



From Diagnosis to Therapy for Genetic Diseases:
Setting the Political Agenda

EPPOSI Dinner Debate Report
Strasbourg, 27 May 2002

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Executive summary

From May 24-27, 2002 the 34th Conference of the European Society of Human Genetics (ESHG) took place in Strasbourg. For the European Platform for Patients' Organisations, Science and Industry (EPPOSI), this conference was a perfect occasion to meet with representatives of patients, science and industry to discuss the issue of European politics in relation to the diagnosis and therapy issues of genetic diseases. This was especially true because of the fact that the European Commission proposed at the end of 2001 to review the EU's pharmaceutical legislation. Key-note speakers at the dinner debate to address these issues were IJsbrand Poortman, Alastair Kent, Jean-Jacques Cassiman and David Meeker. At the end of the debate there was also an important contribution from the newly elected president of the ESHG Gert-Jan van Ommen. This report starts with a description of the review process of the EU pharmaceutical legislation and continues with the contributions of the several speakers at the dinner debate on the evening of May 27 in Strasbourg.

'The EU pharmaceutical review process : What is in it for patients ?'

On 26th November 2001, the European Commission adopted a proposal for review of the EU's pharmaceutical legislation. This aims to rationalize and speed up the approval process for medicinal products, deliver faster access to innovative medicines for all EU patients and guarantee a high level of health protection.

EPPOSI welcomes the adoption of this legislation as a positive step towards increasing patient access to innovative medicines. The new legislation will provide an impetus to increase Europe's competitiveness in the world market, and will help to harmonize the major medicinal regulatory systems globally.

The following issues will be critical to patients, science and industry in order to achieve the objectives of promoting a high level of public health, ensuring faster access to innovative therapies and increasing Europe's competitiveness:

- * Accelerated review, conditional approval and compassionate use of new therapies
- * Expansion of scientific advice from the EMEA to ensure a continual dialogue during the whole drug development and registration process, and
- * Information to patients

CENTRALISED PROCEDURE (SCOPE) (Regulation, Article 3.1)

The Commission has proposed that all biopharmaceuticals and all new active substances (NASs) be granted marketing authorizations through the Centralised Procedure of the European Medicines Evaluation Agency (EMA).

Established in 1993 through Regulation 2309/93, EMA was set up to promote the completion of the internal market through the adoption of uniform regulatory decisions based on scientific criteria concerning the placing on the market and use of medicinal products. It has since proved its value in providing common EU-wide assessment and authorization of innovative substances, including biopharmaceuticals for which the centralized procedure is

mandatory.

A marketing authorization granted through the Centralized Procedure as established in Regulation 2309/93 is valid throughout the Community. Assessed by EMEA, it ensures a common agreement during the review process, on the scientific criteria for assessing a new product. It confers the same rights and obligations on all Member States. It therefore guarantees to all EU citizens the same standard of assessment wherever the final marketing of the product in the EU.

EPPOSI welcomes the work of EMEA to date, and calls for all biotechnology and new active substances to be approved through the centralized marketing authorization system of the EMEA. The capacity of the EMEA should be strengthened to ensure its ability to maintain a state of the art, scientific, centralized marketing authorization procedure. A strong centralized procedure will allow the introduction of new aspects providing flexibility within this system to ensure the most effective patient access to medicines.

ACCELERATED REVIEW, CONDITIONAL APPROVAL (AND COMPASSIONATE USE) (Regulation, Article 13 and Article 68)

Article 6.4 of Regulation 2309/93 establishes that EMEA “shall ensure that the opinion (on a request for marketing authorization) is given within 210 days of the receipt of a valid application”.

Accelerated Assessment Procedure

Recognising the importance of therapeutic innovation, the Commission has proposed to reduce this time period for marketing authorization from 210 to 150 days in the form of accelerated assessment procedure for ‘medicinal products of major interest from the point of view of public health and in particular from the point of view of therapeutic innovation’. This ‘accelerated assessment’ registration process would ensure that EU scientific assessments for major new medicines are as fast, if not faster than those performed by the US FDA, and to increase the availability of new and innovative medicines on the European market, while maintaining the same stringent standards of review prior to approval.

EPPOSI welcomes the introduction of the accelerated assessment option, granting marketing authorization in 150 days for innovative medicines that address unmet medical needs in serious and life-threatening diseases, including orphan medicines.

From Exceptional Circumstances to Conditional Approval

The current EU pharmaceutical legislation allows for applications in exceptional circumstances (annex G of the Directive), a situation which is retained in the Commission proposal.

The marketing authorization under exceptional circumstances may be granted if the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

* the indications for which the product in question is intended are encountered so rarely that

- the applicant cannot reasonably be expected to provide comprehensive evidence, or
- * in the present state of scientific knowledge, comprehensive information cannot be provided, or
 - * it would be contrary to generally accepted principles of medical ethics to collect such information,

The granting of such marketing authorization will include specific obligations on the marketing authorization holder such as an obligation to complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile.

EPPOSI welcomes the Commission proposal to retain the possibility of granting marketing authorization under exceptional circumstances, and calls for Annex G of the Human Use Directive to become the standard option for marketing authorization of ‘Orphan’ medicines.

Compassionate Use

There is currently no formal EU-wide definition of compassionate use or expanded access programmes for medicinal products. Most EU countries currently have some form of compassionate use programme, such as the French ATU programme, but there is no harmonisation. As such, a patient with a life-threatening disease may or may not benefit from early access to therapies depending on their place of residence.

Article 68 of the modified Regulation is a new proposal aiming to establish some consistency among compassionate use programmes in the EU. It allows for medicines of major public health interest to be made available to certain patients prior to full marketing authorization, under certain conditions. These products may be made available until they are either actually placed on the market in Member States, or a negative opinion for marketing authorization has been granted by the EMEA.

Compassionate use programmes differ from the ‘exceptional circumstances’ as outlined above in that the product may be provided in serious or life-threatening cases to treat a patient before the formal marketing authorization is finally granted.

EPPOSI welcomes a proposal for a more systematic implementation of compassionate use programmes Europe-wide for products which have been submitted to the regulatory approval process and have significant therapeutic benefit. EPPOSI has organised a Workshop on Timely Access in Barcelona in June 2002, for which a separate printed report is available. The report provides also for some recommendations related to compassionate use programs in Europe, including the implementation of an ATU-like system in Europe.

SCIENTIFIC ADVICE (Regulation, Article 51)

The Scientific Advice process integrated in EMEA’s Centralised Marketing Authorisation procedure provides a key to ensuring a positive result for the applicant. Marketing Authorisations granted by the EMEA are based on the three criteria of quality, safety and efficacy, as

laid out in EU pharmaceutical legislation. The scientific advice process does not, in itself, ensure a marketing authorization, but rather allows for continued dialogue, and effective focus of research capacities.

In this process, EMEA advises companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products and in particular, on compliance with good manufacturing practice.

The ongoing scientific advice is of particular benefit for SMEs with little experience of the complex marketing authorisation process, or in those cases where previous experience with a medicine is limited, eg for new therapeutic breakthroughs, innovative products for severe conditions or rare disease, orphan medicinal products. This is often the case for innovative biotech products.

An effective scientific advice process must include not just a ‘once off’ consultation on the application, but become a continuous dialogue between the applicant and EMEA, allowing early information and discussions on possible issues. This process should include regular checkpoints and meetings between the applicant and EMEA/rapporteur.

EPPOSI welcomes EMEA’s commitment to the scientific advice procedure for centralized applications, and calls on EMEA to expand this to a continual and improved dialogue with applicants. We regret that patient participation is not foreseen in this key process.

INFORMATION TO PATIENTS (Directive, Article 10.4)

A five year pilot scheme is to be developed in collaboration with pharmaceutical companies and EMEA which would allow patients to request information on AIDS, diabetes and asthma from pharmaceutical companies in certain circumstances.

This issue has long been a hot topic in Europe, particularly since the developments of electronic information media such as the internet. The right of patients to access information directly is sometimes confused with product advertising.

This scheme however is a timid attempt of the European Commission to address the issue. We are particularly surprised by the fact that areas which would benefit proportionately greatest from shared information, such as in the case of rare diseases, have not been included in the proposal. Patients suffering from rare diseases have already developed important systems.

EPPOSI welcomes the Commission proposal to address the issue of information to patients. We call on the European Parliament to recognize the special situation of life-threatening and serious diseases, including rare diseases and importance of access to information for these diseases which by their nature attract less attention in broad media, policy and scientific circles. We call for the establishment of a clear framework for ethical principles on provision of information based on transparency and dialogue.



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Programme

‘Welcome’

by IJsbrand Poortman, Chairman EPPOSI
with ‘Statements from the Patients’ Perspective’

Keynote speaker:

‘The EU Pharmaceutical Review Process: What is in it for patients?’
by Alastair Kent, President EAGS

Reflections from Industry

by Dr. David Meeker, Genzyme
‘Development of Therapies for Patients with Genetic Diseases’

Reflections from Science

by Prof. Dr. Jean-Jacques Cassiman
‘Diagnosis of Genetic Diseases’

Closing Remarks

by Prof. Dr. Gert-Jan van Ommen, president ESHG

EPPOSI would like to express its gratitude to Genzyme Europe
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EPPOSI Dinner Debate

‘From Diagnosis to Therapy for Genetic Diseases: Setting the Political Agenda’

‘Welcome’

by IJsbrand Poortman, chairman EPPOSI

As chairman of EPPOSI, I most heartily welcome you to this dinner debate. I thank you for accepting our invitation and for your willingness to share your views and experience with us.

Since its foundation in 1994, EPPOSI has organised various debate activities in the area of modern medicine. These discussions broaden our horizons and deepen our insights. They lead to well balanced and well documented standpoints which are put forward to the Commission and to the Parliament or made available to the public at large via our series of publications.

EPPOSI’s mission is to have a European partnership of patients’ organisations, science and industry working to healthcare policies towards treatment and prevention of serious diseases. EPPOSI is currently involved in a number of topics such as rare disorders. EPPOSI encourages research on orphan medicinal products and fast market access. On June 6 and 7, EPPOSI will organise an expertmeeting on this subject in Barcelona under the title ‘Timely access to New Medicines’.

In October EPPOSI organises her third annual European conference on orphan diseases and orphan drug development in the Senate venue in Rome.

Some other subjects are policy development and regulations relating to innovative medicine and east-west collaboration between patient organisations within the EU- context.

EPPOSI promotes dialogue concerning the acceptability, the limitations and ethical implications surrounding new innovative technologies including gene and cell-based therapies, devices and proper regulation of these advances.

A fundamental point of action of EPPOSI is the partnering of patients’ organisations together with science and industry on subjects of common interests. This dinner meeting tonight is as such an example. The time and place creates the right ambiance.

For the past 800 years Strasbourg was a free town and the place in Europe where European politics has been shaped. It has a central position in Europe. It is not surprising that the European Society of Human Genetics chose Strasbourg as the venue for its 34th Congress.

This location was chosen probably also to give a political sign, because we need to realise that Europe is still behind in comparison with the United States and Japan, a situation that will be discussed, this evening here in Strasbourg and tomorrow in Madrid.

In Madrid the first meeting will be held of the European dialogue on health and innovation. It is clear from all these discussions that we are making up for arrears. There is not too

much time for discussion while many families are waiting for new, effective drugs for their disease, and while the media bring almost every day the news about new discoveries, new technologies and new perspectives for drug development. We have to act now, adequately, rationally, responsibly and together. We have to weigh the risks and the chances and realise what is at stake. We have to use the opportunities of the new genetics and biotechnology. We have to develop a positive climate for new and innovative medicines in Europe.

EPPOSI Dinner Debate

‘The EU Pharmaceutical Review Process: What is in it for patients?’

by Alastair Kent, President EAGS

Alastair Kent, President of the European Alliance of Genetic Support Groups (EAGS) and a patient representative on the Committee for Orphan Medicinal Products (COMP), shared his personal views on a recent proposal of the European Parliament: ‘Review of the Pharmaceutical Regulations in Europe (26th November 2001)’.

EU Pharmaceutical Review Process

The aim of the Review is to rationalise and accelerate the approval process and thereby bring new medicinal products to the market in the interest of EU patients. The process involves scientific advice, provided by the European Agency for the Evaluation of Medical Products (EMA), conditional approval and the compassionate use of new therapies. The review process will also ensure the usual high standard of health protection. Its aims are admirable.

However, it is important to take care that in the rush to get effective and promising developments to patients, companies do not compromise their ability to pursue further scientific research. In this regard the new European Pharmaceutical Regulations are not entirely adequate. “On a scale of complexity from 0 to 9: they score about 300”.

EMA Collaboration

The proposed expansion of EMA’s scientific advisory role is important, because, with the progress of genetics, common disease categories will gradually fragment into smaller subsets of genetic diseases. As a result the present demands by regulators for efficacy and safety established in Phases I to III trials will not be tenable. A Phase III trial currently involves thousands of patients, scattered amongst different centres throughout Europe. Such trials will not be practicable in the future. For example, if one of the new disease categories were to occur in only 5000 patients across Europe, a Phase III trial involving 2,500 to 3,000 would leave few patients to serve as a market for the product.

Consequently, regulators will need to work with the pharmaceutical industry, the biotechnical industry, academics, patient organisations and the clinical community to determine a set of the necessary and sufficient criteria to provide for safety, efficacy and quality. Clearly, the manner in which regulators, industry, academia and science work together will have to be revisited.

Registering Products for rare diseases

The new regulations also refer to 'exceptional circumstances', when conditions are not right for traditional clinical trials. This provision applies particularly to rare genetic diseases. Some diseases can be so rare that scientific knowledge about them is currently inadequate. Furthermore, rarity can make it impossible to assemble all the information needed for a traditional dossier that would satisfy the Committee on Proprietary Medical Products (CPMP). Indeed, it may not even be known what would constitute the evidence to support a concept and move the debate forward.

A different situation arises when a treatment is seen to be probably effective. It then becomes unethical to withhold it from patients who would benefit. In that case post-marketing surveillance could be brought in to gather information in a sustained systematic way. I hope that Parliamentarians, officials in the European Commission and EMEA, people in industry and scientific advisory groups who work with the Commission, will find a rational way to accomplish this and then devise a reasonable set of criteria.

Compassionate Treatment

While nobody would argue against providing treatment compassionately to patients in urgent need, there is in fact no common European definition of 'compassionate use'. So, another matter that the Review of the Pharmaceutical Regulations should address very soon is how to standardise what is meant by 'compassionate use', when patients with life-threatening diseases cannot wait for treatment because they will be dead. It is the ultimate failure of clinical medicine if a doctor cannot deliver a potentially effective treatment because regulations are not in place.

Academic and Clinical Collaboration

About 8000 different rare disorders have been listed, and more would exist if subcategories were included. By contrast, a limited range of specialist knowledge is to be found within the Committee for Orphan Medicinal Products, the CPMP and EMEA. Therefore, when the EMEA deals with rare disorders or fragments of common disorders, it needs to draw on independent experts. Thus it is critical that academics, clinicians, and scientists working in the public sector, come forward spontaneously and engage with the EMEA to provide expertise. In collaboration with the regulatory authorities they could determine what should be stated in a dossier, so that regulators can be convinced when a satisfactory case is presented for market authorisation. This expert input would avoid much wasteful research and ensure that research programmes are focussed and effective. It is obvious that such guidance would also help niche companies, new enterprises and small to medium sized enterprises which may not be as familiar with assembling a dossier and processing an application, as some big pharma companies.

Patient Information

A great deal of hot air has been generated about giving patients information on genetic therapy. It has quite incorrectly been linked to the issue of direct advertising to patients. Few Europeans would wish to see unrestrained, direct advertising to patients that promotes medicinal products. On the other hand, information telling patients what they can expect from proposed therapies, their scientific rationale, limitations and possible side effects would be valuable. Here, too, the EU proposals are quite insufficient.

Quo Vadis?

The 'Review of the Pharmaceutical Regulations' proposes a five year pilot study to determine how best to develop communications between regulators, industry and patients. The study is restricted to AIDS, diabetes and asthma - just these three diagnostic fields! It will be followed by an evaluation, before further action. This is ridiculous. Why consider just AIDS, diabetes and asthma and not cancer or haemophilia? Do patients with diseases other than these have less need of access to information over the next five years? Of course they don't! The proposal by the Commission to highlight just these diagnoses is to me nothing other than a stalling exercise. They don't know what to do, and a pilot study is simply patronising to patients.

It is obvious that information provided by companies is partial. Their research is not a complete exploration of all possibilities, under every conceivable condition. Also, some people might have a vested interest in obscuring aspects of the information. Conversely, patients can evaluate the information they receive and consult with their physician, before deciding whether a proposed treatment is likely to be good, bad or irrelevant. Numerous patient groups, representing a wide range of diseases are asking for information now and they will evaluate it. The idea of conducting a study in three diagnostic indications, then to reach a conclusion after a further five years, is quite frankly a delaying tactic that should be resisted. The European Parliament should reconsider this idea, because it is unworkable.

Conclusion

Mr. Kent concluded, however, that there is much to welcome in the 'Review of the Pharmaceutical Regulations', but it should include a process of continuous dialogue, an iterative, evolutionary process to develop and accelerate regulatory approval. "I hope that eventually we shall have a system that enables new innovative, effective treatments to reach patients quickly, on the basis of need rather than geography, ability to pay or other non-medical factors that currently stand between us and the treatments we need."

Alastair Kent's remarks were entirely personal and should not be taken to indicate the policy of any organisations with which he might be associated, however loosely.

EPPOSI Dinner debate

Reflections from Science

By Prof. Dr. Jean-Jacques Cassiman
'Diagnosis of Genetic Diseases'

From simple chromosome analysis in the sixties, genetic services have been able to progressively translate new insights into the Human Genome, combined with a spectacular progress in technology, into a set of methods, which allow an ever more precise and rapid identification of chromosomal and DNA defects, sequence variants and polymorphisms in individuals affected by a genetic disease or carrying a disease trait. Nevertheless, at present only about 1500 genetic diseases from the presumed 10,000 entries in the OMIM database can be identified by these methods.

In the last twenty years the achievements of science and technology have also opened the way for predictive testing, which allows the presymptomatic identification of individuals who have a 100% risk of developing a genetic disease, such as Huntington disease, later in life. More recently, predisposition or susceptibility testing was introduced for frequent and life threatening cancers, such as Breast/Ovarian and Colorectal cancer. Clearly such susceptibility testing, the identification of a very high or high risk for frequent physical or psychiatric diseases will become quantitatively the most important testing activity in the future. Indeed all frequent diseases and behavioral variants have a genetic component, which in time will be uncovered. In the future it will become theoretically possible to draft a gene-pass for an individual, which will contain all the gene variants, which increase his risk for a particular frequent disease or behavioral trait. In a similar fashion, the genetic predisposition of a person to metabolize particular drugs in a variable way will be tested using sets of SNPs (Single Nucleotide Polymorphisms).

Rather than submitting an individual to repeated testing for these different indications at different times of his life, it will probably become routine to test newborns for all genome variants and to keep this information in their medical file until the information can be put to practical use at different times of their life. The combination of prenatal or pre-implantation diagnosis, allowing the potential elimination of all serious diseases, including autism and chromosomal defects, before birth, with newborn screening aimed at selecting the best prevention strategy and at establishing individual drug profiles to avoid hypertension, rheumatoid arthritis or osteoporosis and many other debilitating diseases would result without any doubt in a carefully laid-out life long prevention strategy, which would be responsible for a dull, depressing and boring life for all citizens. Creativity would have been eliminated together with predisposition to unacceptable social behavior while all interest in sex would have greatly disappeared, as more human clones will grow up without the ability to respond to pheromones.

Before we move into this specter of a 'Brave New world' we should, however, realize that even today genetic testing is still in its infancy and therefore shows all the signs of infantile diseases. Testing services are provided mainly by research laboratories, which in many cases lack all the strictly controlled service procedures and protocols. This leads to intolerable high levels of errors (around 10% or more) as shown by the different external quality schemes for genetic testing organized at the European level. Due to a lack of regulation in many countries, whoever is interested in genetic services, can set up a laboratory. While many tests should be done after an appropriate genetic counseling session, over the counter testing kits could find an unusual high number of naïve customers. As long as our family physicians are not appropriately trained in providing basic information on the meaning and limits of genetic tests, one cannot accept that a request for testing is formulated outside the context of appropriate counseling.

Informed consent has as many variable meanings as there are physicians. Even in genetic centers, the way to obtain consent from an individual may vary between geneticists. Clearly, the need to standardize and organize all aspects of genetic services in centers, under internationally recognized accreditation norms, is becoming a necessary step to guarantee uniform quality services.

Many genetic diseases are rare diseases. For some of these the number of patients all over Europe may not exceed a few hundred to a few thousand. The availability of testing facilities for these diseases in all countries would therefore be a non-sense. A limited number of centers, expert in these diseases and willing to provide high quality testing services for all European patients, would be meaningful providing that the National authorities allow the testing outside their borders, which is not always the case. The same can be said about the cost of these tests. The advent of the Euro has made it clear that genetic tests have different economic values in different European countries. It must be a harrowing experience for a patient to try to find quality genetic services in different European countries at an affordable price. The situation is even getting worse as genetic tests are moving from the genetic labs into other service labs of the hospitals. Harmonization of this service does not seem to exist in the European dictionary. While genetic testing is definitely in need of getting organized, some 'colleagues' have not been able to resist the temptation of implementing the few and barely relevant predisposition tests for genetic susceptibility. Using home made tests or impressive micro-array systems a few gene variants can be tested in the predisposition to endometriosis, diabetes, rheumatoid arthritis and even pregnant women can be given a risk figure for the normal outcome of their pregnancy. The obtained risk factors have not been validated and are in most cases meaningless. This illustrates how a lack of harmonization and consensus can lead to excesses.

The committee on Professional and Public Policy issues of the European Society of Human Genetics has produced a background document as well as guidelines on the implementation of population screening programs for genetic diseases. This document, which is available on the Society's website, gives an excellent overview of the limits and benefits of screening and suggests clear and well considered criteria by which these screening programs should abide. It could be translated fairly easily into a European Directive, providing the European Parliament is willing to consider it. And our clients in all this? Geneticists can consider themselves lucky that they can get away so easily with less than optimal services. People trust human geneticists almost blindly. Of course our genuine efforts to help them, in sometimes emotionally difficult situations, has gained us a positive appreciation. We cannot, however, rest too long on this wreath of lauders.

In conclusion, genetic tests are and will be powerful tools, which can be put to the benefit of the health of society if correctly applied, with respect of the individual freedom of choice and accompanied by correct information about the procedures and their potential consequences. Together with the patient organizations, we should be able to convince our democratically elected representatives in the European parliament to draft a directive which creates the framework that will guarantee optimal and correct use of genetic tests and genetic services at affordable cost for the benefit of every citizen.

EPPOSI Dinner Debate

Reflections from Industry

By Dr. David Meeker, Genzyme

‘Development of Therapies for Patients with Genetic Diseases’

Dr. Meeker reviewed the achievements, hopes and obstacles, special to orphan drug development. He noted that orphan drug legislation in the US has provided the incentive for more than 50% of the biotech start-ups since the mid-eighties. From 1995-2000 almost 50% of approved biopharmaceutical products were orphan drugs. Over 230 therapeutic agents have been approved as orphan drugs since 1993, benefiting ten million or more people. Progress has been incredible.

Today, four companies are investing significantly in the field of lysosomal storage diseases, a subset of the field of rare genetic disorders. The results, so far, are two enzyme replacement therapies (ERTs) for Fabry’s disease, an ERT (Aldurazyme) for mucopolysaccharidosis (MPS I) that has completed Phase III trials and is moving through the registration process, and therapies for MPS II, MPS VI, Pompe’s disease and Niemann-Pick B disease that are now in development.

The Ceredase/Cerezyme example

The clinical focus of Genzyme is lysosomal storage diseases and the experience gained in developing a treatment for Gaucher’s disease provides an excellent lesson about the challenges inherent in developing therapies for rare diseases.

Gaucher’s disease (glucocerebrosidosis) is caused by a missing enzyme. The idea of treating it by enzyme replacement was quite obvious. The practical problem, however, was to produce the enzyme in sufficient quantities. This was achieved by Rosco Brady at the National Institute of Health, U.S.A, who ground up human placentas and extracted enough of the enzyme to treat a very small number of patients with Gaucher’s disease. With this therapeutic start Genzyme launched its first therapy about 10 years ago.

As there was no animal model, the money raised for the first trial was largely based on the results of a single patient. The trial then extended to twelve patients, treated ‘open label’ and their condition improved. There was no control group. Subsequently, Ceredase was approved as a medicine. Today, a child born with Gaucher’s disease and treated with Cerezyme (a recombinant form of Ceredase) can expect to lead a normal life, albeit with a genetic defect requiring a bi-weekly infusion, but no longer needs to perceive of him or herself as a patient.

Quite soon it was realised that 20,000 placentas per patient were needed to make enough enzyme to treat one patient for one year. Clearly, it would be an incredible undertaking to treat all patients worldwide, even though the disease is rare.

Nor was it an easy task to obtain regulatory approval to manufacture an enzyme extracted

from 20,000 placentas, especially in the early 1990's when AIDS was very much an issue. This required a phenomenal cooperative effort between regulatory agencies, industry, physicians in the field and patients.

Drug development delays

The principal requirement in conventional drug development is to demonstrate to the regulatory authorities that a treatment is both safe and effective. The process is long and it conflicts with the needs of those patients not in the trial who require treatment immediately. Why is the process so long?

Dr. Meeker cited many factors that delay the progress of orphan drugs. The number of patients for clinical trials is small and scattered, they must be found, and many will have to travel far to the study centre. In order to provide regulatory authorities with proof of efficacy a placebo control group may be needed, especially when subjective evaluations are utilized as the primary endpoints. In that case the trial design requires even more patients. Dose-finding studies when possible are extremely important but this also requires additional development time. In parallel, enough drug must be manufactured to complete the trials and satisfy future demand. Lastly, regulatory approval takes time.

Placebo controlled trials

Dr. Meeker then discussed the need for placebo controlled trials. Subjective, efficacy endpoints require a placebo control group to prove that apparent responses to treatment are genuine treatment effects. For example, the enzyme deficiencies of Fabry's disease and mucopolysaccharidosis (MPS I) are characterised by pain and restricted joint movements, respectively. It is very well known that these symptoms can improve considerably with placebo, since they are subjective. So responses to placebo must be subtracted from apparent drug effects to obtain a true estimate of efficacy.

One way to minimise the need for placebo would be to compare the results of drug treatment with data recording the natural history of the disease in each participating patient. This could be achieved if patient organisations would organise carers to document the natural history of disease in every patient afflicted, well in advance of potential therapy emerging from research. The data would make clinical trial findings more certain, reduce the development time and greatly increase the chance that placebo may not be needed.

Dose-finding studies

In the development of a drug it is necessary to produce proof of principle, maybe by an animal model if such exists. This evidence is obtained in the course of Phases I/II trials, conducted to provide dose information. In the case of Gaucher's disease, however, Dr. Meeker stated that the dose was selected quite arbitrarily, on the basis of how much material was available. "The choice was incredibly lucky. Had the dose been too low, the conclusion could have been that enzyme replacement therapy does not work. The entire project might have been thrown out." By contrast, in Fabry's disease a small, but conventional, Phase I trial included three different doses, allowing us to select a dose that had the best ratio between safety and efficacy. Nonetheless, it is still not certain that the selected dose is the best dose for every patient.

Availability of medicines

Genzyme is currently developing enzyme replacement therapy for Pompe's disease and both a transgenic form of the enzyme, as well as a cell culture variant, show clinical activity. Dr. Meeker pointed out that the original trial with transgenic material included four infants and three juvenile patients. In the natural course of this disease, almost all infants die within one year. The four infants are still alive well beyond one year. Although enzyme replacement therapy for Pompe's disease works, the transgenic program was stopped; not because of transgenic methods, but because of production issues.

The dose required to treat an infant is almost 40 times higher than for other enzyme deficiency diseases (Gaucher, Fabry and MPS I). It was not possible to make enough protein, with transgenic rabbits. The programme is still not viable. It was possible to treat a few patients, but not all of those who will need treatment. With Pompe's disease there is evidence that the treatment works, but not in every case. It remains necessary to establish the correct doses for infants and adults. However, regulatory approval may be given to treat infants who die within one year, but an endpoint has still to be decided for adult studies, and a placebo controlled trial may be necessary.

Compassionate use

One problem with the compassionate use of a drug was illustrated by Pompe's disease, above, where sufficient material exists only for patients in the trial. In the case of biologic products where manufacturing can be a significant challenge, the scale up of the manufacturing process occurs in parallel with the clinical development. The manufacturer must insure that they have enough product to continue to treat all patients entered in the trial. Dr. Meeker said that if the treatment were given compassionately to cases outside the trial, the pace of development to an approved medicine would be slow increasing the time until treatment was available for all patients with the disease. It is a difficult trade-off.

Collaboration is the answer

Dr. Meeker's conclusion was that the key to a successful outcome in orphan drug development lies in a partnership between patients, physicians, industry and the regulatory authorities. It should be stressed, however, that the goal is not simply approval for marketing. Registration of a medicinal product unfortunately does not mean its immediate availability. Reimbursement procedures, in certain countries, may take more than one year after formal EMEA approval. In short the ultimate goal is not simply drug registration but actual treatment of affected patients in all countries.

Drug development for rare diseases is expensive. Timelines may be delayed. On the other hand there is tremendous hope. New medications are being developed for more and more diseases. Companies are willing to invest in rare diseases. It is a new era. From a company perspective good medicine is good business. Take care of the patients and the business will care for itself.

EPPOSI Dinner Debate

Patients' Organisations: Communication is Crucial

by IJsbrand Poortman, EPPOSI

In response to David Meeker mr. IJsbrand Poortman, Chairman of EPPOSI and former Vice President of the International Pompe Association (IPA) recalled that a patient with Pompe's disease in Holland, 25 years ago, refused to accept there was no treatment for her condition. Her insistence started up a dedicated group with the mission to find a therapy. The researchers solicited asked how many patients with the disease were known?". In Holland there were five. Today that count has grown to eighty and a Pompe's Disease Group exists in 34 countries. Worldwide there may be 20.000 patients with Pompe Disease. The IPA together with the national groups try to trace them via website and other activities.

Patient groups for other diseases may be encouraged by the success of the International Pompe Association, which every two to three months organises a telephone conference so that the board of IPA and top managers of Genzyme can discuss progress and reflect on the state-of-the-art. Participants do not agree about everything, but they communicate about everything. It is a model that other disease groups could emulate. Regularly, information has been sent to the members (see websited: www.pompe.org.uk; www.worldpompe.org).

The lesson shows that communication is very effective. We are entering a new era that brings entirely new problems. Communication will help us to deal with them and patient organisations can play a strong role. However, most patient organisations have yet to invent the wheel. They are not trained for these new task and so need to learn from other groups. This was the case with the Pompe Association that followed the Gaucher Disease Group, which was the first to set up interactive discussions with Genzyme.

It is for parents with children with fatal diseases very frustrating to read in the papers that scientific research resulted in an effective drug and then to learn that it may take years before such drug is available. The many bureaucratic and time consuming procedures science and industry must follow cannot find much understanding. Therefore timely available, reliable, target group tailored, adequate communication for the families involved is very necessary for good understanding of the situation.

Good and top level communication between all stakeholders is vital This can avoid confusion and misunderstanding and also shorten the road towards therapy. Moreover, it can pave the way towards efficient and updated legislation and regulations and more focussed investments in basic and applied research.

EPPOSI Dinner Debate

Uncertain Prospects for Monogenic Therapy

By Prof. Dr. Gert-Jan van Ommen, President ESHG

Mr. Cees Smit, director of EPPOSI introduced Professor Gert-Jan van Ommen and said that EPPOSI was honoured to be host to the newly elected President of the European Society of Human Genetics (ESHG), who then gave his first public address in that capacity.

Prof. Van Ommen referred to the hopes of patients and patient organisations, that had been raised by the sequencing of human and mouse genomes, comparative analyses, new drugs and new technologies, which will lead to important therapeutic discoveries. It was encouraging, too, that at least one-thousand people, representing many professions, had attended the ESHG congress this year and listened to papers about the testing and screening of children and adolescents. This ESHG congress was in conjunction with the EMPAG, the European Meeting on Psychosocial Aspects of Genetics and was timely. "We all have such high hopes".

Impediments to Genomic Research

Nonetheless, Prof. Van Ommen was troubled that these hopes may not be realised because of misconceptions at the interface between science and society. It is possible that the therapeutic promise will not be realised if governments continue to regard personal freedom as their highest principle. The policy must be rethought. At present, many epidemiologists, worldwide, cannot access their sample collections because of privacy considerations. They had never considered to ask donors, at the time of donation, sometimes long ago, for consent to innovative experiments found only now to be necessary. People in all countries are currently fearful of what might be discovered in their DNA. Their thinking is simple: "Tell me what are your genes and I shall know who you are." However, this fear is unrealistic. For example, blood pressure is normally measured by putting an inflatable cuff around the arm, listening and reading from a gauge. Will anyone substitute tests for twenty genes and fifty environmental variables, each contributing 1%-2% of the value (and requiring years of validation), rather than squeeze a rubber bulb? The authorities exaggerate too much. The real issues are not so dramatic.

He continued by referring to a potential danger when politicians watch scientists and ask "Can we trust them to do the right thing?" or "Should we have that reviewed by ethicists and social scientists?" While interactions and co-evaluation between these disciplines is valuable, we, as medical scientists should be firm and clear. Some matters are debateable and others are wholly scientific. We can seek a consensus or vote for reproductive cloning, a ban on cloning, or only therapeutic cloning, but we cannot debate about the temperature at which water boils. Scientists must put more effort into explaining to politicians and the public at large, that certain issues lie at the interface of science and society, but others are entirely scientific. Many people who see the potential benefits of genomics to society are today concerned that society may be insufficiently receptive and not ready to accept the gift and translate this in a fundamental mistrust of even hard scientific outcomes.

Monogenic versus Multifactorial Diseases

Prof. Van Ommen was also concerned that the focus of interest today risks shifting too much from monogenic diseases to multifactorial diseases. He mentioned pressures from politicians, industry, and even scientists, for genomic research to be switched solely to common, multifactorial diseases. He argued, that scientists should not relinquish research on monogenic disorders and how to implement their findings. All that is beneficial to patients has resulted from the initial research into diseases like Duchenne, Cystic Fibrosis or Huntington's disease. "I know perfectly well what I am talking about because the first DNA-based prenatal diagnosis ever made, using DNA-markers, prior to finding the gene itself, concerned Duchenne muscular dystrophy and was achieved by our laboratory in 1985. In other words, the oldest person who owes his or her life to DNA diagnostics is now only 17 years old." Despite developments since then touching many diseases, much remains to be discovered about prenatal testing, and presymptomatic testing in children, minors and adults. That avenue of research cannot be abandoned in order to enter a multifactorial arena.

Clearly, the scientific community is supposed to negotiate with politicians and other interested parties and discuss with them what should be done about predictive tests for multifactorial diseases. All I am saying is that the methodology employed will not be different from that used in monogenic studies. As many have said, due to high resolution technologies of genomics multifactorial diseases will often be reduced to components that are much more monogenic than hitherto supposed. Consequently, the general public, politicians and industry must be told that, if we want to obtain the best social return from implementing our accumulated knowledge, we should base the implementation of common disease testing into society firmly on the ongoing research for monogenic disorders.

Reimbursement for Orphan Products

Prof. Van Ommen then turned to financial reimbursements. Governments must understand that without an adequate reimbursement policy, companies will not develop the technologies we devise. This is something that is often overlooked. From an industry point of view, a scientist who comes with a new treatment that works could lead a company to financial disaster if material cannot be produced for more than a handful of patients. The need for a reimbursement structure must be foreseen early in the developmental stage of a drug. It cannot be allowed that a company will go through all the proper channels and then discover that nobody knows how to obtain a refund for a drug that will earn only \$20,000 or \$30,000 a year. These issues are, in fact, much closer to the activities of scientists than had been thought so far.

Envoi

"For a time it was wonderful, we thought that 'in some far future' we would actually develop drugs for genetic diseases. However, many scientists like myself and colleagues have suddenly become aware that the problems just described do not lie ahead, they are with us now even while they will continue long into the future with regard to further diseases. I hope we can resolve these serious issues together with industry and political leaders, because we cannot find the answer alone."



EPPOSI'S MISSION: a European partnership of patients' organisations, science and industry working on healthcare policies towards treatment and prevention of serious diseases

KEY QUOTES FROM THE DINNER DEBATE

I hope that eventually we shall have a system that enables new innovative, effective treatments to reach patients quickly, on the basis of need rather geography, ability to pay or other non-medical factors that currently stand between us and the treatments we need.

Alastair Kent, president EAGS

Together with the patient organisations, we should be able to convince our democratically elected representatives in the European Parliament to draft a directive which creates the framework that will guarantee optimal and correct use of genetic tests and genetic services at affordable cost for the benefit of every citizen.

Prof. Dr. Jean-Jacques Cassiman, University of Leuven

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Dr. David Meeker, Genzyme Europe

For a time it was wonderful, we thought that 'in some far future' we would actually develop drugs for genetic diseases. However, many scientists like myself and colleagues have suddenly become aware that the problems just described do not lie ahead, they are with us now even while they will continue long into the future with regard to further diseases. I hope we can resolve these serious issues together with industry and political leaders, because we cannot find the answer alone.

Prof. Dr. Gert-Jan van Ommen, president ESHG

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