EURORDIS Position Paper on Research Priorities for Rare Diseases

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.

In response to the Commission Public Consultation "Rare Diseases: Europe's challenges", EURORDIS has developed a Position Paper on Research Priorities for Rare Diseases. This document 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.

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 prices 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/EMEA 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.