

# REPORT OF THE SEVENTH EPPOSI-WORKSHOP ON PARTNERING FOR RARE DISEASE THERAPY DEVELOPMENT

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## “POSITIONING RARE DISEASES ON THE HEALTHCARE AGENDA”

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*A Workshop organised by*  
European Platform for Patients' Organisations,  
Science and Industry (EPPOSI)  
*Madrid, 26-27 October 2006*

**Chair of the Workshop, Rosa Sanchez de Vega, FEDER,  
Federación Española de Enfermedades Raras, Spain**

Every effort has been made to ensure that these proceedings are an accurate reflection of contributions made by the speakers during the Workshop, bearing in mind that this is not a verbatim report but rather a summary. Relevant sections of the draft were forwarded to each speaker for verification, and the final text has taken into account comments received before the deadline for responses. EPPOSI does not accept responsibility for eventual errors that were not communicated to the rapporteur.

*Published by*  
**European Platform for Patients' Organisations,  
Science and Industry (EPPOSI)**

## ACKNOWLEDGEMENTS

EPPOSI would like to thank the IMSERSO, Spanish Ministry of Labour and Social Services for hosting the event.

EPPOSI gratefully acknowledges the support from the following sponsors:

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EPPOSI wishes to thank the following associations for sponsoring the respective dinners:

EBE, European Biopharmaceutical Enterprises of EFPIA  
EuropaBio, the European Biotech Industry Association  
Farma Industria

EPPOSI also recognises the support of the following organisations:

Dutch Steering Group Orphan Medicines (WGM)  
Edelman  
EDMA, European Diagnostic Manufacturers Association  
EGAN, European Genetic Alliance Network  
EMA, European Medicines Agency  
ESHG, European Society of Human Genetics  
EURORDIS, European Organisation for Rare Disorders  
FEDER, Federación Española de Enfermedades Raras  
FDA, U.S. Food and Drug Administration, United States  
Genetic Alliance of America  
NIH, National Institutes of Health - Office of Rare Diseases, United States  
Orphanet

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Layout: Grafiks, B-3051 Sint-Joris-Weert  
Printing: De Coster, B- 3090 Overijse

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## PRECONFERENCE PAPER

The European Platform for Patients' Organisations, Science and Industry (EPPOSI) will hold its "Seventh Workshop on Partnering for Rare Disease Therapy Development" at the Spanish Ministry of Labour and Social Services IMSERSO, Calle Ginzo de Limia 58) in Madrid on October 26-27 of this year. Spain has always expressed a keen and special interest in rare diseases. Recently, the Spanish Senate has unanimously approved the creation of a special Working Group on this subject. In 2007, with the full support of the Spanish Ministry of Labour and Social Services, the first medico-social Center of Reference for patients with rare diseases in the city of Burgos will open. Thereby, the Spanish Government will further contribute to the improvement of the life of patients with rare diseases and their families.

This year's Workshop will give the opportunity to evaluate 5 years experience of the European Regulation on Orphan Medicinal Products. We hope the Workshop will boost further practical and successful application of this regulation. The sessions will be organized around the following questions:

- How to enable the appropriate assessment of new therapies?
- How to assess the benefit of therapies for patients and their families?
- How to enable the development of orphan indications of marketed drugs?
- How to ensure optimal access to treatment?

As with all EPPOSI past and future Workshops on partnering for rare disease therapy development, the aim is to provide a platform for the cultivation of partnerships between industry, patients, academia, together with European authorities, so as to convert policy issues and scientific developments into therapies for rare diseases.

All Workshop sessions will feature high-level speakers and experts, representing the different EPPOSI parties and stakeholders, with each session allowing time for an in-depth debate and discussion with selected panel speakers. This year's Workshop will be the second with an international scope, gathering not only European authorities and stakeholders, but is also supported by both the National Institutes of Health (NIH) and the Food & Drug Administration's (FDA) Office for Rare diseases.

This event follows six successful EPPOSI Workshops in the Federal Parliament in Brussels in September 2000, the French Senate in Paris in October 2001, the Chamber of Deputies of the Italian Parliament in Rome in 2002, and three hosted by ministries in The Hague (2003), Berlin (2004) and London (2005).

## EXECUTIVE SUMMARY

### **Towards more Collaborative Efforts in Positioning Rare Diseases on the Healthcare Agenda**

Two days of active discussion between more than 120 patients' representatives, academia and industry from both sides of the Atlantic took place in Madrid (Spain) on 26-27 October, 2006. This was the 7th Workshop dedicated to partnering in the field of rare diseases organised by EPPOSI (the European Platform of Patients' Organisations, Science and Industry). Each year, a workshop is organised in a different European capital to provide a platform for debate on ways to improve developments and accessibility of therapeutic solutions in Europe. Key players in the US are also invited to contribute to the discussion. **This year the workshop focussed on the question of positioning rare diseases on the healthcare agenda.**

The first question to be addressed was the impact that the Clinical Trials Directive of 4 April 2001 is having on clinical research in the field of rare diseases. It was shown that, although the general aims of the Directive are appropriate, the way it was written, in not differentiating between the level of risk and the nature of risk in research projects, has created an unnecessarily bureaucratic system, over-protecting patients for most projects. The fact that the Directive has been implemented in a slightly different way in EU countries adds another difficulty for sponsors and investigators, since most trials are international. The Directive seems to be responsible for a drop in the number of patients recruited, an increase in the costs of trials and delaying their start by several months. It was decided to collect evidence to come up with suggestions for improving this Directive, which is essential to guarantee public confidence in research activities.

The proposed EU Regulation on "Advanced Therapy Medicinal Products" is still under discussion. The patient representatives expressed their concern that the "O-risk" culture could ruin their chances of getting innovative treatments for their disease or condition. Both sides of the problem have to be considered, which means appreciating the benefit/risk balance, as opposed to only considering risk. The patients' representatives are in favour of maintaining a centralised system via the EMEA for the evaluation and approval of these products.

Biotech companies expressed their concern that post-marketing commitments imposed could, in some cases, mean that their days are numbered. They wish to see EMEA establish a service to help them handle these commitments for products authorised in the 27 EU Member States.

Long discussions were dedicated to the appreciation of the medical “added value” of new therapies, which is the basis of the price negotiation. It was felt that there would be enormous gain in sharing data and analysis between national committees. Participants were reminded that, while the scientific evaluation is carried out centrally at EMEA to allow the delivery of an EU-wide marketing authorisation, the following step is done at country level. This consists of evaluating the drug in a more global context including organisational, ethical, economic and societal aspects. If this step remains at country level, bearing in mind that healthcare systems are national, it may be possible to avoid duplicating activities by working together. This is likely to happen thanks to the EUnet HTA project which establishes the framework for collaboration between Health Technology Assessment agencies in Europe. A very welcome initiative...

The affordability of drugs was also the topic of intense discussions between patients, payers and industry representatives. Through the example of the prophylactic treatment for Haemophilia, the issue of major inequalities in access was investigated. Participants agreed that the example of what was achieved for AIDS could serve as a model. The issue of the willingness of society to pay for expensive drugs was perceived in different ways by the participants. If solidarity is still the principle applied in Europe, the various healthcare systems are increasingly unfair. Participants agreed on three issues: (1) Transparency is required at all levels: in the way cost-effectiveness studies are conducted, in the way prices are agreed and regarding the cost of innovation. (2) It is of utmost importance not to misuse the Orphan Medicinal Product status and, additionally, to reassess the effects of the Regulation very regularly. It is also essential to ensure an optimal prescription framework in order to avoid wasting resources while maximising the number of patients with real needs being treated. (3) Ways to reduce the cost of development of Orphan Medicinal Products should be identified by the interested parties and solutions implemented.

A session was dedicated to further investigation of potential orphan indications for drugs already marketed for another, maybe major disease. Participants were reminded that orphan indications remain true orphan medicinal products, because the requirements to obtain a marketing authorisation are similar. It may be that development costs are lower if the pre-clinical data available are still valid. In this case, the final price will also be lower. The problem in this sector is the difficulty academic researchers have in accessing the drug to be tested, as many companies refuse to provide it, for liability reasons, amongst others. Incentives have to be developed because the current situation is not in the patients’ best interests. Many old drugs could be very efficient in treating patients with rare diseases. These new indications should be given the chance to be tested. Academic funding is crucial in this sector. Up to now, only France and Italy have set up grant programmes to support independent clinical research, which includes trials to test new orphan indications, as well as trials to compare available drugs or to test new

protocols combining several drugs. It was announced during the Workshop that the Spanish Drug Agency will launch a similar programme in January 2007. This is excellent news for Spanish researchers. With 3 countries now supporting academic research in the field of orphan drugs, the time for a more collaborative effort will soon be upon us.

The patients reminded participants of the final goal: to achieve access as quickly as possible to a maximum number of safe, efficient and affordable medicines. This will be obtained only if there is a single market for orphan drugs in Europe and, if we work more closely with other regions of the world, a common framework for doing so – starting with the USA. The experience of the Critical Path Institute in Arizona was highlighted as a possible model for action. It was proposed by the participants that coordination between the main stakeholders should be more firmly established. This will be explored.

**EPPOSI will organise its 8th Partnering Workshop on 18-19 October 2007 in Copenhagen.**

# CONFERENCE AGENDA

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## DAY 1

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### OPENING SESSION

#### Welcome and Introductory note

*Michael Griffith, EPPOSI, Chairman (\*)*

#### Introductory remarks

*Rosa Sanchez de Vega, FEDER*

#### Welcome remarks

*Alfonso Jimenez Palacios, Director General of Quality - Ministry of Health & Consumer Affairs*

### SESSION 1 – How to enable the appropriate assessment of new therapies?

*Chaired by Michael Griffith, Chair EPPOSI (\*) and Alfonso Jimenez Palacios, Director General of Quality - Ministry of Health & Consumer Affairs*

#### **Impact of the trial directive and of the advanced therapy regulation on clinical trials for rare diseases: the point of view of Academia**

*Bruce Morland, Birmingham Children's Hospital*

#### **Impact of the clinical trial directive and of the draft Advance Therapy Regulation on clinical trials for rare diseases: the point of view of Industry**

*Maria Pascual-Martinez, Cellerix*

#### **Interactive discussion**

### SESSION 2 – How to assess the benefit of therapies for patients and their families?

*Chaired by Pauline Evers, EGAN and Josep Torrent y Farnell, EMEA/COMP*

#### **Assessment of the therapeutic added value: methods and their limits**

*Panos Kanaos or R. Ömer Saka, London School of Economics (\*)*

**Assessment of the therapeutic added value: the point of view of Industry**  
*Andrea Rappagliosi, Serono, EuropaBio representative to the European Commission High Level Pharmaceutical Forum*

#### **Assessment of the therapeutic added value: the point of view of Regulators**

*François Meyer, HAS - Haute Autorité de Santé de France*

**Assessment of the therapeutic added value: the point of view of Patients**  
*Andrea Buzzi, Italian Haemophilia Society*

**Assessment of the therapeutic added value: the point of view of Payers**  
*Ad Schuurman, Medicine Evaluation Committee (MEDEV) of the European Social Insurance Fund*

#### **Interactive discussion**

### SESSION 3 – How to enable the development of orphan indications of marketed drugs?

*Chaired by Jan Inge Henter, Karolinska Institute and Miguel Angel Izquierdo, Pharma Mar*

#### **Orphan indications which could be developed**

*Valérie Thibaudeau, Orphanet*

#### **The development of orphan indications: the point of view of EMEA**

*Channa Debruyne, EMEA*

#### **The development of orphan indications: the point of view of FDA**

*Marlene Haffner, FDA*

#### **The development of orphan indications: the point of view of industry**

*Pierre Vankan, Santhera*

**Support to the development of orphan indications by academic groups**  
*Ségolène Aymé, Orphanet*

#### **The development of orphan indications: the point of view of the Mutual Benefit Societies**

*Heidi Goethals, AIM - International Association of Mutual Benefit Societies*

#### **Interactive discussion**

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## DAY 2

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### SESSION 4 – How to ensure access to optimal treatment for patients?

Chaired by Dianne Dorman, NORD and  
Kerstin Westermark, COMP

#### **Would Centres of Reference contribute to better treat patients?**

Ségolène Aymé, Rare Diseases Task Force

#### **How to speed up access to orphan drugs in Europe?**

Yann Le Cam, EURORDIS

#### **Reimbursement policies: what can be shared between health technology assessment agencies?**

Finn Børlum Kristensen National Board of Health - Danish Centre for Evaluation and Health Technology Assessment

#### **Responsibility of Industry in facilitating access to drugs**

Erik Tambuyzer, Genzyme, EuropaBio/EBE representative to their Joint Task Force on Orphan Medicinal Products

#### **Interactive discussion**

### SESSION 5 – Positioning Rare Diseases on the healthcare agenda

Chaired by Lisa Wise, Genetic Alliance of America

#### **Where do we go from here?**

#### **Round table with representatives from:**

- EMEA: Channa Debruyne
- COMP: Kerstin Westermark
- NIH-Office of Rare Diseases: Stephen Groft
- FDA: Marlene Haffner
- Genetic Alliance of America: Lisa Wise
- NORD: Dianne Dorman
- EURORDIS: Yann Le Cam
- French Ministry of Health for the French Action Plan: Alexandra Fourcade (\*)
- Co-chairs of the Organising Committee: Ségolène Aymé - Fernando Royo - Rosa Sanchez de Vega

#### **Interactive discussion**

#### **Summary of Recommendations & Outcomes of the Workshop**

Ségolène Aymé

#### **CLOSING REMARKS**

by Maria Teresa Pagès, General Director of Pharmacy and Health Products -  
Ministry of Health & Consumer Affairs (\*)

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(\*) Change in programme occurred.

## REPORT

### 7TH WORKSHOP ON PARTNERING FOR RARE DISEASE THERAPY DEVELOPMENT

*Madrid, 26-27 October 2006*

*“Positioning Rare Diseases on the Healthcare Agenda”*

**Venue:**

IMSERSO

Spanish Ministry of Labour and Social Services

Calle Ginzo de Limia 58, 28029 Madrid

**Chairs of the Organising Committee:**

*Ségolène Aymé, Orphanet*

*Fernando Royo, Genzyme*

*Rosa Sanchez de Vega, FEDER*

## DAY 1 - Thursday, October 26, 2006

### OPENING SESSION – Welcome and Introductory Remarks

*Erik Tambuyzer, Vice Chair EPPOSI*

I am stepping in for Michael Griffith, chair of EPPOSI, who unfortunately cannot be here with us because of illness.

I am happy to welcome you to Madrid.

EPPOSI is the European Platform for Patients' Organisations, Science and Industry. It constitutes a group of volunteers representing organisations, institutions and patient groups. It aims to position policy issues on the healthcare agenda, by discussing them in a balanced way with equal participation of all the stakeholders. We ensure that we discuss these things openly and transparently. EPPOSI does not take up its own positions, but reflects those discussed and agreed upon in workshops.

The title of today's conference is 'Positioning Rare Diseases Firmly on the Healthcare Agenda.' Each year, we try to organise a workshop on rare diseases, therapy development in a different European capital. Madrid is the seventh capital we are visiting. Next year we will be in Copenhagen.

We are organising another workshop on the value of innovation in Dublin under the auspices of the Irish Minister of Health in January 2007. Value of innovation is an important topic on the healthcare agenda in Europe at this time. As a society, we need to find a balance between beneficial innovation and cost.

I would like to thank the sponsors of today's meeting. As EPPOSI wants balanced representation, the participation costs for a certain number of patient and scientific representatives are being paid by the sponsors.

Furthermore, I wish you all welcome and a very good workshop.

*Rosa Sanchez De Vega, President of Spanish Alliance for Rare Diseases*

Welcome to Madrid. Madrid is an open and cosmopolitan city where everybody is welcome. The Spanish Alliance for Rare Diseases was established in 1999. It now has 112 members. One of our priorities is to put rare diseases onto the healthcare agenda. This is in line with the aims of EPPOSI. There is a working group at the Spanish Senate studying the problem of rare diseases. This group is charged with making recommendations to the Government for the national plan for rare diseases.

I am happy that this EPPOSI workshop is being held this year in Madrid because this week we are celebrating rare disease awareness week. Each day of the week is focused on a different target, a different interested party. I am glad to see patient groups represented here. They play a key role in raising awareness and gathering expertise. In the field of rare diseases, patients and patient groups are experts. Their opinion on therapies is very important. The awareness week has had a big impact on the media. This is one of our aims. The week has the support of very important authorities, such as the Royal Family and the General Secretary of Social Affairs.

Our first session is on how to enable the appropriate assessment of new therapies, a subject I know is important to everyone who is involved in rare diseases.

*Alfonso Jimenez Palacios, Ministerio de Sanidad y Consumo Nacional de Salud y Alta Inspeccion*

Lamentamos no poder incluir el discurso de bienvenida del Sr. Alfonso Jiménez Palacios (Ministerio de Sanidad y Consumo) debido tanto a la falta del soporte escrito del mismo, como al desafortunado incidente técnico ocurrido al principio de la conferencia que impidió la grabación de su ponencia.

Nos hubiera gustado poder compartir con todos Vds. en este informe del simposio, el caluroso mensaje de bienvenida del ponente así como la comunicación enviada por su Ministerios a todos los participantes de EPPOSI. En dicho escrito se hacía hincapié en la importancia que tiene EPPOSI como plataforma para dar a conocer los puntos de vista de los diferentes sectores que la engloban: industria, pacientes y mundo científico; y la oportunidad que representa el compartir sus respectivos problemas teniendo como objetivo la mejora de la calidad de vida de los pacientes que ven, en muchos casos, sus vidas amenazadas por enfermedades debilitantes y crónicas.

El Sr. Jiménez Palacios también hizo hincapié en el interés que el Ministerio de Sanidad y Consumo ha venido mostrando últimamente por el tema de las enfermedades raras, como por ejemplo, el Decreto de ley de Centros de Referencia, el Instituto de Investigación de Enfermedades Raras y sus redes temáticas de investigación y los recién creados CIBER, Centros de Investigación Biomédica en Red sobre enfermedades raras.

Reiteramos una vez más nuestra gratitud al Sr. Alfonso Jiménez Palacios por su valiosa contribución a nuestro simposio.

—————  
We apologize for not being able to include Mr Alfonso Jiménez Palacios' introductory speech. The reason being that on one hand Mr Jimenez Palacios did not use any written support for his speech, and on the other unfortunately enough, the recording system used during the 2-day workshop faced a technical problem at the very start of the workshop just when Mr Jiménez Palacios was speaking. Again we sincerely regret we can not share with you in this EPPOSI report his warm welcome and the message conveyed by his Ministry to all the participants of our workshop according to which the EPPOSI platform is of utmost importance for all stakeholders involved to understand the problems faced by all sectors represented and particularly for the patients whose lives are threatened by a long and debilitating disease.

Mr Jiménez Palacios also insisted on the interest that the Ministry of Health has been showing lately in the rare diseases field, taking as example the Law Decree on Centres of Reference, the Rare Diseases Research Institute and its linked research networks and the recently created CIBER (Network of Centers for Biomedical Research for rare diseases).

We would like to again express our deep thanks to Mr Alfonso Jiménez Palacio for his valuable contribution to our workshop.

## SESSION 1 – HOW TO ENABLE THE APPROPRIATE ASSESSMENT OF NEW THERAPIES?

*Chaired by Marlene Haffner, FDA and  
Yann Le Cam, EURORDIS*

### Impact of the Clinical Trial Directive and of the Advanced Therapies Regulation on Clinical Trials for Rare Diseases – An Academic Perspective

*Bruce Morland, Birmingham Children's Hospital*

#### THE CLINICAL TRIAL DIRECTIVE

##### 1. Background

###### *a) Aims*

One cannot argue with the aims of the Clinical Trial Directive. Its objectives are to provide greater protection to individuals who participate in clinical trials, deliver quality and harmonise the Regulation and conduct of clinical trials throughout Europe.

###### *b) Issues*

Some issues have arisen since the Clinical Trial Directive came into force in May 2004. There is no differentiation between commercial and non-commercial trials with regards to fees, good clinical practice, good manufacturing practice and pharmaceutical vigilance. Why should there be such a differentiation? The reality is that for those undertaking trials in a non-commercial environment the burden of bureaucracy has become almost unsustainable.

###### *c) UK law*

A directive is not law. Each individual member state had to translate the EU directive into law. In the UK, the Statutory Instrument 1031 put the Directive into place. The Directive was implemented in each member state in slightly different ways. This has proved to be an incredible challenge to those of us participating in international collaborative trials because everyone is doing things slightly differently. Harmonisation has not really been achieved.

##### 2. Sponsorship

###### *a) Harmonisation*

The Directive speaks about the need for a single European sponsor. Germany is insistent about the idea of a single European sponsor. In Belgium, up until recently, there had been so much debate about clinical sponsorship that no clinical trials had happened for almost two years. This issue has been dealt with. In the UK, we have put into the law the fact that we do not recognise the need for a single European sponsor. This is fine for us but when I try to collaborate with Germany, this is a real problem.

###### *b) EURAMOS trial*

A concrete example of this is a European study of osteosarcoma or bone tumours. This is a collaborative study with a number of European groups and the United States. It took us four years to do this trial. We realised that we needed a single sponsor for this study. Eventually, the Medical Research Council in London assumed the role of the single sponsor. This took four years to achieve. We have devolved some of those responsibilities to trial centres. This is an example of how bureaucracy has slowed down our ability to carry out clinical trials.

##### 3. Definition of Investigational Medicinal Products (IMP)

###### *a) Definitions*

The definition of IMP is also becoming a real problem. Almost every study in children's health defaults to being defined as an IMP. The impact of this is to increase bureaucracy. Some investigational medicinal products are not IMPs. For example, carboplatin is a very commonly used cytotoxic drug. We have been using it on children for at least 20 years. It is not licensed for use in children, however. Every time we use carboplatin in a clinical trial, it defaults to being an IMP.

###### *b) Legislation*

In the UK, we had an amendment to the Clinical Trial Directive earlier this year. This reinforces some of the compliance issues for good clinical practice. However,

it is imposing more administrative burdens on all of us. One provision that will particularly affect us is the need to have investigational brochures for every product used in a clinical trial.

#### *c) Clinical trial*

If you are using an IMP, does it automatically become a clinical trial? This may not be the case. As long as you can define standard care, the studies that you put into place need not necessarily be a clinical trial. Many academic groups in Europe are trying to get round the EU Directive by calling or not calling their studies clinical trials. This is a real concern. All this is doing is dumbing down our research.

### **4. Burden of Bureaucracy**

#### *a) Impact*

Some publications have begun to look at the burden of bureaucracy. These have shown that opening new trials decreased from 19 in 2004 – before the Directive – to seven in 2005. One third less patients have been recruited. Trial costs are up 85%. The initiation of the trials was around five months slower.

#### *b) Safety reporting*

Safety reporting has to be good. However, there has been a huge expansion in the administration of managing safety reporting. We have to report back to multiple organisations: investigators, competent authorities, ethical committees, drug companies and others. This demands a very significant infrastructure. Is there any evidence from this that we have started to conduct safer clinical trials in Europe? Do not misunderstand me. My prime concern in a clinical trial is to ensure the safety of the patients. However, there needs to be a balance between ensuring safety and the administrative burden.

#### *c) Challenges*

Multinational clinical trials are the norm. You cannot do clinical trials of rare diseases in single institutions. Rare diseases often push the frontiers of therapeutics. Trying to avoid regulation is impossible. There are very few examples of being able to define standard care. We are dealing with vulnerable patients, children for example. Many patients have pre-existing co-morbidities that make clinical trials challenging. It is very expensive to conduct clinical trials and extremely hard to run them through academic groups. Small- and medium-sized biotech companies will struggle to get the resources and infrastructure in place to conduct multinational, collaborative trials. The incentives to develop drugs are not matched by the facilitation to undertake clinical trials.

### **5. EU Regulation on Advanced Therapies**

#### *a) Aim*

A discussion document came out towards the end of last year looking at three types of therapy: gene therapy, somatic cell therapy and tissue-engineered products. The aim of the Regulation is to align these therapeutic measures with conventional drug therapy. The aims of the Regulations are sensible.

#### *b) Tools*

The tools being developed to implement this Regulation include the creation of a central marketing authorisation procedure, the creation of the Committee for Advanced Therapies within the EMEA and the creation of control of the quality and safety of these products. The legislation also speaks of respecting the ethical autonomy of individual member states. Some of these therapies are challenging from an ethical point of view.

### **6. Conclusions**

#### *a) Clinical Trial Directive*

The EU Clinical Trial Directive has to be more reactive to risks versus benefits. At the moment, it is too weighed down with a focus on risk. We need to find a balance. This is about delivering new therapies. We are now running the risk of impairing access to new rare disease therapies. The administrative burden on me as an individual is the same whether I treat one patient every five years or 100 patients each year. This cannot be right. Rare diseases demand different solutions, but this does not mean a dumbing down of science. We must not compromise safety.

#### *b) Advanced Therapies Regulation*

Standardisation and harmonisation are key, as is the expert committee at the EMEA. My worry is that the development of all of these products will occur through the nightmare of the EU Clinical Trial Directive.

# Impact of the Clinical Trial Directive and of the Advanced Therapies Regulation on Clinical Trials for Rare Diseases – An Industry Perspective

*Maria Pascual-Martinez, Cellerox*

## ADVANCED THERAPIES REGULATION

### 1. Background

#### *a) Optimal framework*

The Advanced Therapies Regulation covers three types of products: gene therapy, cell therapy and tissue engineered products. The number of advanced therapy products developed by small- and medium-sized enterprises targeting rare diseases is increasing rapidly. In order to consolidate these emerging technologies, we need to generate a favourable framework.

We need to have the corresponding directives, regulations, guidance documents on technical requirements to proceed with development. In emerging fields, it is always desirable to have access to patients and sponsors.

A harmonised framework will bring many advantages: high standards, harmonised requirements, patient and public confidence, accessibility and more efficient processes.

#### *b) What do we have now?*

Gene and cell products are already classified as medicinal products and thus already within the pharmaceutical legislation. There is a big gap for tissue engineering, however. The Regulation aims to gather together these three types of products. This is an important step. Centralised procedure is a key issue for the industry. The committee in the EMEA is also important.

#### *c) Current status of the Regulation*

The key decisions of the Regulation have to be adopted by the European Council and Parliament. The next step is to debate the draft report, make amendments and vote. The guidance documents will follow. There is an urgent need for these documents to be developed. For example, we are waiting cell-based product

guidelines covering pre-clinical, quality and clinical aspects and technical requirements.

#### *d) Sponsors*

We feel there is a lot of support available for the development of advanced therapies. There is well-known scientific and product assistance, but also new tools such as EMEA briefing meetings, the small- and medium-enterprise provisions promoting innovation and incentivising development.

## 2. Impact on Design and Implementation of Clinical Trials

#### *a) Special requirements*

Cell-based products are heterogeneous. Each product would require its own guidelines. Guidelines in this area need to take the form of principles. Pharmaceutical vigilance is a huge issue. We hope that regulators will be able to find a good balance between the necessity for a regulation and the need to limit bureaucracy.

#### *b) Risk management*

Long-term patient follow-up and post-authorisation monitoring will be crucial. We still have questions in these areas. Will there be a public, centralised risk management system for these therapies? Will risk management be the responsibility of the applicant?

#### *c) Embryonic stem cells*

According to the proposed Regulations, every country has the right to take its own position in this area. Member states should be transparent in their decision. They should make clear what will be prohibited in advance so that industry will be able to develop its products accordingly. Some argue that individuals must have free choice of therapy and that national bans could result in inequities.

#### *d) Required changes to current Directives*

The Clinical Trial Directive and the Good Manufacturing Practice Directive require amendment. A consistent regulatory framework for authorisation and reimbursement of advanced therapies across Europe is a prerequisite for further developing promising technologies. Even the best products can fail as a result of regulatory inconsistencies. The success of such a framework will rest heavily on the quality of the guidelines that are yet to be written. Further harmonisation with the US approach is crucial for the global development of these therapies.

## Questions and Answers

**Chairman:** It was good news that the report was rejected by the Parliament in September. We are faced with two challenges. Firstly, embryonic stem cell therapies might be excluded from the scope of the Regulation. Secondly, there was much lobbying from certain member states to exclude centralised procedures from the Regulation. We are now hoping for these issues to be addressed and for a better policy to be formulated. Policymakers in Europe today are conservative, both on the left and right of the political spectrum.

**Erik TAMBUYZER, Genzyme:** It is important that we give the message to the European Parliament that we have to distinguish between the need for a good working practical Regulation and concerns about research in gene therapy. The issue of embryonic stem cells is for each member state to decide upon. If we mix all of these things in one bag and lose the centralised procedure in this process, it would be a very bad development. We have to separate the issues out in order to arrive at pragmatic regulations applicable everywhere in a harmonised way.

**Maria PASCUAL MARTINEZ:** We should not focus on ethical issues at the expense of the main goal of having a centralised, harmonised access to therapies. This is crucial for success.

**Marianne MAMAN, Novartis:** Dr Morland, you have stressed the importance to strike the right balance between risks and benefits, whenever evaluating products, be they marketed or investigational ones. Given the fact that we live in an environment that has become extremely averse to risks, what would you advise to best achieve this balance?

**Bruce MORLAND:** We all recognise that there is a range of different investigational products currently used. I struggle with the idea of where to strike the balance. There are simple risk assessment tools that you can put in place that can help the clinicians conducting these trials and the regulators understand what the quantity of risk might be. What lever of risk is the individual patient prepared to take? A person with a life-threatening disease may have a very different attitude to someone with a manageable condition. I do not have a perfect answer, but future revisions of the Directive need to make clear that we cannot approach clinical trials in a hostile manner, one completely focused on regulation and safety. The most powerful voice is that of the patient. We have not capitalised on this enough.

**Participant:** I fully support this. The balance of risk and the promotion of appropriate research are decided by policymakers, who are influenced by different sources. We have been too silent on this issue. Today, we live in a zero-risk society. As a result, we have an increasing administrative and financial burden, which

destroys innovation. On one hand, society is asking for zero risk. On the other hand, it is asking for management of the healthcare budget.

**Catarina EDFJAELL, Celgene:** With the new conditional approval systems coming into force, we will see a majority of orphan drugs being approved in this way. This will result in a very big burden on the companies to maintain the license. Although we have to manage the risk, it is essential that we find the right balance and that we do not create post-approval commitments for the sake of it. It has become very complex to make a clinical trial application in the EU. There needs to be a European body to which companies and academic researchers can turn for support. This would be extremely helpful and would alleviate the situation.

**Bruce MORLAND:** I agree. In academia, few organisations have grasped the nettle and taken forward truly collaborative international clinical trials. Cancer is one of the few fields that has managed to achieve this. However, it requires significant resource and infrastructure.

**Peter STRENG, European Alliance of Neuro-Muscular Disease Associations:** An informed patient is the one who can best make an informed decision. Patients have to be informed. Researchers need support. They need to be focused on research and not administration.

**Ségolène AYME:** I propose that we create a scale of risk. People working with dangerous chemical and biological products use scales to describe the level of risk faced. I do not know why we cannot come up with a similar approach for clinical research. Have you investigated this idea?

**Bruce MORLAND:** You are right. We could put together a risk assessment matrix looking at all sorts of issues like the vulnerability of the patient, the underlying condition, the type of drug and so on. This could give us a quantitative score on the likely risk-benefit for a clinical trial. The more difficult part, however, is for regulators to accept that there are degrees of risk. I am not sure if our regulators are prepared for the complexity implied by this. I am sure, however, that this is the way forward.

**Wills HUGHES-WILSON, Genzyme:** While the Clinical Trial Directive had good intentions, it is not working. It is not enough to say that we have a problem. There is going to be a review of the Directive. We have the opportunity to improve the situation. We should wait until the report of experiences is published rather than gathering input now. I would urge all actors to give their input. We have to work together to improve the Directive. Otherwise, we will have to live with this situation.

**Participant:** What is the timeline of the review?

**Wills HUGHES-WILSON:** In all Commission tests, there is foreseen a time for transposition. For a period of five or six years, the Commission is called upon to

publish a report of experience to date. On the basis of this, they publish a recommendation to update or correct any mistakes that have been made in the drafting of original legislation. We now need to start gathering examples, putting them together and submitting them within the next 12 months.

**Bruce MORLAND:** Industry is much better at lobbying Brussels than academic or parents' groups. A coordinated approach through EPPOSI representing all of the key stakeholders within the organisation would be very powerful.

**Kerstin WESTERMARK, COMP, EMEA:** I can sympathise with what Bruce says, but I would also warn against throwing the baby out with the bathwater. The idea of separating commercial from non-commercial trials frightens me. Some academics think that they are exempt from the rules. There are problems with the Clinical Trials Directive but some of it is valuable. It is very difficult to perform clinical trials of rare diseases. It would be helpful if there existed some kind of contract research organisation supported by the Commission, which could carry out in all kinds of rare disease studies.

**Bruce MORLAND:** I was not advocating a difference between commercial and non-commercial clinical trials. A risk matrix should apply as much to commercial trials as it does to non-commercial ones. The current situation, however, promotes bad research because people will try to get around the Regulation because they know how difficult it is.

**Participant:** We are neglecting to mention the national competent authorities. The Commission is the legal guardian of the system. However, later on, these issues should be discussed at national level. We have the power nationally to introduce new concepts that are in line with the legislation.

**Bruce MORLAND:** There is a forum where all the competent authorities within Europe meet. It is currently chaired by Martin Ward from the MHRA in the UK. I agree, but it would be also be useful for people to feed these issues directly into that committee through Martin Ward. The problem with the fact that it was a Directive and not a Regulation is that this has been interpreted in many different ways throughout Europe.

**Participant:** Many fora exist in Europe. We will be stronger if we move together in the same direction.

**Participant:** It was proposed that certain complex advanced therapy trials be removed from the remit of the Directive and to include specific clinical trial requirements in the Regulation for those products. What do you think of this approach?

**Maria PASCUAL MARTINEZ:** If we were talking only about surgical procedures and not medical devices, I would put everything in the same box.

**Peter STRENG:** For many diseases, this can be integrated into the daily and yearly management of disease.

**Participant:** We are very much in favour of lifelong follow-up. This does not have to be heavy and expensive.

**Chairman:** We have had a very good discussion, with a fair amount of agreement that we need to look further and re-evaluate what has already been done and what changes need to be made. We in the United States are equally risk averse, perhaps even more so at the present time. Frequently, there are knee-jerk reactions rather than studied responses. Often, we forget to get the input of the patients.

## SESSION 2 – HOW TO ASSESS THE BENEFIT OF THERAPIES FOR PATIENTS AND THEIR FAMILIES?

*Chaired by Pauline Evers, EGAN and Josep Torrent y Farnell, EMEA/COMP*

### Assessment of Therapeutic Added Value – An Industry Perspective

*Andrea Rappagliosi, Serono, EuropaBio Representative at EU Commission High Level Pharmaceutical Forum*

#### ASSESSING VALUE

##### 1. Terms of Reference

###### *a) Questions*

Efficacy: does it work? Effectiveness: does it work in practice? Efficiency: is it worth it? These are the basic questions that access Authorities normally raise when appraising a new drug. Nevertheless, there are three questions that have not yet been tackled and are paramount to any reimbursement decision: Is the introduction worth its cost? For whom is it valuable? Can we afford it? These questions, although never explicitly raised, still need to be addressed. This leads us to an area of uncertainty.

###### *b) Challenges*

Policymakers face tremendous challenges when trying to make decisions on drugs. It is easy to blame policymakers but their task is not easy. The perceived value of a therapy may differ depending on who and where you are. Where

healthcare allocation decisions are judgmental and values-driven transparency and stakeholder involvement are basic and necessary components.

###### *c) Value*

Value is in the eye of the beholder. Payers and governments may ignore the technologies that patients and professionals consider to be of value.

#### 2. Orphan Drugs

##### *a) Do we need an assessment of value for orphan drugs?*

There exists a myth that says that the value of orphan drugs is unquestionable, the high need for therapies is undisputed, the number of alternative therapies is zero and the budget impact is negligible. The recent literature overturns these presumptions. The affordability of orphan drugs has become a major issue for payers and is a strong driver of tension between the different stakeholders. These drugs have caused much controversy, which have blocked patient access. Some actors, such as the manufacturers and the patients, are quite often left out of the process of definition of risk, cost and benefit.

In order for proper dialogue to occur, there must be greater transparency and an erasure of polemical statements that do little more than polarise the debate.

Which elements should define value?

How do we define value, measure it and reward it? What impact will the drug have on patients and society? It is difficult to do an economic exercise without any treatment.

##### *b) Problems*

It is difficult to apply methodologies that would require a comparator. Contribution to patient care is a much more intangible concept if you have to translate it into numbers. There is a lack of dialogue between regulators and the assessor of economic value on the minimum data requirements. Measurement should be a collaborative effort. Randomised controlled drugs are difficult to conduct when dealing with rare conditions. Surrogate endpoints used for orphan drugs are often not validated and often not well understood. Rarity of patients does not allow comparative analysis. Sometimes you do not have patients in all stages of the progression of the disease. It is difficult to compare and systematically review different trials. The poor epidemiological data in the disease history due to the limited diagnostic skill limit the historical evidence. There is a lack of scientific knowledge of rare diseases.

## CONCLUSION

How do we manage uncertainty when the drug gets market authorisation? It is important to define sufficient assessment points. Sponsors and manufacturers should know what "sufficient evidence" is. How can the regulatory decisions be improved to optimise benefit and risk, and patient care? How can we manage regulatory reimbursement decisions that better reward innovation and progress in medicine? It is not inevitable that new drugs will cost more than existing ones. We have to find better ways of rewarding manufactures and incentives to increased investment. The concept of how to measure value should be linked to sharing of risk. Many of these treatments should be measured in the real-life settings. In some trials, complete phase III will never be possible. Prices of drugs should not penalise patient access to drugs. Ensuring timely access to rational use of medicine for all people is a difficult goal, but there is nothing to say that the allocation of appropriate funding within healthcare systems cannot bring us close to this goal. We cannot continue to say that resources are limited and we cannot grant patients drugs. This is also a matter of priority setting. Sometimes it is easy to say that you do not have the money while you undertake other huge non-medical projects. Discussions of rare disease are also those of quality of access and equity.

## Assessment of the Therapeutic Added Value – The Point of View of Regulators

*François Meyer, Haute Autorité de Santé de France (HAS)*

### INTRODUCING A NEW DRUG

#### 1. Healthcare Systems in Europe

##### *a) 1st step*

At a European level, the first step to introducing a new drug is the licensing organisation. The CHMP within the EMA is in charge of the scientific assessment. The decision-making body is the European Commission.

##### *b) 2nd step*

The second step is the introduction of the new drug into the national healthcare systems. This step may be, as for the first one, divided between assessment and decision. Drugs are evaluated under the principles of Health Technology Assessment (HTA). For HTA, there are many common principles and some national specificities, justified by specificities of national healthcare systems. Decision and implementation is the second step, and remain at a national/local level.

### 2. Health Technology Assessment (HTA)

##### *a) Definition*

This is the first part of the second step, when the new drug is being introduced into a healthcare system. In this definition, 'technology' has a very broad meaning. It can be a drug, a medical device, a surgical procedure, a set of interventions and so on.

##### *b) The decision-making process*

The assessment of new technologies takes into consideration further health consequences and the resources available in the system. It takes into account not only medical concerns but also organisational, ethical and social ones. It aims at providing the decision-makers with appropriate quantitative and qualitative information.

### 3. The French System

##### *a) HAS Committee for Drugs assessment (Transparency Committee)*

In France, there is a separation of the assessment of medical value and the economic aspects. After marketing authorisation a file is submitted to HAS. One of the specialised committees of the HAS, called the Transparency Committee, is in charge of assessing the medical benefits and public health impact of drugs. The opinion of this committee will be transmitted to the Ministry of Health, which then conducts a price negotiation.

##### *b) Medicinal products assessment*

In case of a positive opinion of the Transparency Committee and a successful price negotiation with the Economic Committee, product can be reimbursed and launched. Drugs are listed for a duration of 5 years, and have to be re-assessed by the Transparency committee before renewal of reimbursement. In the mean-

time, all significant new data have to be submitted to the HAS and may lead to an update of the initial assessment.

#### 4. HTA Procedures

##### *a) Criteria*

The criteria are defined in the French regulations and so cannot be changed without a new decree. Cost effectiveness is not part of the legal criteria. However, there is a link between the assessment of the value of the drug by HAS and the pricing negotiation with the economic committee.

There are two main criteria. The first is the drug's intrinsic value. The drug's intrinsic value is made up of two parts: the medical value, on one hand, and, on the second hand, importance for public health and impact on healthcare organisations and resources. The second criterion is the added value. A comparison is made with existing therapies and the added value is rated according to a scale ranging from major improvement (Level I) to no improvement (Level V).

##### *b) The decision*

The decision is made by the ministers in charge of health and social securities and is based on the appraisal for the first criterion, the intrinsic value. However, it depends on the outcome of the price negotiation. If no agreement is reached between the pharmaceutical company and the economic committee, the drug will not be reimbursed. There is a link between added value and price. For example, a drug with a sufficient intrinsic value to justify reimbursement, but no added value over existing therapies can be included in the healthcare system only if it brings some savings. That is, it has to be at a lower price than comparators. When there is an added value, the price may be higher than competitors. To date, most orphan drugs have been recognised as bringing added value and are thus allowed to set a higher price.

#### 5. Challenges to Assessment

##### *a) Efficacy*

The data available at the time of the initial assessment are of experimental nature, issued from clinical trials made in selected populations. The placebo is the most frequent comparator, and outcomes are more often surrogate endpoints rather than clinical endpoints.

##### *b) Effectiveness*

The mission of the HTA is to assess the effectiveness. Assessment of effectiveness necessitates pragmatic trials with few exclusions the choice of current best practice as comparator, and clinical- and patient-focused outcomes. Orphan products are, by nature, innovative. Assessing their effectiveness is thus more difficult. To reduce the risk of inappropriate decisions, very solid data is necessary. To be flexible in an urgent situation is necessary. In France, temporary authorisation is used to allow access to drugs even before market authorisation, but this should not create a precedent for generalisation. This should be limited to very specific situations. Rewarding truly innovative technologies is necessary and has been the case for orphan drugs in France. However, we have to keep within the national healthcare budget.

##### *c) Need for reassessment*

The collection of data and their assessment should be a continuous process. Questions will be raised in practice. What are the real conditions of use? What are the real patient benefits? What are the tolerability aspects in real life situations? In many cases, a need for additional data is identified at the time of the first assessment of a new drug, particularly if it is innovative one.

##### *d) Requirements of post marketing studies*

The number of studies required by HAS has been growing over the past years. The transparency committee assesses about 130 products every year. There are requirements for questions to be addressed by post-marketing studies for 25 to 30 products each year.

##### *e) Risk management*

There are now risk management plans required by the EMEA. These will be taken into consideration in the reassessment of the drug by the transparency committee. However, one must take into account that risk management plans cover only safety aspects. Therefore, there will still be a need for additional data collection, mainly in the form of observational studies after marketing authorisation. It is in the interest of patients, companies and decision-makers to collect this data.

#### CONCLUSION

The assessment of the clinical effectiveness of drugs and their impact on public health is an important and difficult task. The added value of a new drug should take into consideration not only medical questions, but also ethical, organisational and social ones. Appropriate post-marketing studies are required. There should be clearer definitions of the conditions in which these studies should be

performed. The economic impact of orphan drugs on healthcare systems is growing in a way such that it raises difficult questions. The French system, which was quite open to the inclusion of orphan drugs, without difficult price negotiations, may not be maintained in the long term. Healthcare systems are nation-specific. The principle of HTA is that the evidence is global but the decision is local. However, this does not mean that we could not share more on the principles of assessment of drugs. Some national specificities are justified but not all of them. We need to share information and avoid duplication of activities. On the other hand, we have to keep in mind that there are differences in healthcare organisations in Europe and some decisions have to remain at national level.

## Assessment of the Therapeutic Added Value – The Patients' Perspective

*Andrea Buzzi, Fondazione Paracelso ONLUS, Italian Haemophilia Society*

### Haemophilia

#### *a) Fondazione Paracelso*

Fondazione Paracelso is a not-for-profit organisation working shoulder-to-shoulder with Italian haemophilia associations. It was founded in 2004 in the context of infections from blood-derived products.

#### *b) Facts*

Haemophilia is a genetic disorder. The symptoms are quite similar in type A and type B haemophilia. 70% of people get it from a symptom-free carrier, the mother, and 30% without previous cases in the family tree. The symptoms are internal bleeding after injury or spontaneously. Bleeding often occur in joints: knee, ankle, elbow and hips. Bleeding can also occur in internal organs, brain being the most serious case. Repeated bleeding in the same joint can lead to severe arthrosis. Before the 1960s, haemophilia patients had no treatment. In the

1990s, we had to wage a war with governments to get bioengineering treatments that were a little more expensive. The administration of the treatment drug is by intravenous injections. This can be done when there is bleeding or, more appropriately, prophylaxis three times a week. Children should do prophylaxis to avoid arthrosis from around one year of age. Prevalence is similar all over the world. One baby in 10,000 is born with haemophilia type A and one in 50,000 is born with haemophilia type B. The World Federation of Haemophilia says that there are 131,000 diagnosed people, 75% of which have no access to treatment.

#### *c) Benefits of an adequate therapy*

An adequate therapy is a matter of life and death. Haemophilia does not have an orphan drug but a situation of economic orphanhood for three-quarters of the world. Haemophilia is relatively easy to administer. It takes so little to achieve so much. The problem is money. A haemophilia patient in Italy costs EUR120,000 per year in treatment. An untreated patient will cost more than this, however, due to the severe disabilities that are the consequences of lack of therapy. This argument does not always work. Short-sighted local or national payers tend to look to the end-of-year budget. The task of our foundation is to show these decision-makers how expensive insufficient treatment can be. This argument only works in countries with welfare systems. The healthcare system in Albania, for example, does not offer any drugs. Here, the public administration does not pay for expensive products, nor does it pay for the consequences of the lack of treatment. Albania is not the worst case. In many countries in Africa, for example, haemophilia patients have no treatment. These patients are completely dependent on international aid and marketing strategies. As long as profit and power rules everything in the world, this is highly unlikely to change.

# Assessment of Orphan Drugs – The Reimbersers' Perspective

*Ad Schuurman, Medicine Evaluation Committee of the European Social Insurance Fund (MEDEV)*

## REIMBURSEMENT

### 1. Equal Burden of Disease

#### *a) Justification*

What is society's willingness to pay for members of society who are sick? We represent the payers, but we are not against industry or new drugs. We want good medicines and healthcare for our citizens. We give those with orphan diseases the same rights as those with other conditions.

Within MEDEV we try to cooperate on a European level to cope with the problems over ever rising health costs: The principal purpose of MEDEV is to provide national health insurance organisations with timely analyses about drug related trends and innovations at both national and European level (<http://www.esip.org/publications/pb51.pdf>)

#### *b) Support in society*

In the Netherlands, 3% of the government's budget is allocated to health care. This is the EU norm. Even if we wanted to spend more on healthcare, we would face problems at the EU level. Hospitals have to balance applications of resources. If they pay for a very important but expensive drug, they have to limit the number of nurses. Hospitals make decisions like this every day. Next month, premiums will go up 10% to 15%. Our healthcare is too expensive. We cannot go on like this. We want to maintain solidarity in the system. We do not want a two-tier system, one for the rich and another for the poor.

#### *c) Transparency*

If people do not understand why orphan drugs are so expensive – why they are so difficult to develop – they will not want to pay for them. It is important for industry to be transparent in how prices are set. If we do not understand how prices are set, we find it difficult to accept them. For instance, are the research

costs high because of lack of competition? We are prepared to pay for innovation.

#### *d) The price of orphan drugs*

Government wants to minimise prices and stimulate development. The pharmaceutical industry can only innovate if they make enough profit to survive. Until now, there has been a constructive partnership between those developing orphan drugs and patients, payers, industry and government. I hope this can be maintained. Orphan drugs have an expensive image. We thus have to be careful about the misuse of orphan drugs. What is society's limit? What is it willing to pay for a drug or a patient?

#### *e) Equal treatment*

We want equal treatment for patients but we do not want equal methods used in the development of orphan drugs. Until now, we have made it easy for orphan drugs to be authorised.

## 2. Definition of Orphan Drugs

### *Real versus unreal orphans*

We have problems with the concept of orphan drugs as it is used now. The registration process tells us that we should treat all orphan drugs the same. However, there are orphan drugs that we cannot explain to ourselves or society. We do not want to pay new, high prices for existing drugs for a new indication involving very little R&D or drugs that existed in the pharmacy and now get an official label. The definition of orphan drug is too broad. If we put our money somewhere, we will put it in diseases that cannot be adequately treated. We want to pay less for drugs that are improving existing treatments. We are going to differentiate between real and unreal orphans in a particular country. In the Netherlands, we focus on extremely rare diseases with no existing treatment. This means less than 400 patients, who are the real orphans. We want to put the money in the academic research hospital.

## 3. Stimulating the Pharmaceutical Industry

### *a) Market situation*

We want to stimulate the pharmaceutical industry, but it depends on the market situation. The price-volume contracts in France are an interesting instrument to share risk and stimulate development. In stimulating development, there is room for EU cooperation.

### *b) Should all orphan drugs be available?*

We cannot pay EUR10 million a year per patient. We have to make choices. The gap between resources and need in Europe is growing. We have to make ethical and technical decisions. We have to assess drugs in a more sophisticated way at a local, EU and global level.

## Questions and Answers

**Chairman:** For the COMP and EMEA, the differentiation between real and unreal orphans is a false one. All orphan drugs are orphan. Many are innovative, some are less so. Some of them need more investment to fulfil all the registration requirements. The idea, however, that national authorities can reinvent classifications, putting orphans and unreal orphans in different categories, will create conflict at a European level.

**Ad SCHUURMAN:** We try to work together with countries so that there is harmonisation, but in The Netherlands we feel we have to distinguish between different categories of orphan drugs because of reimbursement issues.

**Kerstin WESTERMARK:** What would the consequences be? Are we going to reinvent the Orphan Regulation? Are we going to redefine what an orphan drug is? Most of us can appreciate that there has to be some differentiation made. We are entering dangerous territory if we reinvent orphan drugs.

**Ad SCHUURMAN:** If you do not, the concept will not be accepted by European society. You might not do it, but the reimbursement authorities and premium payers will.

**From the Floor:** It still has to be carried back to the Commission. It has to be discussed. This has to be done in an open way. Stakeholders such as patient organisations will have to have their say and if it is done openly and not within the reimbursement realm, it may be possible.

**Ad SCHUURMAN:** I say it here openly. The Commission does not handle reimbursement. That is for the national authorities to decide.

**From the Floor:** It will have a bearing.

**Peter STRENG:** The opinions expressed by Ad Schuurman reflect a way of thinking that needs adjusting, in my opinion. He is thinking about budget and not about how we in orphan drug development have to look for new and innovative ways to reduce costs. This is where we should aim. Why is the development of

orphan drugs so expensive? It is expensive due to the fact that regulations developed for common drugs are applied to orphan drugs. We need to look at new ways to develop drugs.

Andrea Buzzi mentioned the importance of timing of data collection. In my opinion, once a patient is diagnosed you should keep him in sight. Patients need to be kept informed about upcoming trials. If you do not lose the patient and you ask him to cooperate in collecting data, it is also possible to recruit them for trials. This is a way to cut costs in data collection and research.

**Hans SCHIKAN, Genzyme:** Peter's remark about following the patient is essential. In this way, we can reduce the cost of developing an orphan drug. In the evaluation of orphan drugs, we need to find some way to include rarity, ultra-rarity, severity of disease and the impact it will have on the patient, family member and society. The price of a drug is very influenced by the rarity of the disease.

**Catarina EDFJAELL:** I want to return to my previous comment on post-approval commitments and link it to this session. For orphan drugs, there is an increasing amount of post-approval commitments that have to be done by companies after approval. These are highly costly. We sometimes cannot do orphan clinical trials to the standards set for common drugs. There are sometimes very small populations, which means we cannot get enough data prior to approval. There needs to be harmonisation with the US in terms of post-approval commitments. It is important that there is also a discussion within the national agencies of Europe so that we do not have different demands in the different member states. We need good dialogue in Europe to ensure that we do not add to the burden. This would suffocate the development of orphan drugs. We need to send strong signals that innovative research will be rewarded but 'me too' orphan drugs not necessarily.

**François MEYER:** The burden of additional studies has to be taken into account. In France it is taken into account in the price negotiation process. We have to avoid duplication of data collected. Decision-makers will not pay if they have no information on what happens in real life. The requirements have to be reasonable. We have to cooperate.

**Chairman:** Is there transparency in the French system? Is there a summary of decisions made available?

**François MEYER:** We are starting an analysis of what has been done to date in added-value assessment. We are exchanging this data with industry. Industry does not believe that assessors are consistent in their appraisal of benefits. We have no written documents currently available to clarify the criteria of assessing a major improvement. We have to make these available. The question of transparency is of utmost importance.

**From the Floor:** Reimbursement is a national issue. Is there any hope on international guidance on how you should do this assessment? In different countries,

the evaluation of added value might be more or less the same but the decision on whether to reimburse might be different.

**François MEYER:** When I started to work in the field of assessment for reimbursement in 2002, there were only national activities. There was no international cooperation at all. Three years later, there are many international fora.

**Ad SCHUURMAN:** When the Commission imposes cooperation, it is not accepted because it is seen as a local responsibility. Cooperation will grow because it leads to greater efficiency. Not only authorities but industry, too, needs to be transparent about prices. It is important for European citizens to understand why prices are as they are. If the prices are realistic, there is no problem. There are initiatives ongoing like MEDEV and things initiated by NICE in UK and HAS in France.

**Chairman:** If we leave all these initiatives in the hands of member states, some of them will respond and will be very active. Others will be more reluctant. What can society do to force our national authorities to cooperate and share experiences?

**Ad SCHUURMAN:** Benchmarking could be used. Different countries should have to explain their systems. When an expensive orphan drug is launched in Romania, whether we cooperate or not, it will not become available to patients. Patient organisations and industry can play a role in the benchmarking process.

**Andrea BUZZI:** We need to find ways of ending uncertainty. We have to move ahead and accept that if a drug has received market authorisation, certain guarantees exist and there is no reason to refuse access to the drug.

**Ad SCHUURMAN:** In Western Europe up until now, this has been the situation. As the amount of orphan drugs increases, the situation will change, however. It will not be so easy. Harmonisation will help.

**From the Floor:** What is sufficient data? What is sufficient for orphan designation versus unreal orphan?

**Ad SCHUURMAN:** There is insufficient data available both for orphan drugs and common drugs. Often we reimburse based on trust without sufficient data.

**François MEYER:** What is sufficient data? At the time of a first assessment for reimbursement, we have data and we make some assumptions based upon data collected in clinical trials about what will happen when using the drug in the real life situation. This is why we need data to be collected after this. We can live with assumptions. I am quite used to making assumptions. However, our decisions have impact on patients, organisation, resources and so on. Assumptions should be solid. If there are question marks, we should get the answers using appropriate data collection. The standards are not different for orphan products. The regulations clearly state that patients with rare diseases are entitled to receive treat-

ments of the same level of quality, safety and efficacy than other patients. For this reason, the treatment should go through the normal evaluation procedures.

**Erik TAMBUYZER:** The Commission have estimated that orphan drugs cost about 0.7% to 1% of the total cost of medicines. That is a published number. Efficiency gains in the UK are 3% per year. It is important to look at individual methods for products, but it is equally important to look at how the healthcare system is organised. The political willingness to change the healthcare system is key. Changes may also mean job losses. The subject is far wider than budget for healthcare medicines alone.

**Ad SCHUURMAN:** In the Netherlands, for every new drug, the company can give HTA reports. You can be more expensive if you have benefits in other areas. It is the same in several countries.

**Erik TAMBUYZER:** Is there a move toward looking at the total healthcare system and its efficiency?

**Ad SCHUURMAN:** In the Netherlands, we have just changed our entire system. I hope it will be more effective.

**Chairman:** Andrea Buzzi, do you have any data in EU countries on managing diagnosis or prophylaxis? Is the situation for haemophiliacs acceptable and similar in all countries?

**Andrea BUZZI:** Patients do not like change. Their life is problematic enough. Many are used to living with haemophilia and suffering with bleeding. A new generation of patients in Italy, however, is moving towards regular prophylaxis.

**From the Floor:** What are important are not the costs but the benefits. Patients need to be involved in assessing these benefits.

**Chairman:** François Meyer, is there an easy way to join the concepts of intrinsic value and added value?

**François MEYER:** There is a close link between these two concepts.

**Chairman:** This is a hot issue. We should not lose focus on patient needs. We need to assess benefits for society. This brings with it the idea of affordability. Not all orphan drugs are innovative. Some can be considered followers or 'me toos'. Is rare disease on the political agenda? Inventing strategies to reduce cost is significant. Do we know the real cost of orphan medicines? Do we know the cost of developing 'me toos' that bring incremental innovation?

**Pauline EVERS, EGAN:** Patients need to be involved in these discussions. Patients need to be involved in the assessment of the dossiers. This should be on a much broader, international level also. This is not just about cost and money but also about quality of life and user-friendliness of therapies. Only patients can judge this.

## SESSION 3 – HOW TO ENABLE THE DEVELOPMENT OF ORPHAN INDICATIONS OF MARKETED DRUGS?

*Chaired by Jan Inge Henter, Karolinska Institute and Miguel Angel Izquierdo, Pharma Mar*

### Orphan Indications that could be Developed

*Valérie Thibaudeau, Orphanet*

#### ORPHAN INDICATIONS

##### 1. Panorama

###### *a) Numbers*

There are about 10 new orphan designations made each month. Up to now in Europe, there are up to 450 designated indications covering 161 rare conditions and applying to 221 designated products.

###### *b) ORPHANET follow-up*

ORPHANET is interested in following the clinical development of orphan indications. It looks at all the different stages of development from the designation stage to the market approval and availability of products in European countries. Currently, we have identified clinical development for 14 designated orphan medicinal products (OMP). 11 orphan drugs are in clinical development to extend their indications.

###### *c) Drug databases*

All the information collected on clinical developments of OMPs is collected on the

ORPHANET database. A new website that will be available from next year will allow more visibility of the clinical development of OMPs. This portal offers the unique opportunity to promote the diffusion of information about ongoing trials. This complements the transparency of clinical trials. It also facilitates the recruitment of patients to trials.

##### 2. Focus of ORPHANET Efforts

###### *a) Identifying the needs of academia/valuation of academic initiatives*

A year ago we carried out a survey in Europe to identify potential orphan indications. We contacted clinicians, investigators and patient support groups to identify the products already commercialised for another indication but that could be developed for an orphan indication. We asked for the name of the drug, if there was a market authorisation for another indication and if the production has stopped. So far, the survey has identified 217 potential orphan indications and 148 products that could be developed for orphan indications. The objective is to help physicians get in contact with industrial sponsors, set up trials and establish partnerships in the development of a product.

###### *b) Results of survey I*

The first products identified by the survey are designated OMPs. Some products that have received designation status could be developed for a different orphan indication. We propose delving deeper and investigating the real feasibility of such products. We try to stimulate partnerships between industrial companies and reference centres. We also encourage international collaboration within academia.

###### *c) Results of survey II*

We identified orphan indication for products in early development. We wanted to encourage international collaboration and to try to convince industry that these products could be made valuable to academia.

###### *d) Results of survey III*

We identified orphan indication for old molecules. Many clinicians would like to explore unknown mechanisms of known products. They want to set up studies to develop new protocols and new formulations. This could be useful in setting up a validated protocol at the European level. These are products with market authorisation. They are used off label in children. There is the need to support more paediatric trials. We need more academic funding. Early stage products are not targeted by industry. We need funding to validate new dosing or therapeutic approaches. We need access to the molecule to set up the trial.

### 3. Difficulties in Clinical Trials for Rare Diseases

#### a) Availability of drugs

The major difficulty is the availability of drugs. We need to convince industry that they should provide a drug for testing once it is already commercialised. Should any marketed drug be made accessible for trials? There is a need for dialogue between clinicians and industry on the topic of drug access.

Clinicians and investigators complain that it is difficult to set up non-therapeutic studies, which are very necessary. For rare diseases, trials have to be performed in multiple centres. Thus, there is the need for international collaboration. Researchers are complaining that in Europe it is difficult to be involved in studies funded elsewhere.

Early-stage projects are not targeted by industry. We need to find academic funding for this type of project. There is the need to set up a national structure to support investigators.

## EMEA Experience with the Development of Orphan Indications

Channa Debruyne, EMEA

### ENABLING THE DEVELOPMENT OF ORPHAN INDICATIONS OF MARKETED DRUGS

#### 1. Background

##### a) Legislation

The legislation is applied to any medicinal product for human use. It does not differentiate between novel therapeutic products or marketed ("old") medicinal products. So far, the COMP has expressed a positive opinion on the designation of 422 orphan products. 182 applications were withdrawn or had a negative outcome. Currently there are 30 applications ongoing for designation. We have

30 OMPS authorised on the European market. Five of these are medicinal products that were previously on the market in non-orphan indications. They cover 26 different orphan conditions. The majority of these conditions have a prevalence of less than 1 in 10,000.

### 2. Criteria for Orphan Designation

#### a) Prevalence or insufficient return on investment criterion

Applications submitted for orphan designation are based either on the "rarity" of the condition defined as "prevalence of the whole condition is not more than 5 in 10,000 in the Community" or on the "non-return of investment" criterion, defined as costs of development (necessary investment) will be higher than the expected revenues (return). Most of the orphan applications are based on the prevalence being less or equal than 5 in 10,000.

#### b) Seriousness

This criterion is defined slightly different depending if the orphan application is based on the above mentioned prevalence criterion or on the non-return of investment criterion. The orphan condition should be life-threatening or chronically debilitating if one applies under the prevalence clause. The orphan condition should be life-threatening, seriously debilitating or serious and chronic if one applies under the non-return of investment.

#### c) Available methods

The third criterion is based on the available methods for diagnosis, prevention or treatment of the condition, also called the "significant benefit criterion". We try to evaluate the significant benefit criterion as the "potential relevant clinical advantage" of the MP compared to existing methods and/or authorised medicinal products in the orphan indication for the patients.

### 3. Potential hurdles for "old" MPs to become an OMPs

#### a) Significant benefit

Significant benefit refers to a clinically relevant advantage or major contribution to patient care.

#### b) Similarity

A MP containing a similar active substance of substances as contained in a currently authorised orphan medicinal product and which is intended for the same

therapeutic indication needs to show clinical superiority in order to obtain a marketing authorisation.

#### *c) Clinical superiority*

This refers to a medicinal product that is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised OMP. This can be based on greater efficacy, safety or major contribution to patient care.

### **4. Possible Scenarios of when there is a need to look at significant benefit**

#### *a) Example I*

The first scenario is that there exists no satisfactory methods and thus, per definition, no medicinal product is authorised in that orphan condition. Celecoxib was such an example. The orphan indication was for treatment of familial adenomatous polyposis. The OMP was authorised in the EU as NSAID for osteoarthritis and rheumatoid arthritis. As the standard of care at the time of MA consisted of endoscopic surveillance and/or surgery (often highly mutilating in the young population) it was considered that there were no existing satisfactory methods and thus no need to evaluate significant benefit.

#### *b) Example II-III*

The second and most common scenario in the development of OMPs is where there are some satisfactory methods. Here, there is a need for establishing a significant benefit assumption over the current "standard of care". Two categories are possible:

- Other different medicinal products are authorised or commonly used in that orphan indication and thus a potential benefit could be based on e.g. improved efficacy, favourable safety profile (e.g. ibuprofen iv), different formulation with clinical relevant contribution to patient care etc.
- The active substance is already authorised or commonly used in that orphan indication and thus a potential benefit could be based on e.g. different formulation (e.g. busulfan iv versus oral), clinical relevant different pharmacokinetics, and/or availability in the Community etc.

#### *c) Example IVa*

The fourth example is where there is already at least one OMP authorised in the same orphan indication and the products are not similar. Significant benefit over the authorised OMP should be established. These are probably the most difficult cases but a potential significant benefit could be based on e.g. different/new

therapeutic class with new mechanism of action linked with relevant efficacy and substantially clinical relevant different safety profile (e.g. sildenafil citrate). The use in combination with or as an add-on to current authorised MP could also give an improved efficacy and thus be basis for significant benefit. In any case the sponsor should provide evidence of a clinical relevant significant benefit over the authorised OMP.

#### *d) Example IVb*

The final scenario is where the second product coming to the market is considered to be similar to the first orphan medicinal product authorised. For similar drugs, you have to show clinical superiority, normally by doing a comparative study to the existing orphan drug. If you have clinical superiority, it will per definition offer significant benefit to the patient.

### **CONCLUSION**

We have to realise that there is no difference between old and new drugs in obtaining orphan status. The same designation criteria apply. The same requirements exist at the time of marketing authorisation. The advantage of the old medicinal products is that we usually know a little bit more about their safety profile. There is a need for a separate marketing authorisation application with a different trade name, which will provide a legal certainty that the benefits of market exclusivity can be enforced.

# Development of Orphan Indications – The FDA Perspective

Marlene Haffner, FDA

## ORPHAN INDICATIONS FOR MARKETED PRODUCTS

### 1. Background

#### a) US definitions

The US definition of an orphan drug is one that affects either fewer than 200,000 people in the US. It could be a vaccine or a prevention drug used in fewer than 200,000 in a year. It also could be a product that would not be profitable within the first seven years of marketing.

#### b) Evaluation a request for orphan drug designation

The disease being treated has to have prevalence of less than 200,000. There has to be rationale for the use of the drug to treat the disease or condition. A sponsor may request orphan designation of a previously approved drug, a new orphan indication for an already marketed drug, or a clinically superior drug to a product that is already an orphan and in the marketplace. More than one sponsor may receive orphan designation of the same drug. Only one will be approved unless there is a clinical superiority issue. One must submit a request for designation prior to submitting for marketing authorisation.

### 2. Process for Developing Orphan Indication for Marketed Drug

#### a) Possibilities

Developing an orphan indication of a marketed drug may take longer or shorter than the product already available in the marketplace. Considerable safety data may already exist or you may have safety data available for short-term administration and now your new product is going to be used chronically. You may be able to do only one clinical trial. You may be able to do just pharmaceutical equivalence. You cannot make the simple statement that you are doing a new indication and therefore it will take less time. Will the same sponsor be developing the

product? If the product is long off-patent and the interested sponsor is not interested in adding another indication, they may be willing to share the drug master file so that a new firm may develop the new indication.

#### b) Market approval

One sixth of US Orphan products have more than one indication, one of which may be an orphan indication and one or more of which may be a non-orphan indication. Some orphan designations are made for marketed drugs previously used for a different indication(s).

Some orphan drugs are approved for multiple indication(s). This probably has to do with the mechanism of action of the drug and methodology of approval.

One indication can have several sponsors. A single drug can have several indications. We have seen several products with two and even three approvals. This is true of 35 of the 39 products that have more than one approval.

There are designations for a marketed product that is already approved.

More recently we have begun to look at products that came off the marketplace and have either been reintroduced or are being designated or developed to be introduced as orphan drugs.

#### c) Why not more approved orphan indications of approved drugs?

We talk a lot – or we certainly did at the time that orphan drug laws were initially passed – of all the products out there that just need a little further development to get approval. We have never done a survey. There are probably several products out there waiting for additional approval, which are being used anecdotally or have never been developed at all. Incentives do not really exist to develop a second and third indication in the US. Products can be used off-label, particularly if they are to be taken orally and do not need to be administered in an institution. However, our grants programme has looked at several products that are available in the marketplace to see if they work under certain conditions.

#### d) Designated market products for distinct orphan population

We count paediatrics and, to lesser extent, pregnancy as a separate meaningful subset. Products are frequently not studied in children or the pregnant patient.

## CONCLUSION

We would need to do another study to find out the cost of approving already approved products. I think the cost is lower than in a new product. What the actual cost is remains unknown.

## Questions and Answers

**From the Floor:** You show us how you can have orphan drug status protection in cases where the old drug has a new formulation. In these cases, there are often different kinds of patent protection. In the case of the drug being given to the patient in the same formulation already marketed the interests of the patient is to get the drug as soon as possible. What does the industry gain, however?

**Marlene HAFFNER:** I agree. There are no incentives for industry. This needs to be further explored. Industry does get exclusivity for that indication. That is something. It can be advertised in that way. Patients and clinicians know that there is an approved therapy. For market authorisation, there would be a waiver of filing fees in the US. I do not know what the situation is in Europe. This, too, is an incentive. A marketing authorisation requires much work. I do not know whether these incentives are sufficient.

**Harrie SEEVERENS, Ministry of Health, the Netherlands:** As the population increases in the US, the prevalence ratio of orphan drugs is decreasing. Did you ever consider raising this figure? There may be orphan indications close to the 200,000 figure that are no longer eligible.

**Marlene HAFFNER:** Changing a law in the US is not something I would like to entertain. You are correct that the numbers are being eroded. The US is still the most generous of countries with our numbers. We are about one in 1,350. Europe is about one in 2,000. Japan is one in 2,500. The most stringent is Australia with around one in 4,000. The 200,000 figure was used as a surrogate for profitability. If you look at it this way, this 200,000 figure will stand in time. We know now that we can make a profit on a lot less than 200,000 patients. Some diseases have fallen out, but not many.

**Erik TAMBUYZER:** Exclusivity is the most important incentive of the OMP Regulation in Europe. Exclusivity largely depends on the definition of similarity. Similarity depends on the definition of therapeutic indication. Therefore, I was puzzled when I saw that there was a product approved with a slightly broader therapeutic indication. For me, the interpretation would be that this product would only be approved for a broader therapeutic indication than another product that has already received market exclusivity or has been approved for another therapeutic indication encompassing that. Is this a correct interpretation?

**Channa DEBRUYNE:** There is a lot of confusion in the area of similarity and significant benefits. It is a very sensitive issue. For example, as soon as there is an overlap in therapeutic indications, there is a need to assess similarity. It does not matter how significant the overlap is. In terms of significant benefit, if the second MP is not similar to the first one then it can be approved. All three criteria of sim-

ilarity need be present (same principal structural features, same mechanism of action, same indication).

**Erik TAMBUYZER:** The basis for approval was not the therapeutic indication but a different therapeutic class, the method of action.

**Channa DEBRUYNE:** Yes. A new mechanism of action resulting in a relevant efficacy can be considered as a significant benefit. A slightly different mechanism of action with no clinical relevance would not be considered a "clinical relevant significant benefit"

**François MEYER:** A recent law in France makes it possible to have drugs used in clinical trials funded by national health insurance, even if it used out of marketing authorisation. You could have a drug funded by the national health insurance for its development in a new indication. The public authorities believe that industry should sponsor new indications. However, the law makes it possible for orphan indications to be funded by national health insurance. Pressure should be put on the Ministry of Health to ensure that this is possible.

# Development of Orphan Indications – An Industry Perspective

*Pierre Vankan, Santhera*

## 1. Background

### *a) Santhera*

Santhera is a small biotech company based near Basel in Switzerland. It focuses on small molecule therapies for mostly orphan neuromuscular diseases.

## 2. Why Develop an Orphan Indication?

### *a) Business case*

A positive business case is required for all drugs, both orphan and non-orphan. The key point is the money one puts in has to come back. This is the bottom line. Investors have a very clear idea of what they want in return for their investment. High risk should give a high return. The successful drug should also finance the failures that are inevitable when developing drugs for the market.

### *b) Risk assessment*

When assessing risk, one looks at a number of factors. Pre-clinically, one looks at whether there is a good scientific rationale for developing the drug. The manufacturing of the drug should not have too many visible hurdles early on. Clinically, it should fulfil a medical need according to experts in the field. A compound in an orphan indication usually does have a clear medical need. The regulatory requirements should be considered manageable by the regulatory specialists. An orphan may pose greater challenges because very little is known about orphan diseases. Hence it is difficult to assess early on which data will be required by health authorities and which data can be generated to support an approval.

### *c) Return on investment*

Based on the risk assessment and the patient population size an industry calculates the sales volume to see if they will get a sufficient return on investment. Orphan indications usually only provide sufficient sales volume if exclusivity is

guaranteed. Even with this exclusivity guarantee, total market volume still tends to be too low, particularly for the ultra-orphan diseases. Therefore, unfortunately, many orphan indications may still be unattractive to industry, despite orphan protection.

## 3. Orphan Development versus Conventional Development

### *a) Endpoint selection*

In a conventional indication, authorities and clinicians usually have a clear idea of what is relevant and provide guidance to industry. In orphan indications, authorities and clinicians usually have insufficient information for identifying clear endpoints. Even opinion leaders see too few patients to have a clear idea of what is clinically relevant. As a result, there is a tendency to put too many assessments into clinical studies because the clinical profile of any development compound is not known. One does not have the luxury of running both a phase two and three because there may not be sufficient patients to do so. Ultimately, one runs the risk of missing the endpoint because the patients are overloaded with assessments.

### *b) Operational management*

In a conventional trial, recruitment of patients takes place in the regular flow to hospitals or doctors. If this is not enough, one opens more sites and goes to other countries. In an orphan trial, there is a low chance that any advertising will reach patients. The epidemiology is often not well described. One may be recruiting among the wrong groups or in the wrong geography. Often there is insufficient epidemiological information. There is no regular patient flow into hospital. However, there are very well organised patient organisations and the numbers of centres treating patients are concentrated.

### *c) Establishing efficacy*

For the development of a conventional drug, one talks with the authorities to agree on an approvable endpoint. One talks with the health authority at the end-of-phase-two meeting about the relevance of the phase II data and confirms the findings on the agreed upon endpoint in phase III. With an orphan drug, establishing an endpoint in Phase II and confirming this in Phase III is usually not an option due to the small population size. One may be able to do a pilot study and no more. What do you do then? Conventionally, one hands in the MAA/NDA file showing significant p-values and applies for an approval. With orphan indications, one needs to start a discussion with the authorities to agree on a potential approval with limited data, which means added risk, because it is usually not clear upfront how limited data will be accepted. The EU guidelines recognise that

primary endpoint selection is oftentimes not possible and acknowledge that approvals on limited data are feasible. The US guidelines are not that clear and make for a case-by--case discussion. For approval of orphan drugs one has to forget the current standards in drug development in terms of required data. This is not possible for many orphan diseases.

#### *d) Business cost*

We have to accept that if one wants to achieve the successful development and marketing of orphan drugs, particularly of ultra-orphan drugs, one either has to increase the price, compared to standard drugs or lower the costs of development. As current pricing of orphan drugs demonstrates, the small patient populations automatically lead to a higher price per person. Opportunities to lower costs in development might be a route worthwhile exploring. Of course the standards for safety cannot and should not be lowered for orphan diseases. Yet there remains a potential for cost saving. Some development programmes require fewer resources due to the smaller size clinical trial programmes. However, other and quite significant parts of the programme are identical to conventional drug development programs. If biotech companies can save costs early on, they will be able to run a better study later on. Marketing and distribution costs are lower in orphan diseases due to the small patient population size. On the other one misses the economies of scale and cost are not reduced in a linear way with the size of the population. (A distribution network has the same set up and maintenance costs no matter if a large or a small quantity of products is moved through it) Authorities need to talk with companies about creative ways of getting the drugs to the small patient populations.

#### *e) Regulation*

The alignment of the FDA and EMEA would be helpful. If the authorities could agree, one might be able to limit the amount of studies that have to be provided for an approval. There are many small requirements in the standard guidelines that could be taken out for the development of an orphan drug. Authorities need to discuss with industry what could cut out without compromising the safety of the patient.

#### *f) Exclusivity*

Orphan legislation allows the development of orphan treatments by creating a niche market. A Company needs the full market potential of small indications in order to make the development and marketing of a product economically justifiable.

## **CONCLUSION**

Orphan guidelines offer market exclusivity for otherwise unattractive compounds and create niche markets. The main challenges to get there for a company is to clinically define and agree on the right endpoints, to find sufficient patients to generate evidence of efficacy, to generate sufficient safety data in the available population and to keep costs in proportion. The road is long. There are many stakeholders and many rules. We need to create commercially viable products for those patients that would otherwise be a forgotten minority.

## Development of Orphan Indications – Academia’s Perspective

*Ségolène Aymé, Orphanet*

### THE VIEW OF ACADEMIA

#### Background

##### *a) Independent research*

There is a need for academic research in this area. There is a need to improve knowledge of efficacy and safety of the drug for market authorisation. We cannot just rely on industry sponsors. Work has to be done by the academic world. There is the need for independent research. In many situations, there are several possibilities and industry sponsors are not happy about funding comparative studies. New indications and subsets of patients will emerge over time. What is happening in the orphan drug field is the same as has happened for the paediatric oncology field over the past years.

##### *b) Reintroducing drugs*

Academic research is needed on marketed drugs whose patent has expired and for which new therapeutic indications are foreseen for rare diseases. There are studies in early stages of development which only the academic world could invest in. There is a need for a lot of money in this sector if we want innovative solutions for patients.

##### *c) Funding*

In France, the Ministry of Health has a fund to support clinical research in public hospitals. It is possible to get funding from the Institute of Rare Diseases. In total about EUR6 million is set aside for clinical development. Funding is offered for new indications, a combination of products, and a treatment for a subgroup of patients or a complication of a rare disease. The applications for funding were not as good as those made in other fields of medicine. This means that the tradition of trials in the community of clinicians in charge of rare diseases is not as developed as that in other areas of medicine. There is room for training and improvement. Protocol assistance will be given to prior to the application. It is the duty of

government and national agencies to provide funding for essential research. More countries should consider supporting clinical research in the field of rare diseases. Now that efforts are underway in several countries, it is time to start collaboration. It would be better if these trials were done on an international level.

## The Development of Orphan Indications – The Mutual Benefit Perspective

*Heidi Goethals, International Association of Mutual Benefit Societies (AIM)*

### INTERNATIONAL ASSOCIATION OF MUTUAL BENEFIT SOCIETIES AND ORPHAN DEVELOPMENT

#### 1. Background

##### *AIM*

AIM represents a group of autonomous health and social protection bodies operating according to the principles of solidarity and non-profit making. World wide, we have around 44 federations and are represented in 31 countries, mostly in Europe. The federations provide coverage against medical and other social risks to more than 160 million people either by participating directly in the management of compulsory health insurance, by providing voluntary health insurance or by delivering directly health care and social services through own facilities.

Mutualities are not only payer organisations; they are also the spokesmen of their healthy and sick members. We promote a social security system whose backbone is the patient and whose parameters are quality, equity, accessibility and durability. We have a long-term vision of social insurance and endeavour to obtain the best possible value for money.

#### 2. Orphan Drugs

##### *a) Enabling development*

Implementing these principles characterises the problems we have today. What is the use of enabling the development of orphan drugs if at the end the patient

will not have access to them due to the fact that the healthcare systems are not able to deal with them?

There are over 7,000 orphan diseases and as a result of genomic research it is reasonable to expect further growth in the number of orphan conditions and also in the number of targets of orphan drugs. This will impose substantial costs on the healthcare systems what could mean that we will no longer be able to treat patients with common diseases. We want to be able to treat all patients. Therefore a relevant representation of the civil society should set priorities for drug research and development. Society and not just industry should decide which treatments become available as it is civil society who is at the end responsible for the funding of pharmaceutical drugs. Thus, we recommend much more public funding for priority setting as well as for all types of research. This does not mean that we do not support the role of the pharmaceutical industry. However, we believe that we should have alternative ways to the development and as a consequence to pricing of orphan drugs as to stay able in the future to help all patients at bearable costs.

#### *b) Setting priorities*

We should generate a priority list of all the gaps from a health perspective. This list should be drawn up by patients, academics and health professionals. The methodology should be transparent, the criteria sound. The rationale for decisions should be publicly available and reconsiderations should be possible through transparent procedures. We should have a public database of all the orphan drugs in use. We support ORPHANET in carrying this out. It is important that all knowledge is shared. This will give us transparent, independent, public processes.

### **3. Research**

For all types of research public funding should be increased be it the research programs itself or the networking infrastructure. Publicly funded academic research is orientated towards science there where industry research is orientated towards business and intellectual property. Public research facilitates knowledge.

We need to grow the numbers of centres of excellence. These centres facilitate networking and the development of expertise. Public funding allows for the dissemination of clinical trial protocols. Positive and negative results are then made available so that people can learn from them. We need to focus on hard parameters when possible. We should still aim for long-term efficacy, long-term safety and quality of life data.

### **4. Access**

#### *Ex-factory price*

One of the most important actual issues of access is the price of orphan drugs. Actually the monopolies of the pharmaceutical companies give raise to extremely high prices of the medicines which will endanger healthcare system budgets.

Transparency of the ex-factory price should become mandatory as to come to equity in prices: what are the real costs of the compounds of the transfer price, R&D, marketing... AIM has already requested this in the working group on prices of the Pharmaceutical Forum of the European Commission.

### **5. Reimbursement**

#### *Reimbursement committees*

Knowledge of rare diseases is also rare. We should have special committees including doctors and health insurers to make reimbursement decisions. We also need follow up of treatment.

Education is key. Academia needs to raise awareness of rare diseases.

### **CONCLUSION**

We strongly recommend that public funding become more important in priority setting and in all types of research. Secrecy is a barrier to innovation. We support the development of regional centres of excellence and networking among experts. We recommend the establishment of a database of drugs already on the market. ORPHANET is carrying this out at the moment. We would also support a specific programme for off-patent molecules. We also need transparency in pricing.

## Questions and Answers

**Peter STRENG:** In the Netherlands, we identified a number of times that drugs were used in other indications that have potential for neuro-muscular disorders. When we tried to approach the company with the patent, we always had negative responses. The same happened when we approached academia. Pierre, why is your company interested in developing Idebenone while other companies are not?

**Pierre VANKAN:** Idebenone is an old drug. It was on the market before. However, it cannot be called a fully marketed drug. It was developed originally for Alzheimer's disease and failed. It was only allowed onto market in Italy and Portugal. In all other countries, including the US, the drug is not approved. If the drug came on the market, it would get a patent and there would be no competitor. It probably failed due to dosage. The old product was faulty. We do not see the old product as a serious competitor. It has another label and will not be reimbursed in the indication we are going for.

**Peter STRENG:** Did you use all the data from earlier development of the drug?

**Pierre VANKAN:** We talked with both the EMEA and FDA. In Europe we had to prepare bridging toxicology. In the US, we had to run a full programme. The FDA is risk adverse and does not differentiate a lot between an orphan and standard.

**Ségolène AYME:** Why can we not find a positive answer from pharmaceutical companies when we approach them to develop new indications for a promising drug?

**Pierre VANKAN:** Industry calculates the expected profit margin. A big pharmaceutical company is differently structured to a small one. You do not need a big sales force to sell an orphan drug. The sales force costs of a big company are larger than the return on an orphan drug. Some companies are beginning to realise that you can be creative and market without a big sales force. Indeed, you can save money. This is an ongoing process. It is still more favourable to put your investment into the bigger drugs. As long as there are big drugs to develop, why would they develop small ones? This creates a niche for small companies. Small companies are the ideal ones to develop these drugs.

**Bruce MORLAND:** Heidi was talking about the need to rationalise resources in a transparent way. I think you are right. Ideally, we should have an easily understandable matrix to prioritise spending in health services. I fear it is not as easy as this, however. As a commissioner of health services, would you prefer to improve the quality of 50 patients by 1% or one patient by 50%? This is the reality. For patients with rare disorders, the bar is always set at a much higher level than for

more common diseases. I do not think it is ever likely to be an equitable or fair playing field.

**Heidi GOETHALS:** We spend a lot of money on 'me toos,' for example. It is up to society to decide what it wants. Perhaps this is idealistic. Society needs to make a new analysis of priorities. There is money.

**Bruce MORLAND:** This is a real issue. Society's values are very personal. What is likely to affect me? The things that concern society are cancer and cardiovascular disease. Society's view of rare diseases is very limited. My worry is that by asking society, you will perpetuate the situation we have at the moment in which rare diseases are forgotten.

**Heidi GOETHALS:** We need to look for alternative ways. We have to prioritise. If orphan drug prices continue to rise, they will become too expensive to buy. We need to optimise the resources we have. There should be no waste. Why do pharmaceutical companies always insist on 20% returns when banks can make a fortune with 3%?

**Pierre VANKAN:** If I want a 3% return, I would make shoes. Why would I invest in a project with a 99% chance of failure and only a 3% return? No investor would accept that. The 'me toos' make drugs cheaper because they introduce competition.

**From the Floor:** We have a competitive market. However, we cannot continue like this. We have to rethink the way the business is run. Citizens and governments will not continue to accept the status quo.

**Pierre VANKAN:** I agree. I am describing the reality we are coping with. The sales force problematic is something that pharma companies themselves would rather be without. If you start regulating too much, however, the companies with all the expertise might go somewhere else.

**From the Floor:** Do national health authorities have the resources to support clinical development?

**From the Floor:** It is society and the health authorities are, ultimately, paying. If the situation that exists today continues, they will end up spending a lot of money. There is money. There should be new initiatives to stimulate health authorities. Europe also has a lot of money and can do a lot. Pharmaceutical companies will always have a role, but there needs to be alternative ways to develop.

**John McGregor, Orphanet:** Western societies are not aware of what is happening in Africa with HIV. Someone as famous as Bill Clinton had to make quite a lot of fuss to induce the big boys in pharma to reduce their prices to a level appropriate to the people of Africa. The issue is the same for other diseases in Africa.

Would it be possible for small biotech companies to be funded by government?

If there is success, the company would be requested to pay back the loan. Is it possible to create a climate of collaboration between biotechs and people who can take the risk to give them a chance of success?

**From the Floor:** Most biotechs are open to creative funding solutions. In biotech, cash is king. Many biotechs get their money from venture capitalists, who are interested only in profit margins. Any economically viable proposal can be discussed.

**From the Floor:** Maybe you should try doing more business in France, where there are bodies who will put forward up to 50%. The EU has also been going in this direction.

**From the Floor:** Biotechs are always in need of money. Any model that leads to a viable product and a certain return is welcome. The development of drugs is based on development experience in large indications. Do we need all of this for an orphan disease? If we cut you some of the requirements for orphan drug development, it would significantly change the cost picture.

**Wills HUGHES-WILSON:** We talked about the need for a certain level of return. This is correct. We have to cover for failures. It is important, however, that we can look at things in another way: cutting costs and failures. Less risk may mean lower return on investment. I would like to draw your attention to the Innovative Medicines Initiative (IMI), which is being developed under the Seventh Framework Programme. This is a public-private partnership between big pharma, academics, patient groups, biotechs, SMEs and governments. It aims at removing four big bottle necks in pharmaceutical research and development: toxicology, efficacy, knowledge sharing and education. What we learn from IMI could cascade into the orphan section.

**From the Floor:** There are misconceptions concerning 'me toos.' When a new class of therapeutic products is developed, several companies embark on the development of a product in that class. The first one coming to market gets the lion's share. New indications come out not because other companies were copying the first but because they were doing later parallel research. 'Me toos' may turn out to be more valuable than the first product because they may show benefits that were not clear in clinical trials.

If public funding was the right way to go, it would have been available now for a long time. It has not been shown to work. Public funding kills the development of innovative products. Innovation requires flexibility, focus and drive. Public funding does not offer this.

We also have to be careful not to put all projects in the rare disease field into one basket.

**Juan BALLESTEROS:** The key question raised in this afternoon's discussion is how to change things so that patients can get marketed drugs effective for rare diseases. Should an orphan drug status protection not come with the requirement that the reimbursement is associated with the indication of a rare disease?

**Ségolène AYME:** The reimbursement issue is one for member states. The only way to help states make the right decision is to ensure that the process they follow is the right one. Most orphan drugs developed for rare diseases are effective. There is no reason why they would not be reimbursed provided that the cost is acceptable to society. This brings us back to the main discussion of the day: the limit that society sets on spending. Are we going to set global priorities? Should we consider orphan drugs as different to common drugs? How will society face the resourcing constraints? We will never be able to escape the obligation of setting priorities. Priorities have to be set taking into account the views of all stakeholders. In the end, we will have to make very difficult decisions. The best we can do is to put in place mechanisms to create real data and to train our colleagues. I see no other way than providing evidence for decisions that will be taken in the future anyway.

## DAY 2 – Friday, October 27, 2006

### SESSION 4 – HOW TO ENSURE ACCESS TO OPTIMAL TREATMENT FOR PATIENTS?

*Chaired by Dianne Dorman, NORD and Kerstin Westermark, COMP*

#### Would Centres of Reference Contribute to the Better Treatment of Patients?

*Ségolène Aymé, Rare Diseases Taskforce at the European Commission*

##### CENTRES OF REFERENCES

###### 1. Background

###### *a) Expertise*

If orphan drugs are available, they need to be prescribed and the patients need to be followed up. This will be done by experts. The optimal organisation of the healthcare system in Europe will ensure that we make the most of available drugs. Centres of reference have always existed. Up to now, however, if you were not in a medical setting it was difficult to find out where the experts were working. Thanks to the availability of information in the Internet, more and more people are able to find out the right experts who are working with their disease.

###### *b) Budget constraints*

There are major budget constraints everywhere in Europe, even in teaching hospitals. Teaching hospitals have to restrict their activities to serving the patients. In the past, we were quite free to use research money for care and vice versa. Now, we have very strict analytical budgets, which make this impossible. Only a few

centres will have the resources to perform clinical research. Patients are now travelling to visit the best centres.

###### 2. Rare Disease Taskforce Report

###### *a) Centres of reference*

Two years ago the Rare Diseases Taskforce was requested to look at this issue in detail and provide an overview to a high-level European working group for health services and medical care. In the report we issued last year, we discovered that centres of reference for rare diseases exist only in a few countries: Sweden, Denmark, Italy and France. Spain and Bulgaria are working to implement them. Centres of reference do exist in other countries that cover some rare diseases: Belgium, Czech Republic, Greece, Ireland and the UK. Centres of reference are not always labelled as such by a governmental body but exist due to the reputation of the leaders of these centres. These are called centres of reference by reputation. These exist in all countries, of course.

###### *b) Definitions*

We discovered that in Europe there is no agreement on the definition of what a rare disease is. Denmark defines rare disease as one in 10,000, while France defines it as one in 2,000. The concept of centres of reference differs also. Sometimes they are regional centres and other times national centres. In some countries there is financial support for their activities, in other countries not at all. The reasons for establishing centres of reference differ from one country to another.

###### *c) Conclusions*

Centres of reference are needed. If the patients are rare, so too are the experts. The experts need to be identified and accessible. Expertise can only be found at an international level. Most countries are too small to deliver all of the expert care that is required. Clinical research is badly needed and can only be developed in major centres. Society will not accept the price of orphan drugs unless they are prescribed very wisely. We want to have centres of reference but we do not want to see patients travelling. Language barriers, travel expenses and distance from family and friends are real problems. Centres of reference may not be ready for a flow of patients coming from all the surrounding countries. There are limits to the size of the patient clinics. Centres of reference are needed for two main reasons. Firstly, we want quality for patients and non-expert clinicians. Secondly, we need to concentrate manpower and funding, speed up research, and improve quality of care. Centres should have a common label. Centres of reference not working with patient support groups should not be seen as expert group. In the past years,

at least three countries – Germany, Spain and France – have decided to put money into the networking process. This has improved research and improved care for patients. There is real added value to networking. They can share case management systems, databases and so on. Within a network, there will be the diversity of expertise required. The funding of expert opinion is a real problem. In centres of reference, 80% of the activity is giving advice to other colleagues. This is not recognised as a real activity by the managers of the hospital. We should encourage the development of electronic tools.

#### *d) Impact*

The European Commission has listened to our advice. Already this year, they have funded six networks of centres of references. This is the first step. We think that we are going in the right direction for improving delivery of care. Funding research and expertise is the right approach. What we are doing in the field of rare diseases could be a model for other areas of medicine. Our problems are common to all chronic diseases.

## Positioning Rare Diseases in the Healthcare Agenda

*Yann Le Cam, EURORDIS*

### HOW TO ENSURE ACCESS TO OPTIMAL TREATMENT FOR PATIENTS?

#### 1. Orphan Diseases

##### *a) Optimal treatment*

Optimal treatment is to achieve the quickest access to affordable treatments with real therapeutic added value for all rare disease patients in Europe.

##### *b) Unmet medical needs*

It is nice to have 400 products designated. However, I would like to see more products in areas where there is no treatment. This is what we need. Innovation means aiming for a cure. Addressing unmet medical needs could be a driver for

EU innovation and competitiveness. We need big industry to get involved with unmet medical needs. We still have a long way to get there. The pharmaceutical industry and the regulatory framework need to be driven by patient needs.

##### *c) Patients' real access to authorised orphan drugs*

Patient access can be measured by comparing prevalence of the disease to the availability of treatment.

## 2. Proposals

##### *a) First proposal: EU and US harmonisation*

**We want all the orphan drugs;** the one developed in the US and the one developed in Europe. It is time for US and EU harmonisation on orphan drugs. 50% more orphan drugs have been designated in the US than in the EU over the past six years. There is a gap. Payers must understand that not all designated orphan drugs will arrive on the market. Only a portion of them – 20% to 25% – will be marketed. The time of development varies according to disease area from 8 to 12 years. We need to explore the reasons for this. We would like to see the harmonisation of the form and content of orphan drug applications. I see this as a start. It gives the message that we are serious about speeding up the process, but it is only the start of a larger effort to seek converging regulatory requirements.

##### *b) Second proposal: Incentives*

**It is time for more and better incentives.** We should add value to the EU market exclusivity. We want real, strong significant benefit. It should make a difference in medical practice and for the patient. We also want continuity of EU fee waivers and reductions. It is time to work on tax reduction for orphan research at national level. Very few efforts are made in this area in the EU at the moment. We want to try to put in place a clinical research grant programme for orphan drugs designated in the EU through the 7th Framework Programme (2009-2013).

##### *c) Third proposal: EU unique market on orphan drugs*

**We want orphan drugs for all.** We do not have a unique market in the EU. The single market in Europe works for consumer goods, insurance and banking. However, when it comes to health and rare diseases, a single market is an illusion. Innovation exists only if it reaches the patients. If not, it is only an invention. If there is not a unique market, there will be fewer incentives for innovation and competitiveness. We are building a regulatory system but not a market. If only the lucky few get the treatment, is this ethically correct?

### 3. Real Patient Access

#### a) Legal base

Patient access to medicines in the EU has a legal ground. Access is not an option; it is a right. There is an European law which stipulates that member states place the drug on the market within 90 days after its marketing authorisation; it can be extended to 180 days if questions. This time frame is too often not respected and exceeded.

#### b) Payers

The system is becoming increasingly hypocritical. Payers are responsible for the management of the healthcare budget. However, are payers looking at what patients and society are asking for? Patients face a triple penalty. Firstly, they have a rare disease. Secondly, they live in a society that dreams of zero risk. Thirdly, when a drug is produced, they do not get access to the treatment because it is too expensive. "Am I worth it?"

#### c) Partners

Some of the stakeholders are building consensus on which actions to implement. Now patients, industries, regulatory agencies, member states and the European Commission need to move forward together.

#### d) Coordinating member states

We need an EU working group for orphan drugs transparency of volunteering member states first to pull together expertise and to share the information in order to speed up the therapeutic added value assessment, and second to negotiate with marketing authorisation holders an EU ex-factory reference price. We do not need a regulation to do it now. We can move forward.

### 4. Actions

#### a) First action: EURORDIS charter

We have worked over the last three years on the development of a charter of good practices for relationship between sponsors and patient organisations for rare diseases clinical trials. This is based on the vision that all along the value chain of drug development, we can work together to bring added value to patients. If we want to save money, we need to look at the right place of orphan drugs in a given therapeutic strategy of a given condition. It would be nice for some of the companies to move from the creation of value for shareholders only towards the creation of value for stakeholders in a broader sense.

#### b) Second action: Building capacities of patient groups across Europe

We need to raise the capacity and competencies of the patient organisations. EURORDIS has developed training sessions for patients, such as reading a clinical trial protocol. These training sessions are performed in partnership with national rare disease alliances and public institutions or private partners. We need to build a common culture that transcends different cultures, healthcare systems and languages. So far, we have trained about 300 patient representatives. We are expanding.

#### c) Third action: Raising policymaker awareness

We need to work together to raise awareness of the public and of policy makers. We need to create a more favourable access environment to treatments. Patient groups are organising the first national campaigns in Spain, Denmark, Greece and France. We are already working with the 10 rare disease alliances in Europe to develop an annual awareness European campaign. In 2008, we will have the first coordinated European awareness campaign. We hope that society will not turn their back on us.

# What Can Be Shared between Health Technology Assessment (HTA) Agencies?

*Finn Børlum Kristensen, National Board of Health - Danish Centre for Evaluation and Health Technology Assessment*

## SHARING HTA TECHNOLOGIES

### 1. HTA

#### *a) Goals*

Many assessments are going on throughout Europe at the same time and on the same topic. This is not cost effective. Technology assessment provides input into decision-making in health policy and practice. It is very practically orientated. It works in a systematic way. It calls for several disciplines and has a wide scope. It contributes to improved health, patient safety, and effective use of health care resources.

#### *b) Definition*

The generic meaning of health technology is the application of scientific knowledge to find practical solutions. Health technologies are the application of research in practice. This is a multi-disciplinary process. It should be transparent, unbiased and robust so that it can feed into policies focused on patients and seek to achieve best value.

#### *c) Examples*

HTA can go into diagnostic and treatment methods, equipment, pharmaceuticals, prevention methods and even support systems like IT systems.

### 2. EUnetHTA Project

#### *a) Goals*

The project is replying to an expressed need expressed by the EU Commission's high-level group for an effective and sustainable network for HTA that can inform policy decisions. We want to connect public national agencies that do HTA

together with research institutions and ministries so that we can have a more effective exchange of information and support policy decisions by member states. The project informs decisions but does not make them.

#### *b) Partners*

There was great interest in this project. All the current member states are participating in some way or other. Norway, Iceland and Switzerland are linked closely and participating. We included in the network important institutions outside Europe, in the US and Australia, for example. The associated partners are built into the project in the sense that they are contributing and receiving resources from the grant. The EUnetHTA forum was set up to allow the exchange of views.

#### *c) Strategic objectives*

The strategic objectives are to try to reduce the duplication that is depressing to see at this time. We want to have better coordination so that there is more effective use of national resources. Hopefully that will lead to increased HTA input in decision-making. Another objective is to establish the links between HTA and policymaking. We want to support those countries with limited experience of HTA.

### 3. Work Packages (WP)

#### *a) WP 4: Common core HTA*

Evidence is global but application is local. Application differs in different countries for various reasons. However, there is a common HTA core. We agree that we need to have a good, rigorous overview of research on clinical effectiveness, for example. We generally prefer to have efficacy data from trials but we would also like to have real-life data on effectiveness from clinical registers or longitudinal studies. If we had a good idea about what kind of patients are included in such studies, it would be robust enough to share across regions, countries and settings. We need to have clarity on a common taxonomy, a common vocabulary. Policy questions become more specific HTA questions. We can work together, then, to formulate evidence of the efficacy of a particular treatment or intervention. It is important that we work on adapting existing HTAs. This will lead to a more standardised way of doing HTA. If you work in a rigorous, transparent way, standardisation is possible.

#### *b) WP7: Monitoring emerging technologies and HTS prioritisation*

One of the deliverable of this WP is designing a structured information service on emerging and new technologies.

# Responsibility of Industry in Facilitating Access to Orphan Medicines

*Erik Tambuyzer, Genzyme, EuropaBio/EBE Representative to their Joint Task Force on Orphan Medicinal Products*

## ACCESS TO ORPHAN DRUGS

### 1. Rare Diseases and Orphan Medicines

#### *a) Shareholders and society*

Benefits for society and shareholders are, in the long term, the same. There is some correlation between what shareholders see as valuable and what the value for society of a company really is.

#### *b) Industry*

There are many rare disorders, most of them genetic. Yann Le Cam says the real number of diseases is around 1,500. Most of them are life threatening. The provision of medicine is a real responsibility. Therapy is often not available. When it is available, it is often not satisfactory. Industry is almost the only source of medicines in all fields and particularly in this field.

#### *c) Challenges*

The time lag from the first doctor's visit to diagnosis can be very long. The prevalence of late or misdiagnosis is also very high, between 60% and 80%. The risks to developing a therapy are often exceptionally high. Nothing has existed in the past. There is nothing to go on. Rarity raises clinical trial challenges. When diseases are rare, they tend to be heterogeneous. The costs of development of orphan medicines are not necessarily lower than that for common diseases. The principle of a drug regulation is that the costs of developing a medicine are not recoverable without economic incentives. Industry needs shareholder support, which means financing. You cannot predict the cost of development of a product before you have it.

## 2. Industry Responsibility

#### *a) Provision of medicines*

The first responsibility of industry is the provision of medicines. The product has to be safe, efficacious and high-quality. This is the same for orphan drugs. What is often forgotten is the link between research and the final product. The manufacturing process is often a huge challenge. Without good diagnostic method, you cannot provide the therapy. It would not make sense to provide therapy to a patient who was shown ultimately not to have that particular disease but something else. Symptoms can often be similar. Orphan drugs are an expression of targeted or personalised medicine.

#### *b) Sustainability*

Industry also has a responsibility to provide sustainability. We are nearly the only source of medicines. If we are not sustainable, if we go bankrupt, the therapy will no longer be available. Financial sustainability – which is linked to pricing – is a must. New products require increasingly heavy investment. There is risk in capital competition. Shareholders invest in risk only when there is reward. Margins of 20% return on investment are not exceptional. You need this or you will not get the money from the shareholders. Market exclusivity does not create monopolies. With clinical superiority, a new product can come on the market based on the same principles. Competition is there and it needs to be taken into account.

#### *c) Transparency*

Since we are nearly the only source of medicines, we have to be transparent about the process of development. Part of this is explaining pricing. Rare disease registries are also part of the required transparency. Registries are set up and governed by medical people using company funding. There is transparency required in how this registry is set up. Communication to authorities and other stakeholders also needs to be transparent. The way in which industry and patient groups work together needs to be transparent.

#### *d) Partnership*

As nearly the only producer of drugs, industry has to be involved in partnerships. Their partnerships need to be long term. Working together on awareness of rare diseases is the first priority for EBE/EuropaBio. We have to work together on building sustainable healthcare systems.

## Questions and Answers

**Chairman:** We have heard about collaboration between healthcare professionals, centres of reference, researchers and HTA agencies. What about collaboration between industries? Would it be possible to share common technologies with other industries?

**Erik TAMBUYZER:** We are living in a competitive environment. Shareholders invest in one company because they prefer it over another. However, there are more signs of competition between companies when you have an effective product for a disease. Do you recommend that companies work on other products first, or do you want to have increased competition for those products that exist? This needs to be discussed. There are advantages to collaboration, but there may also be disadvantages, which we do not understand well enough at the moment.

**Chairman:** My view is that patients' organisations are the leaders in this field of collaboration.

**Marlene HAFFNER:** In the US, and I think it is true in Europe as well, we are looking at drug development today in a similar way as we did 15 years ago. There are better ways to judge efficacy and value. There is a group in Arizona called the Critical Path Institute, which is bringing companies together under their umbrella to discuss common ways of doing things. Some of them are so simple that it is mind boggling, for example, the creation of a single report form that all companies would use to simplify the review process. When we save time, we increase access.

**Bruce MORLAND:** The problem that we are facing becomes too diluted when we talk about rare diseases. The concept of networks and access to drugs gets too diluted in the field of rare diseases. Do we need to be more specific and have two or three very focused targeted examples of compounds and rare diseases and work very closely with the stakeholders to show how to deliver an expert network? At the moment, it is all too conceptual. We need working examples that can be demonstrated to the providers of healthcare throughout Europe.

**From the Floor:** Should the EUnetHTA not only try to find methodologies on how to develop HTAs but also give indications on how to manage uncertainty after market authorisation or launch?

**Finn BØRLUM KRISTENSEN:** WR 7 addresses the issue of when to do prospective monitoring from the point of entry of new drugs and technologies. Often drugs may not be in the centre or mainstream of HTA work. Orphans often call for specific approaches.

**Bruce MORLAND:** There is an opportunity for EURORDIS, the Task Force, COMP, and DG Enterprise to meet together. There has to be some action. These four stakeholders need to come together and work through Framework Seven. We need some concrete actions.

**Yann LE CAM:** We are looking at the figures on rare diseases more carefully. However, now or later, we do not know where rare disease numbers come from. Not having concrete numbers will work against us. Orphanet in partnership with Eurordis publish regularly updated bibliographic survey on "prevalence of rare diseases". We know from this work that by tackling the first 1,500 rare diseases, we certainly cover more than 90% of the affected population. As Bruce said, we could use four examples to promote action.

**Patrick DUPUIS, Orphagen:** Everybody strongly support harmonisation between the FDA and the EMEA. Are there any actions planned in this area?

**Marlene HAFFNER:** We are not going to achieve complete harmonisation. We have different countries, laws, numbers and epidemiology. However, we will be doing things in parallel. We will speed things up. By September of next year, we will have parallel designation.

**From the Floor:** Some of this is already in place. We are all in favour of harmonisation of the application forms, even if we have different prevalence cut off levels and so on. We are ready to move forward.

**Channa DEBRUYNE:** We are all aiming to get this done as soon as possible. We cannot change our form at the EMEA. It is a Commission legal document that we have to change. Companies and academia need speeded up parallel designation of orphan products. I hope that the task will be completed before September next year.

**Peter STRENG:** Yann mentioned that you have started training patient representatives. I am under the impression that in lots of countries patient representatives actually have difficulty in selecting patients able to commit their time. Patient organisations do not have the money to work on this full time. Where should patient organisations go for funding?

**Yann LE CAM:** This is a real problem. How can we develop volunteering capacity? Patient organisations want to get involved in European activities. I am more sceptical about funding, however. It is an area that needs work. EURORDIS does two kinds of training: national training in local languages and local partners, and master classes in English to encourage involvement at the European level.

**Stephen GROFT, Office of Rare Disease, National Institute of Health, US:** We are the office responsible for developing the list of nearly 6000 rare diseases and conditions. Before a disease is added to the list, we do a literature evaluation to see if it has been reported, to what extent and if it does seem to be an

accepted term for a disease or condition. The terms on the list have been examined carefully. They are included on the list for a specific reason and are well documented. We have tried to validate the vocabulary and terminology used on the list. If anyone has a suggestion for adding or deleting a term, disease, or condition from the list, please get in touch with us. There is a down side to limit research to a select group of 1,500 rare diseases. It would limit the development of information from basic research mechanisms that can then be applicable to a number of rare diseases. From the perspective of the National Institutes of Health in the United States, the limitations on research are based on the quality of the research, the novel approaches that are presented in the research proposal, and the availability of sufficient financial resources to support the planned research. We have not limited research to a particular disease or group of related diseases, unless there is a specific program announcement or funds set aside for a special emphasis.

## SESSION 5 – POSITIONING RARE DISEASES ON THE HEALTHCARE AGENDA

*Chaired by Lisa Wise, Genetic Alliance of America*

### Roundtable Discussion – Where Do We Go From Here?

#### Recommendations by the audience discussed

Panelists:

- EMEA: Channa Debruyne
- COMP: Kerstin Westermark
- NIH-Office of Rare Diseases: Stephen Groft
- FDA: Marlene Haffner
- Genetic Alliance of America: Lisa Wise
- NORD: Dianne Dorman
- EURORDIS: Yann Le Cam
- Co-chairs of the Organising Committee: Ségolène Aymé - Fernando Royo - Rosa Sanchez de Vega

**Lisa WISE, Genetic Alliance, US:** International collaboration is essential to the advancement of technologies and services for patients and their families around the world. Genetic Alliance is an international coalition of patient advocacy organisations. We work to build models of success on a patient advocacy level. We help to position the patient advocate so that they can make a valuable contribution to this discussion and help drive the global healthcare agenda.

**Dianne DORMAN, National Organisation for Rare Disorders (NORD):** Ségolène, can you enlighten me on how patient organisations can contribute to the development of centres of reference?

**Ségolène AYME:** The role of patients' organisations is important at every stage in these centres. They should be involved in the first assessment of the labelling process. Diagnosis should always be delivered in a nice environment. They should

also be involved in the post-labelling evaluation. Any document issued by centres of reference with recommendations for practitioners or patients should be produced in cooperation with patient organisations.

**Stephen GROFT:** Within our rare disease clinical research network we have developed 10 research consortia. Within these, there are 30 different patient advocacy groups. We have tried to involve them in all aspects of research. Some consortia have included the advocacy groups more than others. Patient advocacy groups are essential research partners. They represent the glue. Without the patients, we have no research. We ask patient groups to review and comment on the informed consent documents. This offers patients some assurance that they have been looked at by their peers. Tremendous demands are placed on patient organizations. They serve in a number of capacities: aid in patient recruitment, media liaison, communicators, educators and counsellors. Successful research teams always have a strong patient advocacy group as a major component.

**Lisa WISE:** How can patients be most effective in setting the healthcare agenda?

**From the Floor:** Awareness is the most important area to work on. We have overlooked the media so far. In order to increase awareness, we have to include the media more. The national awareness campaigns will help.

**From the Floor:** We are not involving the payers and policymakers enough either. We have achieved a level of consensus among patient organisations, academia and industry. However, the policymakers need to be must more involved. Ultimately, our fate is in their hands.

**From the Floor:** Through the media, we can partly address this.

**Lisa WISE:** We need to support patients in becoming sophisticated patient advocates so that in their relationship to the media they can be as strong as possible.

**Peter STRENG:** We need to acknowledge the role of patient organisations in the process from diagnosis to therapy. At the national level, many organisations lack the acknowledgement of health authorities. This is then reflected in lack of funding. Patients need to work together on a national, European and global level. This way, they will be heard in the process of agenda setting.

**From the Floor:** HTA is a societal issue. How do we allocate funds? How do we handle the healthcare and the guidelines? Society wants drugs for orphan diseases. If patients do get access to orphan drugs, it is a violation of a society's will. Society's wishes needs to be included in HTA assessments. Society sees equity as a prominent force in orphan drug legislation. Equity is not in a cost-effectiveness evaluation. Patient organisations can help to impose society's will.

**Stephen GROFT:** Patient groups need presence and visibility in numerous venues and activities in order to be viewed as successful. The international collaboration between patient groups will continue to increase. Industry also understands this

and is utilizing the resources offered by the patient advocacy groups in their research and educational activities.

**Kerstin WESTERMARK:** Article 9 of the orphan Regulation puts demands on member states not only to promote research but also to increase availability of drugs. We need to make more use of this Regulation.

**From the Floor:** Building on this exchange, I have two proposals. Firstly, we can work with civil society and patient groups. Why do we not do a joint position paper? We could make a transatlantic joint statement asking for a convergent regulatory framework on orphan drugs. Secondly, we have Article 9. COMP is there to advise the Commission on policy. Why do we not prepare a document asking the Commission for coordination in HTA or orphan drugs?

**Dianne DORMAN:** Where do we go from here? What can we do now to move the agenda for rare disease patients forward?

**Sékolène AYME:** The academic world can publish more scientific papers on all the issues we discussed here. The media rely very much on what is published in scientific and medical journals. If the problem is not discussed in a peer review journal, it does not exist. We have plenty of data to report. We are to blame for not publishing more papers on this important issue.

**Bernard DAUVERGNE:** Today, we have many epidemiological dossiers with very good methodology and validated by the EMEA and COMP. We need to have a database of products already on the market

**Sékolène AYME:** Last February, we established an electronic journal on rare diseases. It is fully accessible at no cost. It is a scientific journal. The papers are read by a large audience. We welcome papers. We would like to transform the dossier into a scientific paper. We would invite the FDA to help us in this area. For patients, it is helpful to see that good papers on their conditions are published. I think this project would serve a very large community.

**Marlene HAFFNER:** Perhaps NORD could publish the availability of this journal so that patients would be aware of it. Do you do reviews?

**Sékolène AYME:** It is a traditional journal with a large editorial board. All the papers are peer reviewed. The papers are of a very high quality.

**From the Floor:** We have to realise that some sponsors are doing a very good job assessing the epidemiology of rare diseases and others are not. Do you have any epidemiologists in your peer review? What would we do if an epidemiologist came to a different conclusion?

**Sékolène AYME:** I am an epidemiologist. Two epidemiologists and two disease specialists review each paper. It will be considered a scientific paper independent of the opinions of COMP. We will ask for modifications of conclusions if we think this is the right thing to do.

**Peter STRENG:** Epidemiological data is essential and we need to improve it.

**From the Floor:** At the moment, the data published by the EMEA at the time of designation of a project is purely based on information coming from the sponsor. Some do a good job and some do not.

**From the Floor:** There is a disclaimer attached to every public summary of opinion. It is made clear that prevalence calculations are the sponsor's. We also challenge the calculations. We do not allow sponsors to use the figures from public summary of opinion in their own applications.

**From the Floor:** The data is referred to later as the potential number of cases waiting treatment. When this number is exaggerated, it leads to potential misunderstandings at the access level with the reimbursement authorities about cost.

**From the Floor:** We need to be sure that it is below five in 10,000. Epidemiology is not a concrete science. It implies uncertainty. We do not accept a range above five in 10,000. This is the only certainty we have.

**From the Floor:** Prevalence can change dramatically. COMP has to go for the broadest indication. We are not looking for the therapeutic indication, which will be for a much smaller population.

**Marlene HAFFNER:** Most products developed do not treat the entire disease but an aspect of it. Epidemiologically, this will look different to treating the disease itself. In the future, we will treat total disease. In many areas, however, we are only treating symptoms.

**From the Floor:** It is our joint responsibility to trigger a deeper discussion on how to extend innovation to the area of reimbursement. We need to change the reimbursement paradigm to make the new treatments more equitable and sustainable in the healthcare system. Unless we provide new ways to reimburse cures, we may be blocking the availability of investment.

**Marlene HAFFNER:** There is a high cost for most new therapies. Orphan drugs are not the only expensive drugs. Not all orphan drugs are expensive. We perpetuate the problem by wringing our hands. We need to emphasise that new therapies are expensive. This is a healthcare cost that countries will have to deal with. We need to set priorities. We need to think in broader terms. We need to think of what we have accomplished and what the cost of not treating a disease is.

**From the Floor:** Return on vaccines is often not high. The value that many vaccines offer to society is often not recoverable economically. I wonder if we are missing the opportunity of developing vaccines for many other diseases.

**From the Floor:** 10 years ago we had the same debate about new HIV therapies that were emerging. Governments said that they could not afford to pay for the therapies. When they question cost in this way, you begin to wonder what the

value of your life is. Now, HIV drugs and condoms are being distributed in Europe and Africa and we have not run out of money. The situation is the same now. I just hope it will not take another 10 years for orphan drugs to gain acceptance. Our environment is conservative and reactive to innovation.

**Ellen FEIGAL, Critical Path Institute, US:** In the US, the FDA put out a white paper on the critical roadblocks to innovation in medical product development. They then came out with a list of about 76 projects that, if addressed, might help solve some of the issues. The institute is a non-profit research institute. It acts as a trusted third party to get industry and researchers to work together. Five projects are underway right now. We have put 15 companies together to work on safety concerns in the development of projects. These companies have agreed to work together in this. Our institute will summarise this information and present it to the FDA. Another project is looking at predictors of response. We are getting people who do not normally work together to come together. We have templates for rules of engagement and processes in place for collecting and pooling information. We could develop demonstration projects in which we apply the principles we are all talking about. This is a possible model to consider.

**Stephen GROFT:** We do not have to look very far to find successful models that have led to interventions. The models that succeed pull together all the responsible individuals and organisations and focus on research taking many years. In the United States, we have noticed a considerable increase in reports from our Congressional appropriation committees asking that we provide a focus on research of rare diseases. Once we have received this very specific language from Congress, we develop plans for coordinating research throughout the entire NIH structure. This becomes the research agenda for a particular disease. By adopting successful models, this will lead to successful outcomes, including the development of orphan products.

**From the Floor:** Stephen has done an amazing job of finding money where there was none. If we speak as a community, we can be successful.

**Jean-Jacques CASSIMAN, Catholic University Leuven - Belgium:** If you want to position rare diseases in the healthcare agenda, you need a broader perspective. There are many interventions other than drugs to consider, for example, neonatal screening and genetic testing. This will cost more money, of course.

**Stephen GROFT:** You are right. Even though newborn screening and genetic testing have been available for several diseases for many years, we are noticing considerable growth in the development of tests available to clinicians. Many of the individual states in the United States screen for 30 diseases at birth. It will become even more valuable as technology advances. The problem comes after diagnosis. Are we able to link the patient up with a research or treatment team that can deliver the best possible services?

**Peter STRENG:** On a macro level, it will be cheaper if you start neonatal screening. However, neonatal screening for untreatable diseases is not allowed. Patient organisations are asking for screening, however. It is important to know early.

**Marlene HAFFNER:** We are on the threshold of a paradigm change. Through new-born screening we will know a lot more about causes of disease. We need to set a global health policy agenda for screening.

**Yann LE CAM:** EURORDIS does not only focus on drugs but has a comprehensive approach to rare diseases.

**Ségolène AYME:** The EU is not a political entity but a collection of countries. We need to lobby our governments to work together with other governments. We have been able to influence the French Government enough to try to develop a common policy on rare diseases in Europe. This will work only if you convince your health minister to join the French effort. We hope that the authorities of the host country, Spain, will listen to the conclusions of today's conference.

## Closing Comments

*Cristina Avendaño, Spanish Medicines Agency*

I would like to congratulate EPPOSI in their efforts in supporting and organising this series of events devoted to partnering in orphan diseases and medicines, and in particular for this seventh workshop, that has been so fruitful.

I would like to express my commitment, and that of the institution I represent, in supporting clinical research and the process of assessment and approval of new drugs for rare diseases as well as the support to the implementation of post-marketing commitments for these medicines, which is so important.

Allow me to bring some good news. There is a legal initiative underway for compassionate use. This summer, a new Medicines Law was passed, and now we are facing the development of the regulation for compassionate use in Spain. We have quite a bureaucratic system that does not help patients very much. The procedures at the Medicines Agency should add much more value to the protection of patients, and therefore we are moving to a more flexible approach, one more centred on research and scientific aspects. Within a couple of months, the first draft of this new regulation will be ready and we will invite patient organisations to contribute to the proposal.

In addition, I have the pleasure to announce that the Spanish Ministry of Health has approved a new budget to support non-commercial clinical trials of medicines. This is the first time this has happened in Spain. The call for projects will be launched in January 2007 and orphan diseases is one of the established priorities.

Thank you very much and I wish you all a safe journey home.

## Annex 1

**The European Platform for Patients' Organisations, Science and Industry (EPPOSI) is a Europe-wide partnership of patients, academic science and industry which aims to advance healthcare policies for the prevention and treatment of serious diseases.**

### EPPOSI – Building bridges to stimulate innovation

EPPOSI is putting patients first in the dialogue about human healthcare in Europe. Patients, academia and industry all have a stake in innovation and policies for healthcare, health technology and the health outcomes of patients, especially for those suffering from chronic, life-threatening and serious diseases including rare diseases. EPPOSI's ambition is to develop strategies that benefit present and future generations. Joining this partnership provides the opportunity to participate in key debates and benefit from the pool of expertise and committed people who work for EPPOSI's cause: to have wider, quicker and more affordable access to essential medical technology and treatment.

### Achievements

EPPOSI focuses on building consensus positions and policy recommendations for the benefit of EU consumers.

A selection of the consensus positions EPPOSI has reached concerns:

- the establishment of the European Orphan Medicinal Products Regulation;
- biomedical research and the value of healthcare innovation;
- timely access to innovative medicines;
- from diagnosis to treatment for genetic diseases;
- rare disease therapy development and partnering;
- East-West European collaboration between patient groups.

Reports and proceedings for consensus positions reached are available at [www.epposi.org](http://www.epposi.org)

### Focus areas include

- Development of new diagnostics, treatments, and prevention for life-threatening and chronically-debilitating diseases;
- Access for patients to beneficial treatment and diagnosis;
- Research and funding to create innovative medicines for unmet medical needs;

- Dialogue about new biomedical technologies in healthcare, in particular with regard to benefits, safety, regulatory oversight, and ethical, legal and social issues;
- Factors affecting the supply and distribution of medicinal products, in vitro and in vivo diagnostics, medical genetic testing services and medical devices in the EU;
- Providing patients with information and counselling about all of these.

## WHY JOIN EPPOSI?

**EPPOSI is continuously looking for committed members and partners who are willing to participate in defining and building consensus to improve human healthcare at the European and international levels.**

### Patient groups

Because patient issues are a priority for EPPOSI, they are essential members of the organisation. Based on experience they can identify issues, propose solutions (together with other EPPOSI stakeholders), and bring messages constructively to policy makers in Europe.

### Academia

Scientific and clinical experts who convert their expertise into a language that politicians, policy makers and the general public understand are one of EPPOSI's strengths. The involvement of scientists and clinicians in the work of EPPOSI is of high value, not only because of the need for understanding current scientific developments and innovations, but also because they can contribute pragmatic solutions to the debate.

### Industry

Representatives of the healthcare and health technology industry have a direct interest in becoming members of EPPOSI because it provides them with an open platform to discuss, resolve and progress issues with other key-stakeholders such as patient groups, researchers and clinicians, and governmental bodies. Industry participation in EPPOSI is also a key strength since it increases the practicality of the solutions and converts messages into action.

### Topics of interest to the industry among EPPOSI members include:

- a pragmatic regulatory framework;
- equitable and timely access to and payment for innovative healthcare products;

- involvement of European and Member State bodies in healthcare;
- European and national healthcare policies;
- long-term ethical, legal and social issues and trends.

## Sponsors

EPPOSI offers sponsors a unique platform to partner with the various stakeholders in healthcare, and pave the way for the future. Sponsors benefit from the opportunity to interact directly with the most advanced key players of today's and tomorrow's healthcare field.

## Annex 2

### CHAIRS, SPEAKERS & PANELISTS

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Cristina Avendano, Spanish Drug Agency, Spain  
 Ségolène Aymé, INSERM/Orphanet, France – Co-Chair representing Science  
 Andrea Buzzi, Italian Haemophilia Society, Italy  
 Channa Debryne, EMEA, United Kingdom  
 Dianne Dorman, NORD, United States  
 Pauline Evers, EGAN, the Netherlands  
 Heidi Goethals, AIM, Belgium  
 Stephen Groft, NIH, United States  
 Marlene Haffner, FDA, United States  
 Jan Inge Henter, Karolinska Institute, Sweden  
 Michael Angel Izquierdo, Pharma Mar, Spain  
 Finn Borlum Kristensen, Nat. Board of Health, Danish Centre for Evaluation and HTA, Denmark  
 Yann Le Cam, EURORDIS, France  
 François Meyer, Haute Autorité de Santé, France  
 Bruce Morland, Birmingham's Children's Hospital, United Kingdom  
 Alfonso Jimenez Palacios, Ministry of Health & Consumer Affairs, Spain  
 Maria Pascual-Martinez, Cellerix, Spain  
 Andrea Rappagliosi, Serono, Switzerland  
 Fernando Royo, Genzyme, Spain – Co-Chair representing Industry  
 Rosa Sanchez de Vega, FEDER/EURORDIS, Spain – Co-Chair representing Patients  
 Ad Schuurman, MEDEV, the Netherlands  
 Erik Tambuyzer, Genzyme, Belgium  
 Valérie Thibaudeau, Orphanet, France  
 Josep Torrent y Farnell, Fundacio Dr. Robert, Spain  
 Pierre Vankan, Santhera, Switzerland  
 Kerstin Westermark, Sweden  
 Lisa Wise, Genetic Alliance of America, United States

## Annex 3

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### LIST OF ORGANISING COMMITTEE MEMBERS EPPOSI 2006 WORKSHOP

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Giovanni Asta, EPPOSI  
Ségolène Aymé, INSERM/Orphanet, France – Co-Chair representing Science  
Alfonso Casal, Pharma Mar, Spain  
Jaime Campos Castello, Hospital Clinico San Carlos, Spain  
Emmanuel Chantelot, EBE, Belgium  
Virginia Cuervo, Pharma Mar, Spain  
Miguel Del Campo, Universitat Pompeu i Fabra, Spain  
Jérôme del Picchia, Vienna Medical Academy, Austria  
Tina De Ploey, Genzyme, Belgium  
Beatriz Deza, Farma Industria, Spain  
Wills Hughes-Wilson, Genzyme, Belgium  
Catherine Levinson, Serono, Switzerland  
Dorthe Lysgaard, Rare Disorders, Denmark  
Rod Mitchell, EFCCA, UK  
Roberta Mugnai, EBE, Belgium  
Thierry Nebout, Servier, Belgium  
Detlef Niese, Novartis, Switzerland  
Maria Pascual, Cellnex, Spain  
Maria Rodriguez-Sanchez, Baxter, Belgium  
Fernando Royo, Genzyme, Spain – Co-Chair representing Industry  
Andrea Rappagliosi, Serono, Switzerland  
Rosa Sanchez de Vega, FEDER/EURORDIS, Spain – Co-Chair representing Patients  
Cees Smit, VSOP, the Netherlands  
Peter Streng, EAMDA, the Netherlands  
Josep Torrent y Farnell, Fundacio Dr. Robert, Spain  
Pilar Vacas, Pharma Mar, Spain  
Johan Vanhemelrijck, EuropaBio, Belgium  
Sonja van Weely, Dutch Steering Committee on Orphan Drugs, the Netherlands  
Sara Vidal, Cellnex, Spain  
Melissa Winter, GIG, UK

## Annex 4

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### PARTICIPANTS

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Alonso Falcon Felix, FEDER, Spain  
Asta Giovanni, EPPOSI  
Avenida Cristina, Ministerio de Sanidad y Consumo, Spain  
Aymé Ségolène, INSERM/Orphanet, France  
Ballesteros Juan, OrphaMed, Spain  
Barcelo Riera Montserrat, Trial Form Support, S.L., Spain  
Beitia Igor, GIS, France  
Blumer Karin, Novartis, Switzerland  
Boone Donald, CDC, United States  
Buzzi Andrea, Fondazione Paracelso Onlus, Italy  
Casals Lola, Pharma Mar, Spain  
Cassiman Jean-Jacques, Leuven University, Center for Human Genetics, Belgium  
Cespedes Ana, Serono, Spain  
Chantelot Emmanuel, EBE, Belgium  
Chicharro Rafael, FEDER, Spain  
Coronado Judith, FEDER, Spain  
Cuervo Virginia, Pharma Mar, Spain  
D'amato Sizonenko Loredana, Service of Medical Genetics, Switzerland  
Dan Dorica, Romanian Prader Willi Association, Romania  
Dauvergne Bernard, ADDMEDICA, France  
de la Pena Pilar, FEDER, Spain  
De Ploey Tina, Genzyme, Belgium  
Debruyne Channa, EMEA, United Kingdom  
Del Campo Miguel, Universitat Pompeu Fabra, Spain  
del Transito Olay Maria, Shire, Spain  
Del Val Villoslada Francisco, Genzyme, Spain  
Delgado González Claudia, FEDER, Spain  
Dorman Dianne, National Organization for Rare Disorders, United States  
Dubosq Annick, Orphanet, France  
Dupuy Patrick, Orfagen, France  
Edfjaell Catarina, Celgene, Switzerland  
Evers Pauline, EGAN, the Netherlands  
Feigal Ellen, The Critical Path Institute, United States  
Garcia Bolanos Alicia, FEDER, Spain  
Gicquel Erwan, Pfizer, Belgium  
Goethals Heidi, Association Internationale de la Mutualité, Belgium  
Gonzalez Angeles, Pharma International, Spain

Gonzalez Valdespino Cristina, Autonoma University, Spain  
 Granier Luc-Andre, Advicenne, France  
 Groft Stephen, National Institutes of Health, United States  
 Hackenitz Erica, Stuurgroep Weesgeneesmiddelen, the Netherlands  
 Haffner Marlene, US Food and Drug Administration, United States  
 Henter Jan-Inge, Childhood Cancer Research Unit, Sweden  
 Holm Birthe, Rare Disorders Denmark, Denmark  
 Hughes-Wilson Wills, Genzyme, Belgium  
 Huizer Jolanda, Stuurgroep Weesgeneesmiddelen, the Netherlands  
 Ibanez Auxina Elvira, FEDER, Spain  
 Iborra Amparo, FEDER, Spain  
 Inga Diaz Jenny, FEDER, Spain  
 Izquierdo Miguel Angel, Pharma Mar, Spain  
 Jensen Lene, Rare Disorders Denmark, Denmark  
 Jimenez Palacios Alfonso, Ministerio de Sanidad y Consumo, Spain  
 Kristensen, Finn Borlum, National Board of Health – Danish Center for Evaluation and HTA, Denmark  
 Köpcke Wolfgang, University Clinic Münster, Germany  
 Lasagna Giovanna, CHIESI Farmaceutici, Italy  
 Le Cam Yann, EURORDIS, France  
 Lecomte-Brisset Emmanuelle, OPI, France  
 Leroy Sophie, LEEM, France  
 Levinson Catherine, Serono, Switzerland  
 Mac Gregor John, Orphanet, France  
 Maman Marianne, Novartis, Switzerland  
 Mangon Rawin, Orphanet, The Netherlands  
 Martos Garcia Ines, FEDER, Spain  
 Medrano Andres, Universitat Pompeu Fabra, Spain  
 Merixell Fizon, Servimedia, Spain  
 Meyer François, Haute Autorité de Santé, France  
 Milano Marcello, CHIESI Farmaceutici, Italy  
 Minano Mar, FEDER/Orphan Europe, Spain  
 Mitchell Rod, European Federation of Crohn's and Colitis Associations, United Kingdom  
 Morland Bruce, Birmingham Children's Hospital, United Kingdom  
 Mosquera María Eugenia, Fundación Española de Enfermedades Lisosomales, Spain  
 Nicholls Anita, New Zealand Organisation for Rare Disorders, New Zealand  
 Paloma Yolanda, FEDER, Spain  
 Pascual-Martinez Maria, Cellerix, Spain  
 Patras Vladimir, Slovakia  
 Pellier Patricia, Serono, Switzerland  
 Penarroja Cristina, Universitat Pompeu Fabra, Spain

Perez Campos Toni, ESTEVE, Spain  
 Posada Manuel, Instituto de Salud Carlos III, Spain  
 Ramil José Miguel, Celgene, Switzerland  
 Rappagliosi Andrea, Serono, Switzerland  
 Revuelta Pascual Maria, Correo Farmaceutico, Spain  
 Rivas Jose Luis, FEDER, Spain  
 Rodrigo Carlos, Servimedia, Spain  
 Rodriguez Carmen, FEDER, Spain  
 Rodriguez Francisco, FEDER, Spain  
 Rodriguez- Sanchez Maria, Baxter, Belgium  
 Roussel-Maupetit Caroline, Advicenne, France  
 Royo Fernando, Genzyme, Spain  
 Sanatana Suarez Francisco, FEDER, Spain  
 Sanchez de Vega Rosa, FEDER, Spain  
 Santana Garcia Alicia, FEDER, Spain  
 Schikan Hans, Genzyme, the Netherlands  
 Schiltz Francois, Schiltz Health Care Consulting, Switzerland  
 Schuurman Ad, College voor Zorgverzekeringen - CVZ, the Netherlands  
 Seeverens Harrie, Ministerie Volksgezondheid, Welzijn en Sport, the Netherlands  
 Stefanov Rumen, Information Centre for Rare Diseases and Orphan Drugs, Bulgaria  
 Streng Peter, Myomedicine Europe, the Netherlands  
 Tambuyzer Erik, Genzyme, Belgium  
 Taruscio Domenica, Istituto Superiore di Sanita, Italy  
 Thibaudeau Valerie, INSERM/Orphanet, France  
 Torregrosa Miriam, FEDER, Spain  
 Torrent y Farnell Josep, Fundacio Doctor Robert, Spain  
 Trama Anna Lisa, National Italian Instituto of Public Health, Italy  
 Vacas Pilar, Pharma Mar, Spain  
 Valverde Jose Luis, EMEA, Spain  
 van de Putte Aurélie, EuropaBio, Belgium  
 van Weely Sonja, Stuurgroep Weesgeneesmiddelen, the Netherlands  
 Vankan Pierre, Santhera Pharmaceuticals, Switzerland  
 Vanmolkot Annemie, EPPOSI Internal Affairs Secretariat, Belgium  
 Velasco Calderon Maria, FEDER, Spain  
 Vilar Begona, Genzyme, Spain  
 von Schlösser Filippo, Nadir Foundation, Italy  
 Wästfelt Maria, Karolinska Institutet, Sweden  
 Westermark Kerstin, Läkemedelsverket and COMP/EMEA, Sweden  
 Wilson David, Genzyme, United States  
 Wise Lisa, Genetic Alliance, United States  
 Wong-Rieger Durhane, Institute for Optimizing Health Outcomes, Canada  
 Wuebbels Barbara, Ucylyd Pharma, United States

## Annex 5

### EPPOSI EVENTS SINCE 1994

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- 1994 Ethical aspects of Biomedical Research and the Biopharmaceutical Industry Conference
- 1996 Biomedical Research and Patenting: Ethical, Social and Legal Aspects Workshop – Brussels
- 1997 Biomedical Research and Orphan Medicinal Products Conference- Brussels
- 1998 The patient's role in European Health Policy making Conference- Brussels
- 2000 1st Dinner Debate Conference: Patients and East-West Cooperation in Health Issues
- 2000 1st Rare Disease Therapy Development and Partnering Workshop – Belgian Parliament – ‘Patients in Partnership with Science, Industry and Venture Capital’
- 2001 2nd Rare Disease Therapy Development and Partnering Workshop – French Senate – ‘Patients in Partnership with Science, Industry and Venture Capital’
- 2002 2nd Dinner Debate Conference – Strasbourg – ‘From Diagnosis to Therapy for Genetic Diseases: Setting the Political Agenda’
- 2002 ‘Timely Access to Innovative Medicines’ Workshop - Barcelona
- 2002 3rd Rare Disease Therapy Development and Partnering Workshop – Italian Senate ‘From Research to Development & from Bottlenecks to solutions’
- 2003 4th Rare Disease Therapy Development and Partnering Workshop – Dutch Senate ‘Orphan Therapies: from Clinical Development to Equitable Access’
- 2004 3rd Dinner Debate Conference, 2nd East-West Meeting – Munich – EU Enlargement, Bottlenecks and Opportunities
- 2004 Pharmacogenetics: Technical, Social, Legal and Ethical Issues – Sevilla
- 2004 Value of Innovation Workshop – Brussels
- 2004 5th Workshop on Partnering for Serious Disease Therapy Development – Berlin – ‘A Responsible System for Healthcare Innovation and Access to Care’
- 2004 4th Dinner Debate Conference –The Hague – ‘Bottlenecks and Opportunities in Contemporary Pediatric Therapeutic Research’
- 2005 Forum Discussion ‘Examining the Value and Impact of the EU Clinical Trial Directive: One Year into the New European GCP Reality’ – Brussels

- 2005 6th Rare Disease Therapy Development and Partnering Workshop – London – ‘People with Rare Diseases – No Longer Alone in the World’
- 2006 5th Dinner Debate and Conference – Amsterdam – Data and Bio-Banking for Research – Towards Joint Ventures of Patient Organisations, Science and Industry on the Road to Validated Expertise and New Therapies
- 2006 7th Workshop on Partnering for Rare Disease Therapy Development – Madrid – “ Positioning Rare Diseases on the Healthcare Agenda”

## Annex 6

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### EPPOSI BOARD

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#### Chair of the Board

Michael Griffith

#### Board Members

##### *a. representing Patient Organisations*

- Mary Baker, European Parkinson's Disease Association (EPDA)
- Rodney Elgie, Global Alliance of Mental Illness Advocacy Networks – Europe (GAMIAN), European Patients' Forum (EPF)
- Michael Griffith, Fighting Blindness & Retina Europe, Chair EPPOSI
- Alastair Kent, European Genetic Alliance of Parent/patients Organisations (EGA) & Genetic Interest Group (GIG)
- Yann Le Cam, European Organisation for Rare Diseases (EURORDIS)
- Rod Mitchell, European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), Treasurer EPPOSI
- Ysbrand Poortman, International and World Genetic Alliance

##### *b. representing Academic Science*

- Ségolène Aymé, INSERM & Orphanet
- Ivan Baines, European Life Science Organisation (ELSO)
- Jean-Jacques Cassiman, European Society of Human Genetics (ESHG), Secretary EPPOSI
- Heinrich Schulte, European Society for Clinical Investigations (ESCI)
- Christian Suojanen, European Federation of Biotechnology (EFB)

##### *c. representing Industry*

- Silvia Matile-Steiner, Hoffmann-La Roche
- Thierry Nebout, Institut de Recherches Internationales SERVIER
- Andrea Rappagliosi, Serono International
- Erik Tambuyzer, Genzyme Corporation, co-chair EPPOSI
- Jean-Marie Vlassembrouck, Baxter

#### Honorary Members

- Philippe Busquin, MEP, former European Commissioner for Research
- Cees Smit, Chair VSOP