diagnostic tests and initiate pathophysiological studies of these diseases.

Actions to be undertaken:

- To assemble sufficient collections of biological material corresponding to families and/or cohorts of patients, whose phenotypic characteristics have been correctly analysed. The collection of data and high quality biological samples, as well as their storage and dissemination, are of fundamental importance at EU level, in particular concerning rare diseases. The development and the consolidation of biobanks specifically for rare diseases should be supported and sustainable financing means should be ensured;
- Mapping and cloning of the disease responsible genes; Identification of mutations; Detection of gene deletion or other anomalies of gene dosage.

## **2.3. Pathophysiology**

**Pathophysiological mechanisms involved in rare diseases are largely unknown. The identification of genetic mutations must be followed by**

**appropriate physiological studies to allow the development of novel therapeutic strategies.** This research requires the use of **different approaches:** establishment of pathological cell lines to be used as models, transcriptome, proteome, etc.

It is necessary to develop specific animal models and investigations on how the mutations translate in abnormalities at the organ and system level, using for example imaging techniques to analyse molecular and physiological mechanisms. Many rare diseases are associated with development abnormalities. It is therefore essential to encourage studies devoted to analyse the impact of mutations on the first phases of development

Actions to be undertaken:

- The development of transgenic animal and imaging facilities;
- The support to the analysis of data from the transcriptome and proteome technology, which currently represents a major challenge;
- The identification of the appropriate non-genetic markers, biological, functional etc., to be used for diagnosis, and evaluation of disease progression;
- The development of research on animal models other than mice.

#### **2.4. The improvement of diagnostic performances**

In order to improve the timely care of people affected by rare diseases it is of fundamental importance to **enhance the diagnostic performances in terms of speed of delivery, reliability and accessibility. This would also reduce the costs and human consequences associated with diagnostic delays.**

It is important to develop **new diagnostic tools, to translate knowledge from research development to clinical use, to implement and evaluate new and existing diagnostic methods.** Advances are expected from new technologies, which offer opportunities for performing genetic and/or biological diagnostics.

Actions to be undertaken:

- Large-scale screening projects of gene mutation in order to develop diagnostic tools and diagnostic applications of nanotechnologies, where there is a demonstrated benefit for patients;
- Common projects with the industry and the development of joint DG Research/DG Enterprise projects;
- Projects aimed at developing evaluation methods for diagnostic tools: performance, clinical utility, etc.
- Short-term exchanges between laboratories in different countries to learn about specific diagnostic techniques or therapeutic protocols.

#### **2.5. Therapeutic research**

The **development of therapeutics for patients living with a rare disease is of course the ultimate objective, with a particular focus on children.** The diversity



of the pathological situations, associated with the lack of knowledge of the physiopathology of a great number of rare diseases and the relative lack of interest from the pharmaceutical industry, illustrate the complexity of research in this field, which entails a large variety of approaches. Three main sectors may be identified as priorities:

- **innovative devices to alleviate or compensate disabilities linked with the disease;**
- **Orphan Medicinal Products (OMP), including specific paediatric formulations;**
- **advanced therapy medicinal products (gene therapy, cell therapy and tissue engineered products).**

Actions to be undertaken:

- The establishment of partnerships among various technological fields for the development of symptomatic treatments;
- Projects aimed at searching for chemical molecules potentially interesting in the treatment of rare diseases, following two approaches: on the one hand, high output molecular screening; on the other hand, research of therapeutic molecules based on pathophysiological knowledge of the diseases;
- Projects on tissue engineered products, cell and gene therapy in view of application to rare diseases;
- Projects of pre-clinical therapeutic research and proof of concept studies, which are specifically relevant to orphan drugs and rare diseases.
- Joint DG Research/DG Enterprise/EMA projects for funding the early stage clinical development of designated orphan drugs.
- Support to initiatives aiming at making public any results, both negative and positive, of any clinical trials performed in a rare condition. Such a public database would both help avoid any duplication, ethically, scientifically, and economically unacceptable, and would also represent a precious source of information to foster therapies development.

## **2.6. Research in social and human sciences**

Few research teams work in the area of **social and human sciences** in the field of health, and even fewer on rare diseases. **Research conducted in these fields should measure parameters related to the progress of EU research on rare diseases**, such as the attractiveness of research on rare diseases for scientists and research laboratories, the interest of the pharmaceutical industry in the development of projects on orphan drugs, availability of diagnosis, care and treatments for patients, impact of research and health policies on quality of life and life expectancy, involvement of patient organisations in research. The results obtained from these studies would offer important clues for evaluating the middle and long-term efficacy of the research strategies chosen by the EU.

Actions to be undertaken:

- **Support to research projects in the fields of sociology, economy, history of sciences, psychology, law**, in particular:

- descriptive and analytic research on society and rare diseases e.g. social perception (psycho-sociology, health-economy and ethnology approaches), psychological impact of rare diseases on the patient and his/her environment, implementation of research results into practice, accessibility to care;
- behavioural studies: health behaviour changes, change of practices, therapeutic education;
- public/private scientific co-operation for research and innovation;
- care practices, daily experience of the diseases, self care, health education;
- public research and health policies across EU;
- Development of the concept of “disability studies”: a global social approach (ref. Dr. Gary Albrecht, Univ. of Illinois);
- Development of qualitative studies (by interviews) assessing perception of patients, strengths, expectations; development of pragmatic studies;
- Promotion of pluridisciplinary working groups.

## EURORDIS Specific Contribution: “Specialised Services for People Living with Rare Diseases”

This Specific Contribution to the Public Consultation “Rare Diseases: Europe’s Challenges” focuses on some of Specialised Services which are aimed at improving the daily lives of people living with a rare disease.

The Contribution is largely based on the outcomes of the Rare Disease Patient Solidarity project (RAPSODY) a major project led by Eurordis, involving 10 partners. The project - co-funded by the European Commission, the Baxter International Foundation and Sigma Tau Pharmaceuticals - aims at empowering the rare disease community, covering various aspects of the urgent need to improve quality and access to essential services for rare disease patients at European level. In particular, this paper takes on board the latest developments of the RAPSODY project about Help lines, Therapeutic Recreation Programmes and Respite Care Services, as they have been recently addressed during the European Conference on Rare Diseases held in Lisbon on 27-28 November 2007.

This document was finalised through consultation with the partners and networks’ members of the RAPSODY project, as well as the EURORDIS European Public Affairs Committee, representing a broad range of rare diseases and EU Member States.

### **Summary:**

Improving the quality of care, information and social services is instrumental to the empowerment of people living with rare diseases. Specialised Services in the field of rare diseases must be an important component of national strategies to be incorporated in National Plans for Rare Diseases.

1. **Information services and help lines** increase the opportunities for patients and carers to access and exchange relevant information on the disease they live with and manage daily.

At national level, existing patient-run help line services for rare diseases should be consolidated and long-term plans ensuring their sustainability should be put in place.

A unique EU-wide number for social services, a 116 number, should be established with the support of Member States and the European Commission.

2. **Online communities of patients** are a privileged means to create and maintain contacts among extremely isolated patients before they can be connected with the network. Among the most used tools are mailing lists or new tools which use the potential of the e-technologies.

Tools available to online patient communities in the field of rare diseases, such as e-health tools, should be implemented with the financial support of the European Commission and Member States.

3. **Therapeutic Recreational Programmes** give children the possibility to stop thinking about disease and treatment and to focus on fun and leisure, thus allowing personal development to thrive.

Member States should support Therapeutic Recreation Programmes specially adapted to the needs of children living with a rare disease and foster the creation of new Programmes. Exchanges between Programmes should be encouraged and staff should receive appropriate training.

4. **Respite Care Services** are provided on a short-term basis for disabled people who usually live at home. It gives family members and carers time and temporarily relief, prevents burn out.

Respite care services should be provided as part of a combination of services (centre-based, home-based, etc.), tailored to the needs of each patient. Awareness should be raised on the importance of such services and a cost/benefit analysis performed to demonstrate their positive impact on quality of life and health outcomes.

The European Networks of –respectively- Help Lines, Therapeutic Recreation Programmes, created thanks to the EU-funded RAPSODY project, should be supported beyond the lifetime of the project, to pursue their goals: awareness-raising, exchange of best practices and standards, pooling resources.

## Specialised Services for Rare Diseases

**Improving the quality of care, information and social services is instrumental to the empowerment of people living with rare diseases. Specialised Services are an important part of national strategies for rare diseases.** This should be reflected in the European guidelines for the elaboration of **National Plans on Rare Diseases**, and in each one of the National Plans.

### 1. Rare Disease Help Lines

**Information services and help lines increase the opportunities for patients and carers to access and exchange relevant information on the disease they live with and manage daily.** The production of knowledge through this process is of invaluable importance in the field of rare diseases.

Patients wish to develop a European Network of Rare Disease help lines and information services run by professionals and volunteers. The quality of personalised advice will greatly benefit from a unique EU wide number for services of social value, the exchange of best practices and common tools, such as harmonised answer forms, the creation of a knowledge database, and training for individuals. Consequently, patients would be addressed to the most appropriate centre of expertise, eventually informed about the ongoing clinical trials relating to their

disease. Emergency situations and mobility issues would be better handled. The services would also contribute to establishing contact between very isolated patients.

Actions to be undertaken:

- **Member States should develop or consolidate existing patient-run help line services for rare diseases to achieve a consistent level of service at EU level, and commit to long-term plans ensuring their sustainability.**
- **The European Network of Rare Disease Help Lines, set up thanks to the RAPSODY project, should continue to be supported beyond the lifetime of the project,** to pursue its goals: awareness-raising, exchange of best practices and standards.
- Help lines should develop common tools, a common regulation for validation of information and patient confidentiality. Existing resources should be made available in all European languages.
- **Member States and the European Commission should support the establishment of a unique EU-wide number for social services – a 116 number.** Once the number has been reserved at EU level, national governments should make sure that local help lines are financially supported.
- Funds should be released at both national and EU level for training and financial support of help line operators, and for training of doctors and other professionals, to improve knowledge of rare diseases.
- Finally, continued support should be provided to create and develop connections between European rare disease patients without diagnosis and without association, as they are indeed in the weakest and most exposed situation.

## 2. Online patient communities and e-health in the field of rare diseases

For many rare diseases, the number of patients in each Member State is very small. **Virtual communities** are thus a **privileged - if not the only - means to create and maintain contacts among extremely isolated patients before they can be connected with the network.** Among the most used tools are **mailing lists** or discussion lists, an email communication method for a group of people involved with a particular disease. Under the aegis of EURORDIS, 18 of such mailing lists have been created.

Patients' discussion lists aim to provide information, help in the everyday management of the disease, provide support to patients, their families and carers, break their isolation, share experiences, and possibly support their public interventions (media, scientific and medical circles, public organisations).

Beyond mailing lists, **new tools are nowadays available to patient communities** which use the potential of the e-technologies and the opportunities offered by the web: wikis, blogs, social networking tools... These instruments are promising insofar as they can expand the functions of mailing lists, reinforce online communities by creating stronger clusters of patients, promote the exchange of information and tailored services to patients. In other words, new tools **allow for a greater empowerment of patients.**

EURORDIS therefore supports the Commission's view that "e-Health tools are very efficient and should be a strong part of the EU strategy on RD".

Actions to be undertaken:

- **E-Health in the field of rare diseases (on-line and electronic tools) should be implemented** (Question 5 of the Public Consultation).
- The **European Commission should provide financial support for these activities** through the Public Health Programme and the Framework Programme for Research. **Such measures should also be supported at Member States level.**
- Existing resources should be made available in all EU languages with specific funding.
- An analysis should assess the comparative efficiency of the new e-Health tools on the basis of the real benefit for patient communities.

### 3. Therapeutic Recreation Programmes

Most rare diseases affect children: about 50% of all people affected by rare diseases are less than 19 years old. Starting life with a condition that will impact quality of life, life expectancy, social relations, ability to move, to learn, to accomplish daily life activities is a hurdle, even more unbearable when invasive and complex medical interventions are required.

Personal development, education and learning cannot fully thrive if the life of a child is centred around a disease: children need to enjoy other activities. Children need to play, develop artistic skills, and they need to have fun with other children with or without the same condition.

Siblings also need attention. Leisure and recreational activities will help children gain self-confidence: it opens new fields of activities and new horizons in their lives.

Ultimately, children need a break. They need to spend some days in an environment where they can stop thinking about their disease, where they can meet, socialise and play with other children.

**Therapeutic Recreational Programmes have been created to give children the possibility to stop thinking about diseases and treatment and to focus on fun and leisure.**

Action to be undertaken:

- **Member States should support Therapeutic Recreation Programmes, specially adapted to the needs of children living with a rare disease.** The creation of **new Programmes should also be fostered.**
- The coordination of the Programmes' activities should be facilitated by European funds. In particular, the **European Network of Therapeutic Recreation Programmes, created thanks to the RAPSODY project, should be supported beyond the lifetime of the project,** to pursue its goals: awareness-raising on existing Programmes, exchange of best practices and standards, pooling resources.

- Exchanges between Programmes should be encouraged, so that children benefit from a larger offer of activities and locations, thus favouring cultural and language exchanges; for this purpose the movement of patients across European borders should be facilitated.
- Staff should benefit from training programmes supported both at national and European level to accommodate and to educate children and young adults from different age groups (age ranging from 6 to 25 years old), and also to take care of their medical conditions.

#### **4. Respite Care Services for Rare Diseases**

Living with a rare disease or caring for a child with a rare disease affects its immediate family, social network and relatives. Facing everyday life challenges causes considerable concern, and strain. The rarity of the disease brings additional stress, as families often have to face the lack of knowledge amongst professionals in crucial areas such as medical, social and pedagogical.

**Respite care is provided on a short term basis for disabled people who usually live at home. It gives family members and carers time and temporarily relief, prevents burn out.** Another important purpose is to reveal new abilities of the person living with the disease/disability, allowing him/her to try and perform recreational and meaningful activities.

Respite care services can be offered in various ways, notably: residential respite, i.e. staying with a “respite care family” for a while; domiciliary care; day care centres, nursing homes, institutions or respite care group homes with assisted living facilities; emergency respite services accessible on short notice when unexpected emergency occurs.

Action to be undertaken:

- **Provide respite care services as part of a combination of services (centre-based, home-based, etc.), tailored to the needs of each patient;**
- Raise awareness about the importance of respite care services among decision-makers and professionals at both national and European level;
- Carry out a cost/benefit analysis to demonstrate the utility of such services and their positive impact on quality of life and health outcomes;
- Make a larger range of services available, such as resource centres, sheltered workshops, supported accommodation, residential services, services for people with autistic behaviours...;
- **Support the European Network of Respite Care Services, created thanks to the RAPSODY project, beyond the lifetime of the project,** to pursue its goals: awareness-raising on existing services, exchanges and collaboration among centres, identification of best practices.