SIXTH FRAMEWORK PROGRAMME

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Project acronym:	**ICORD**
Project title:	**International Conference on Rare Diseases and Orphan Drugs**
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Thematic Priority:	**PRIORITY 1** **Life sciences, genomics and biotechnology for health**

Publishable Final Activity Report

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Project coordinator name: **Jan-Inge Henter**

Project coordinator organisation name: **Karolinska Institutet**

1. Project execution

Project objectives

Background

Around 25 to 35 million people in the EU, or 5 to 8% of the European population, are affected by diseases defined as so-called rare diseases. The European definition of "rare" is an incidence of 5 out of 10 000 people. More than 6 000 diseases are at present considered to fit in this category. These rare conditions are often chronic, progressive, disabling, and even life threatening. They can affect babies or can occur later in life – 80% are genetic diseases and the other 20% are of infectious or autoimmune origin. Most of these diseases have no treatment and no cure.

The US, Japan, Australia and the EU have introduced orphan drug legislations, creating incentives for the development of orphan drugs (Fig 1). The European Orphan Drug Regulation was introduced in 2000, and has generated encouraging results. However, there is a need to inform scientists and companies about the possibilities and advantages of the Orphan Drug Regulation. In addition, there is a need to inform the general public and to create awareness regarding rare diseases.

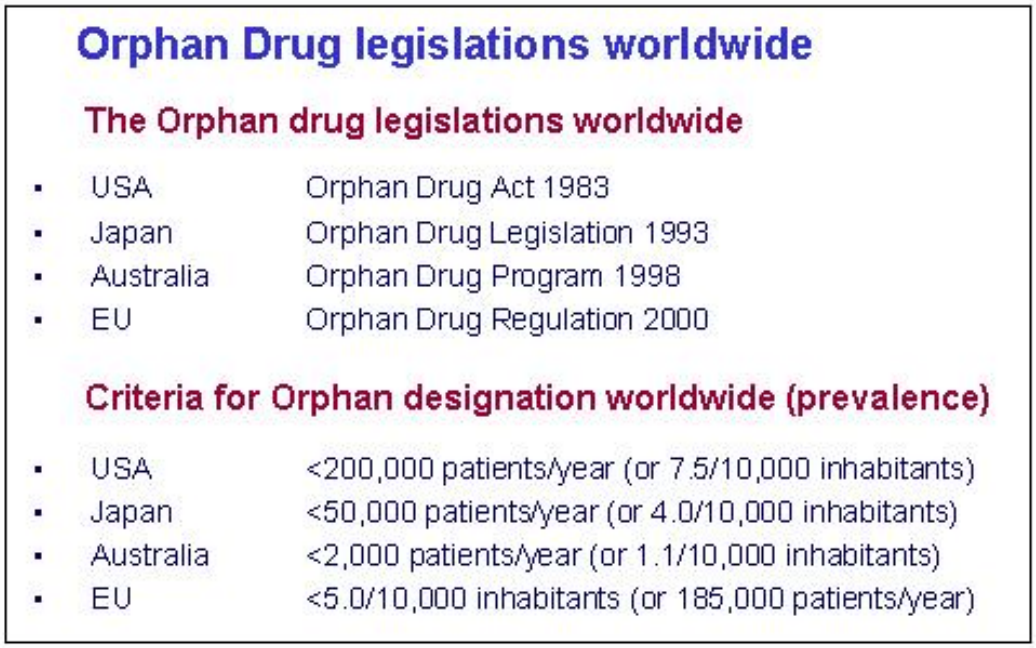

Fig 1. The different Orphan Drug legislations worldwide have similar criteria and the same objective: To stimulate and facilitate the development of treatments for rare diseases

Research on rare diseases involves very small patient groups, thus international cooperation is of utmost importance. The ICORD project addressed the questions of how academic institutions, pharmaceutical companies, patient organisations and public authorities can cooperate within the EU, but also internationally and intercontinentally, to increase the development of treatments for rare diseases. In addition ICORD 2005 created a forum for policymakers in healthcare and politics and patient organisations to share their views and experiences, and to discuss their roles in the future development of orphan drugs.

Overall objectives

- To stimulate international cooperation and translation of scientific research in the rare diseases area, by promoting SME participation and networking activities between private and public partners
- To arrange an international conference on rare diseases and orphan drugs at Karolinska Institutet in February 2005

Specific objectives

- To focus on the cooperative possibilities rendered viable by the Orphan Drug legislation of the EU and the Orphan Drug Act in the US
- To summarise the rare diseases/orphan drug research area at present and identify the crucial points where present work can be improved and the pace increased.
- To describe solutions from a few success stories in this field, related by both academic investigators and by pharmaceutical companies, and discuss what can be learned from these experiences for the future development of orphan drugs.
- To describe ways of funding rare diseases research and emphasise possibilities in cooperative efforts with the patient organisations in order to improve research on rare diseases and the development of orphan drugs.

State of the art

The criteria for Orphan Drug designation by Orphan Drug legislations worldwide are summarized in Fig 1. The European Orphan Drug Regulation (Regulation 141/2000 on Orphan Medical Products) includes in brief: 10 years market exclusivity for the therapeutic indication, creation of a Committee for Orphan Medical Products, access to a centralised procedure for licensing, and protocol assistance. In order for the indication to be eligible, epidemiological (i.e. a disease prevalence of less than 5 per 10.000 inhabitants) or economic criteria have to be fulfilled. It is important to note that the criteria to be filled by an orphan drug, according to the European Orphan Drug Regulation, are that it must be dedicated to a rare disease or that it is a drug that is not viable economically without specific incentives. This broad definition of the term 'rare' means that the orphan drug route can be used to develop treatments for other diseases. These include tropical diseases and other diseases that specifically affect the populations in developing countries, including major communicable diseases linked to poverty.

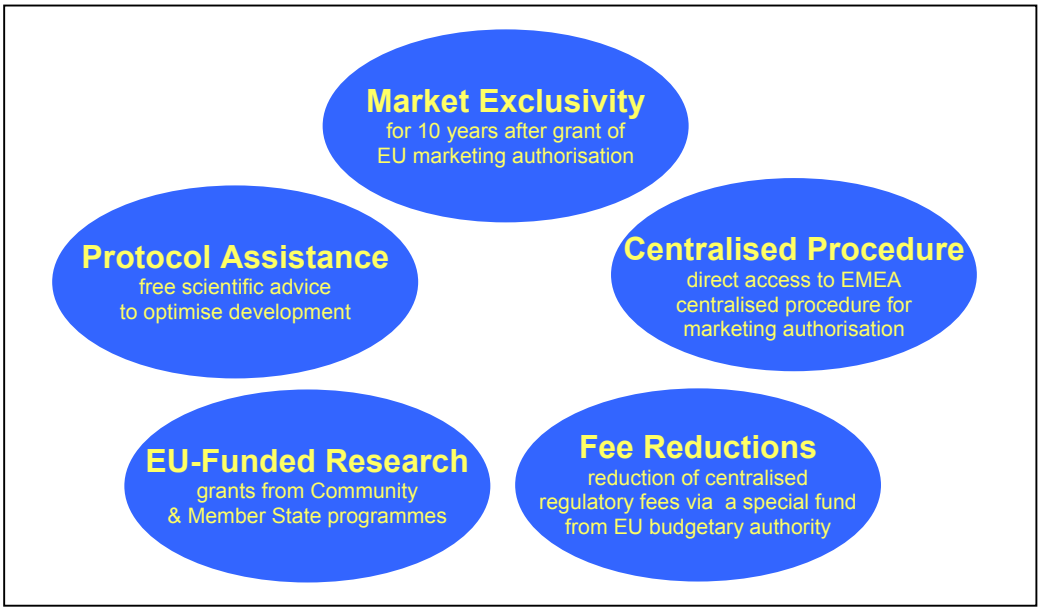

Fig 2. Incentives created through the European Regulation 141/2000 on Orphan Medicinal Products, stimulate scientists and companies to develop treatments for rare conditions and other conditions for which drug development is not otherwise economically viable.

Aims

Our aim is that conclusions from this conference will help the participants to identify how improvements in the rare diseases/orphan drug research field can be accomplished in a rational way, based on facts presented at the meeting and on an optimisation of international cooperation. In order to facilitate future networking between stakeholders, another aim was to create a Network based on the participants of the conference. The conference Website can initially serve as a central information and contact point for these activities.

Contractors involved

Karolinska Institutet was the sole contactor of this project. ICORD 2005, was generously supported by the 6th Framework Program of the European Union, the Office of Rare Diseases at the National Institutes of Health, and Karolinska Institutet.

Work performed and end results

The present report serves to summarize the main topics discussed at ICORD 2005, and highlights important contributions from the panel of outstanding international speakers, as well as the main conclusions of this conference. This summary is structured in accordance with the conference, and is initiated with a background on problems and present opportunities, including legislative aspects and the experiences of these regulations. Then follows academic researcher investigators views and pharmaceutical companies views on the way from disease to therapy. The final parts are on clinical studies on rare diseases, the interaction academia-industry-society, including the collaboration with patient-parent support groups, and future prospects.

Introduction

The 1st International Conference on Rare Diseases and Orphan Drugs (ICORD) was held in Stockholm, 14-16 February 2005, in the presence of Her Majesty Queen Silvia (Fig 3). The conference venue was Grand Hotel, Stockholm. The founding partners of ICORD are the 6th Framework Program of the European Union, the Office of Rare Diseases at the National Institutes of Health, and Karolinska Institutet, Stockholm, Sweden. In addition, a 1-day Swedish satellite meeting on Rare Diseases and Orphan Drugs was organized at the Nobel Forum at Karolinska Institutet, 17 February 2005. The general aim of the ICORD conference (www.icord.cc) was to discuss the diagnosis, prevention, and treatment of rare diseases, and to focus on the improved possibilities for the development of novel treatments for these conditions, following the Orphan Drug legislations in the United States and the European Union. Speakers and participants from academia, pharmaceutical industry, funding and patient organizations, the European Commission, the National Institutes of Health, and other policymaking organizations were present, and the total attendance at the conference was 150.

Fig 3. ICORD 2005 was inaugurated by Queen Silvia, here bringing together representatives from Karolinska Institutet, the European Commission and the National Institutes of Health. (From left: Jan-Inge Henter and Jan-Carlstedt-Duke, Karolinska Institutet; Queen Silvia; Catherine Berens, DG Research - RTD-F2, European Commission; Steve Groft, Office of Rare Diseases, NIH).

Below we have summarized the main topics that were discussed at ICORD 2005, and highlighted important contributions from the panel of outstanding international speakers, as well as the main conclusions of this conference.

Summary of ICORD 2005

PROBLEMS AND OPPORTUNITIES: LEGISLATIVE ASPECTS

The first session at ICORD 2005 was devoted to historical problems in the field of orphan drug research, and to current opportunities provided to the pharmaceutical industry and academic researchers following the US Orphan Drug Act of 1983, and the more recent EU Orphan Drug regulation, in force since 2000. Orphan drug development is limited, in part, by a general lack of knowledge about the underlying mechanisms of these diseases and the relative unavailability of subjects for clinical trials. The major hurdle, however, is the prohibitive cost of investing in a pharmaceutical agent with poor market potential. In his opening remarks, *Prof. Jan Carlstedt-Duke* (Karolinska Institutet) emphasized that rare diseases are, in fact, not so rare. Hence, in Europe, up to about 8% of the population is afflicted with rare or "orphan" diseases (a disease or condition affecting fewer than 5 in 10.000 persons); half of these patients are children.

The first keynote lecture at ICORD 2005 was delivered by *Dr. Stephen Groft* (National Institutes of Health, NIH) and focused on rare diseases research experiences in the United States. Dr. Groft provided an important perspective on collaborative research and development activities, and his lecture served as an inspiration to colleagues from other countries, including the European Union member states. In a related lecture, *Dr. Marlene Haffner* (Food and Drug Administration, FDA) elaborated on the remarkable success of the US Orphan Drug Act. Dr. Hans Hogerzeil (World Health Organization, WHO) addressed the issue of essential medicines, thus placing orphan drugs in a more global perspective, and he raised several important and difficult questions.

Several speakers at ICORD 2005 addressed different aspects of the rare diseases and orphan drugs experiences in the European Union, including *Mr. Thomas Lönngren* (European Medicines Agency, EMEA), *Prof. Josep Torrent-Farnell* (Committee for Orphan Medicinal Products, COMP), Dr. *Kerstin Westermark* (Medical Products Agency, Sweden and COMP), *Mr. John F. Ryan* (Health and Consumer Protection Directorate-General, European Commission), and *Dr. Per Nilsson* (Committee for Human Medicinal Products (CHMP).

The European Medicines Agency (EMEA) is responsible for the evaluation and supervision of medicines in Europe. The Committee for Orphan Medicinal Products (COMP) was established in 2000 following the introduction of the Orphan Drug Regulation, and meets on a monthly basis to review the applications for orphan drug designation. By January 2005, COMP has adopted 265 positive opinions recommending orphan drug designation and 245 medicinal products have been officially designated as orphan drugs by the European Commission. The Committee for Human Medicinal Products (CHMP), which evaluates marketing authorization, received 46 applications for marketing authorization during 2000-2004. Thus far, 19 orphan medicinal products have received marketing approval in the EU. As a consequence, up to 830.000 patients suffering from orphan diseases in the EU stand to benefit from availability of these new treatments. However, the true impact of the orphan initiatives on public health within the EU is being revealed progressively as the number of orphan products reaching the market, and thus becoming available to patients, increases. It was concluded that rare diseases and orphan drugs are a high priority in the EU, and that the current EU Orphan Drug legislation has showed clear benefits for all stake holders, paving the road to fostering important biomedical research in this field. The EU Public Health Programme actions on rare diseases includes the establishment of a task force on rare diseases, and the support of a major conference in June 2005 to review projects supported to date and express the political interest in continued focus on rare diseases.

FROM DISEASE TO THERAPY: ACADEMIC RESEARCH

Several sessions at ICORD 2005 were devoted to the elucidation of specific examples of rare diseases and novel treatments for these conditions. These lectures provided both academic investigators' and pharmaceutical companies' perspectives, as well as a perspective on regulatory aspects of clinical trials for orphan drugs. In his keynote lecture, *Prof. Alain Fischer* (Necker University Hospital, Paris, France) provided a fascinating overview of the Severe Combined Immunodeficiencies (SCID), spanning from disease phenotype description in the 1970s, molecular identification in the 1990s, to advances in therapy from the 1970s to 2005, as well as some remaining challenges, in particular challenges related to the novel *ex vivo* gene therapy for SCID that has been tested in these patients. Based on experiences of SCID and related conditions, Prof. Fischer made several proposals regarding the organization of academic research on rare diseases, including the need for clinical reference centers of expertise, international collaborative efforts, a multi-disciplinary approach to research, and interaction with motivated pharmaceutical companies. The European Rare Disease Therapeutic Initiative (ERDITI), through which academic researchers are provided access to compounds of interest developed by pharmaceutical companies, was presented as an example.

Dr. William Gahl (National Institutes of Health) discussed novel therapies for two rare diseases, nephropathic cystinosis and alkaptonuria. Cysteamine treatment represents a therapeutic success story for the metabolic/lysosomal storage disorder, cystinosis. *Dr. Jean-Pierre Hugot* (Hopital Robert Debré, Paris, France) discussed Crohn's disease (CD), which is characterized by a recurrent or chronic inflammation of the digestive tract. Mutations in a specific gene are found in about 50% of CD patients and 20% of healthy controls. It is expected that better knowledge of host-bacteria interactions in the gut may yield novel preventive actions for CD patients.

Dr. Elisabeth Holme (Sahlgrenska University Hospital, Göteborg, Sweden) focused on the treatment of tyrosinemia type I with nitisinone, an intriguing success story in the field of rare diseases. During the 1980s, it was discovered that a group of herbicidal chemicals were potent inhibitors of tyrosine degradation, and that such a chemical could be an effective drug for the treatment of tyrosinemia type I. The drug was subsequently approved by the FDA in 2002 and was approved for treatment in the European Union just minutes prior to Dr. Holme's lecture at ICORD 2005. Familial hemophagocytic lymphohistiocytosis (FHL) is a rare disease in children, which is fatal within 1-2 months after diagnosis, if untreated. *Prof. Jan-Inge Henter* (Karolinska University Hospital, Stockholm, Sweden) discussed recent success in the treatment where the estimated 3-year probability of survival for the children with FHL is now more than 50%. The FHL success story also underscores the importance of international collaborations to create large series of patients, as well as the importance of collaboration between academic researchers and patient-parent organizations in the area of rare diseases.

Prof. Leena Peltonen-Palotie (University of Helsinki, Helsinki, Finland) discussed studies of rare genetic diseases in the Finnish population, and the advantages of genome-based studies: accurate diagnosis/carrier detection of rare diseases, identification and delineation of new metabolic pathways in humans, new molecular classification of rare diseases, and new avenues of drug development. *Dr. Bruce C. Trapnell* (Children's Hospital, Cincinnati, USA) discussed experiences from the Rare Lung Diseases Consortium, a component of the NIH-funded Rare Diseases Clinical Research Network. Dr. Trapnell also presented important milestones in the history of pulmonar alveolar proteinosis (PAP) research, as an example of how research on rare diseases can increase our understanding of normal biological processes.

Dr. Giovanna Zambruno (Istituto Dermopatico dell'Immacollata, Rome, Italy) discussed future therapeutic approaches for the skin disorders, epidermolysis bullosa (EB) and ichthyosis. Identification of the genes associated with these skin disorders has provided the basis for the design of novel therapeutic approaches, mainly of gene therapy. *Dr. Paolo Moretti* (Baylor College of Medicine, Houston, USA) presented interesting pre-clinical data on a mouse model of Rett syndrome, a neurologic condition affecting mainly girls. Closing the ICORD session on academic research perspectives on rare diseases, *Prof. Jan Andersson* (Karolinska Institutet, Stockholm, Sweden) focused on novel approaches to the development of HIV vaccines. Pre-clinical findings suggest that a therapeutic HIV-1 vaccine based on apoptotic bodies derived from HIV-1 infected cells can be used as a safe immunogen.

FROM DISEASE TO THERAPY: PHARMACEUTICAL COMPANIES

The third keynote lecture at ICORD 2005, entitled "A Journey of Hope", was presented by *Dr. Bo Jesper Hansen* (Swedish Orphan International, Sweden). Swedish Orphan International was founded in 1988 as a direct result of the financial incentives for pharmaceutical companies to develop therapeutic products for rare disorders afforded by the US Orphan Drug Act (1983). Dr. Hansen described some reasons why orphan drugs are attractive to drug companies: a clear definition of the patient population (the market is "reachable"), development steps can be easily planned, clinical testing can be done cost-efficiently, outsourcing of research and development can be done. *Dr. Erik Tambuyzer* (Genzyme Europe, Belgium) gave a comprehensive overview of the experience with orphan drugs in the EU from the industry perspective. Dr. Tambuyzer emphasized the importance of access to treatments and suggested that efforts should be made to develop a coordinated European framework from research to access to treatment in this field. *Dr. Andrea Rappagliosi* (Serono International, Switzerland) elaborated further on the contribution of the biotech industry to the development of treatments for rare diseases. A way forward was suggested by boosting translational research, improving tools to assess safety and medical utility and by improving timely access to orphan drugs throughout Europe.

Dr. Catarina Edfjäll (Actelion Pharmaceuticals, Switzerland) concluded this ICORD 2005 session with an exciting presentation of a small pharmaceutical company's experience of orphan drug development. Today close to 20.000 patients worldwide have received bosentan (marketed as Tracleer), which is an endothelin receptor antagonist used for the treatment of pulmonary arterial hypertension. Dr. Edfjäll concluded that additional protection that rewards pioneering work into new classes of drugs, and a pan-European implementation of national incentives, such as tax cuts and grant programmes, are needed to further stimulate research and development of orphan drugs.

FROM DISEASE TO THERAPY: FACILITATING CLINICAL STUDIES

ICORD 2005 also included lectures on data collection in the context of clinical trials, and related topics. The first speaker, *Dr. Jeffrey Krischer* (National Institutes of Health) discussed the role of the Data Technology and Coordinating Center (DTCC), which provides informatics and biostatistics support for the NIH-funded Rare Diseases Clinical Research Network (RDCRN). *Dr. Roberta A. Pagon* (University of Washington, Seattle, USA) described the NIH-funded GeneTests website, which includes a Laboratory Directory with 580 international laboratories offering clinical and/or research testing for about 1100 diseases. There is also a section called GeneReviews, currently consisting of about 280 peer-reviewed, highly structured disease descriptions that focus on the use of genetic testing in diagnosis, management, and counselling. *Dr. Brendan Buckley* (National University of Ireland, Cork, Ireland) discussed some of the practical issues and problems of clinical trials, from a European perspective. Clinical trial obstacles in a multi-lingual and multi-cultural continent with a diversity of healthcare systems can be overcome by a creative, long-term partnership between academia, patient organizations, industry, legislative authorities, and European governments.

INTERACTION ACADEMIA - INDUSTRY - SOCIETY

The fourth and final keynote lecture at ICORD 2005 was delivered by *Dr. Peter Arlett* (Enterprise and Industry Directorate-General, European Commission), who discussed ways of supporting active collaborations between academia, industry, and society. Dr Arlett emphasized the role of EU working in collaboration with the different stakeholders to enhance cooperation, and the support created by the recent EU initiatives, such as Public Health Programs, Framework Programs, and the EU Orphan Drug regulation.

Next, a series of ICORD lectures were presented by representatives of patient organizations in the US and Europe, thus providing an important patient-parent perspective on rare diseases and orphan drugs. *Ms. Diane E. Dorman* (National Organization for Rare Disorders, USA) focused on "the power of the many", and emphasized that nearly 30 million Americans suffer from one of the 6000 known rare diseases. The National Organization for Rare Disorders (NORD), a federation of voluntary health organizations, is dedicated to helping people with rare orphan diseases. *Ms. Sharon Terry* (Genetic Alliance, USA) also discussed the central role of advocacy organizations in accelerating rare disease research efforts. The Genetic Alliance, founded in 1986, is a coalition of over 600 patient organizations. Ms. Terry focused on the different ways in which advocacy organizations can promote research, for instance by raising awareness of rare diseases and articulating incentives. *Dr. Andreas Reimann* (European Organization for Rare Diseases) elaborated further on the potential of patient organizations to support research and increase awareness of rare diseases. The European Organization for Rare Diseases (EURORDIS), founded in 1997, is a patient-driven European alliance of patient organizations. Dr. Reimann emphasized the importance of moving from a product-centered to a patient-centered point of view in rare disease and orphan drug research and pointed out that it is the value for the individual patient that counts when providing health care services, conducting research, or developing new therapeutic options.

RARE DISEASES AND ORPHAN DRUGS: FUTURE PROSPECTS

In this final session, *Prof. Hans Wigzell*, former President of Karolinska Institutet and Chairman of the Program Committee of ICORD 2005, provided several predictions regarding the future of rare diseases. First, it was suggested that rare diseases will increase in number in several ways. However, as more and more rare diseases become possible to treat and/or cure, the pressure to reduce the cost of these treatments will increase. Finally, Prof. Wigzell proposed the creation of a permanent international hub of information and coordination for rare diseases, with a permanent secretariat and register or database of rare diseases. Next, *Dr. Alain Vanvossel* (Research Directorate-General, European Commission) summarized future EU support to research on rare diseases and orphan drugs. EU provides direct financial support for selected research projects through its Framework Programs for Research, Technological Development, and Demonstration Activities. Finally, *Dr. Stephen Groft* (National Institutes of Health) provided some additional thoughts on future ways of the NIH in supporting progress on rare diseases and orphan drugs. The need for partnerships to foster research on rare diseases was emphasized, as well as the importance of expanding existing research networks as a means to utilize available resources in an optimal manner.

Concluding remarks

ICORD 2005 provided a platform for academia, patient organizations, pharmaceutical companies, and public authorities and policymaking bodies working towards the common goal of improved diagnosis and treatment of rare diseases, and the conference can be considered a great success in many aspects. In particular, there was an active intercontinental dissemination of experiences by representatives from North America, where the Orphan Drug Act has been in force since 1983. The multifaceted and lively discussions on rare diseases and orphan drugs, and the opportunities and challenges that lie ahead of us, both in the European Union and at an international level, were also a source of great inspiration to all participants. Moreover, ICORD 2005 served as a unique meeting place in geographic terms, being the 1st International Conference on Rare Diseases and Orphan Drugs. Indeed, delegates from 13 EU member states plus Turkey attended, and a grand total of 18 countries on 4 different continents were represented at the conference in Stockholm, making this a truly global event.

One of several concrete outcomes of ICORD 2005 was the decision to organize a 2nd International Conference and Rare Diseases and Orphan Drugs, in the Spring of 2006 in Washington, D.C., for further exchange of ideas and experiences. There was also a general consensus among the participants of ICORD 2005 to establish an International Society for Rare Diseases and Orphan Drugs (ISORD), in order to provide a forum for further activities in this field. Representatives of the various stakeholders listed above are to be invited to take part in these activities, thereby facilitating efforts to reach the common goal of further improving the diagnosis and treatment of rare diseases. We believe that an international society (ISORD) along with a series of annual meetings (ICORD) will provide considerable benefit to patients afflicted with rare diseases; these initiatives are also in line with the EU Public Health Programme for 2003-2008, which includes rare diseases as an area for support.

2. Dissemination and use

The International Conference on Rare Diseases and Orphan Drugs (ICORD) focused on the opportunities created by various orphan drug legislations (Fig 1), and how to stimulate international cooperation and translation of scientific research in the rare diseases area.

The ICORD abstract book is available on the conference Website (www.icord.cc). Most speakers have also given their permission to publish their PowerPoint presentations on the Website. Twenty-seven presentations are now available.

We have also produced an extensive summary of the conference and its content in the form of a scientific report. The scientific report will be made available on the conference Website as a pdf file. In addition, we will produce a printed issue of the scientific report. This report will be sent to all participants and to key stakeholders, and will be available, to a limited extent, based upon request. In addition, an executive summary of the scientific report will be offered to interested parties, including Euroabstracts.

The entire ICORD conference was video-recorded. The video recording will be edited into a 1,5-hour long video-DVD, divided into 13 different episodes illustrating the important messages conveyed at the conference. The DVD will be distributed to all participants and will be available upon request at cost price. It will also be made public on the Website. The Website will also contain the abstract book, the scientific report and most of the PowerPoint slides shown at the conference.

We are preparing a review article on “Rare Diseases and Orphan Drugs” for the Journal of Internal Medicine. The manuscript is scheduled to be submitted by August 2005.

In order to facilitate future networking between stakeholders, especially in the international perspective, a decision was taken at the ICORD conference, to create an international society for rare diseases and orphan drugs (ISORD). This society will function as a network based on the participants of the ICORD conference, and serve as a source of compiled knowledge, to be used by policymakers in health care and politics. This network will be able to spread information about rare diseases and treatments, and to create joint efforts acting to influence the pharmaceutical industry and policymakers, for the benefit of patients with rare diseases. In addition, the ISORD society will participate in organizing future conferences for the international rare diseases society.

The conference Website will initially serve as a central information and contact point. We will apply for future support for this network, in order to develop it further as a central contact point, and for dissemination and information purposes.

Taken together, these measures will result in an increased official, professional and public awareness of this major health problem.