WORKSHOP ON ”RARE DISEASES AND ORPHAN DRUGS EUROPEAN PERSPECTIVE”

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Opening and welcome address by Curt ENGELHORN, President of the European Foundation for the Advancement of Medicine

May I greet you and tell you that we are exceptionally pleased to welcome you. We would like to sincerely thank you for having accepted our invitation to this workshop which, I hope, will contribute towards alleviating the conditions of those millions of people who are afflicted with rare diseases and who do not receive adequate medical care.

I would particularly like to thank Marlene E. Haffner of the FDA and Abbey S. Meyers from NORD®, who have taken upon themselves the long journey from the United States to join us here in Brussels.

I also want to express my gratitude to Jack Barnes from the British Department of Health for having accepted to be the Rapporteur Général and to Bruno Hansen from the Directorate General XII of the European Commission for having agreed to chair our meeting.

Last but not least, I would like to express my thanks to both Patrick Deboyser from the European Commission and to François Schiltz from the European Foundation for the Advancement of Medicine who have made this workshop possible.

In Europe today we take access to high-quality health care for granted. For most of us, the threat of disease has receded – at least until we are advancing in years – because of scientific progress and the application of medical science to the development of treatments for the conditions that afflict us. For most European citizens, expectations about the likely duration and quality of their lives are rising, and justifiably so.

A significant factor in this increase in well-being is a result of the introduction of drugs and other treatments to overcome the impact of many common diseases.

But for a substantial proportion of European citizens, there is no such hope. These are the people living in families affected by one of the thousands of different rare diseases that the human race is vulnerable to.

Many, though not all of them, have a genetic cause, assailing many members of the same family and transcending the generations.

For such people, the wish for good health and the desire to see a cure developed is just as strong as it is for those with more common health conditions, but their hopes are doomed to disappointment.

This is partly due to the fact that the European Union is not yet equipped with a specific legislative framework concerning drugs and other treatments to overcome rare diseases. The reason for this was not unawareness or disinterest on the part of the European Commission, but “helplessness” in front of administrative, political and economic barriers which have marked the diversity of the European Union’s territory.

But since the internal market for medicinal products has become a reality, and a uniform marketing authorization is now instituted, nothing whatsoever justifies such a gap in the European Union, and therefore the European Commission made the decision to draft orphan medical product regulations. These are to some extent based on the regulations that have already existed for 15 years in the United States, where over 150 orphan medical products have been brought onto the market, and over 600 “indications” have been granted.

In consideration of the success of the American legislation (and of comparable legislation in Japan and Australia), the decision by the European Commission to introduce similar regulations for the European Union is welcomed by clinicians, academics, patient support groups, industry and, above all, by the patients themselves.

These regulations will provide a range of incentives to help ensure that promising research is turned into useful products for the benefit of patients affected by rare diseases. Some of the measures proposed are financial – for example, the waiving of fees to be charged by EMEA to approve marketing an orphan drug –, or otherwise practical help, such as help with protocol to ensure proof of safety and efficacy. Together they will, we hope, create the right conditions to make the development and manufacture of orphan medical products an attractive proposition.

The European Foundation for the Advancement of Medicine welcomes this initiative by the European Commission, and is prepared to give wherever it can its support to the Commission, but also to centers which provide information on rare diseases or do research in the field of rare diseases and orphan drugs. Therefore, towards the end of this workshop we should try to define the next steps to be taken to guarantee a successful implementation of the regulations worked out by the Commission.

Let me say, to finish, that the Foundation is proud to sponsor today’s conference, and looks forward to the debate by the European Parliament and the Council of Ministers as the orphan medical product regulations are steered towards the statute book.

I thank you for your kind attention. I hope you will find this an interesting event and that you will participate in further discussion as we go on during the day. I would now like to invite our chairman, Bruno Hansen, to take the floor.

Introduction by Chairman Bruno HANSEN, Director Science, Research and Development, European Commission, DG XII

I want to start by thanking the organizers, the newly established European Foundation for the Advancement of Medicine, and to congratulate Mr. Engelhorn and Mr. Schiltz for the very timely choice of the topic they have decided to tackle in the first workshop of the Foundation, namely rare diseases and orphan drugs.

In the field of rare diseases, as in other fields, different players come together and interact: the pharmaceutical industry, the national health policy authorities, the patient groups, the European Medicines Evaluation Agency, and lastly, as a facilitator, the European Commission services.

What we need to do is to identify and to come to grips with the most appropriate forms of interaction between those players. In doing so, we need to refer to the valuable experience accumulated in other regions. As has already been mentioned, the United States addressed this problem back in 1983, with the adoption of the Orphan Drug Act. The U.S. therefore has enormous experience in this field, and we are happy to learn from them. Japan followed with similar legislation in 1985.

Mr. Engelhorn has explained very well why we are now coming as a Union to fill this gap in our legislation. Let me recall the reasons why rare diseases have taken a higher profile on the European agenda.

- First, we need to pool at European level the cases and the expertise. The greatest obstacle for studies on rare diseases is the relative lack of knowledge about them and their treatments. Any evaluation of a therapy is almost impossible in a single country due to the rarity of the patients.

- As for the research aims, we need to pool the resources available in order to have a critical mass of information necessary to conduct research on rare diseases.

- Our policy should serve public health priorities in order to facilitate the development of drugs for the treatment of rare diseases, which generally correspond to life-threatening diseases or severely disabling chronic diseases, when no alternative treatment is available. The ultimate goal is to provide patients with drugs fulfilling the current scientific criteria of quality, safety and efficacy.

In February 1995, DG III and DG XII took the initiative to convene in Brussels an expert group meeting with the objective to discuss research priorities and regulatory issues related to rare diseases and orphan drugs, and many of you here were present at that meeting.

That preparatory work led to the preparation of a European Commission proposal for a Regulation on Orphan Medicinal Products, which will be presented to you this morning by Mr. Deboyser.

Since 1994, under the Fourth Framework Programme, research on rare diseases has been supported, and you will hear more about the details of this research from Mr. Fracchia.

As a matter of fact, research plays an important role in this context. First, as you know, some fundamental physiological functions are common to rare and more frequent disorders. Increasing the knowledge on rare diseases can help the understanding of more prevalent ones. Second, at the individual level, the tragedy of a family with a rare disease – often a child – is 100 %, and modern medicine should offer the same support and treatment as for more common disorders.

Third, progress in the development of treatments, diagnostic methods and cures is slow because of the lack of research funds and investigators.

We are here in a situation where we have to promote, on the one hand, the quality of life of our citizens, whose demand for safe and effective medicines is ever increasing, and who do not have to suffer discrimination because of the rarity of their disease; and on the other hand, to sustain and promote the competitiveness of our pharmaceuticals and vaccines industry in a coherent set of measures of industrial policy. The set of measures, incentives and tools which we have at our disposal, including the Framework Programme for Research, should be sufficient to initiate a sound cluster of activities in support of rare diseases.

Let me spend one word on the Framework Programme. Without pre-empting what other speakers will say during the morning, I want to draw your attention to the fact that the Commission has proposed to continue to fund research on rare diseases in the Fifth Framework Programme (1998-2002), as a support to its orphan drugs policy. This is also in line with the objectives of the Commission's action programme on rare diseases within the field of public health.

I am confident therefore that today's meeting will contribute to the goals which we have set.

You will hear this morning three speakers from the Commission services, who will tell you about the aspects linked to regulation, research and prevention in this field.

Morning Session

The European Commission and the European Agency for the Evaluation of Medicinal Products (EMEA) present their programmes regarding rare diseases and orphan drugs

Patrick DEBOYSER, Head of Pharmaceuticals & Cosmetics, European Commission DG III

The proposal for a European Parliament and Council Regulation on Orphan Medicinal Products

I would first like to thank the European Foundation for the Advancement of Medicine, Mr. Engelhorn and Mr. Schiltz, for having organized this meeting. I know I am credited with some of the merits; I think this is a very good deal and I hope we can renew it – they do all the work and I get half the credit!!

The draft Regulation on Orphan Medicinal Products, which I have the pleasure to present to you today, is known to most of you. I have already discussed some aspects with most of you here today, and I hope that you will recognize that some of the ideas and remarks that you have made to us in recent months have been taken into account. Don't look for too many changes in comparison with Draft 6. The only differences are in the definition of "similarity" in the article on market exclusivity, and the financial statement, which is at the end of the Regulation. When the Commission makes a proposal to Council and Parliament, it must be accompanied by a financial statement which explains how we are planning to fund the new policy which is being proposed. This is what is currently blocking the passage of this proposal through the Commission.

But first, especially for those who are perhaps less familiar with the draft Regulation, I would like to go into the scope of the proposal; the criteria for the designation, which is one of the central clauses in the proposal; the committee for orphan medicinal products which we propose to establish; the procedure for the designation of orphan medicinal products; the benefits, notably market exclusivity, which will go to products which have been designated; and the time-scale and procedure for the adoption of this Regulation.

First, very briefly, the scope. The benefits which will arise from the Regulation will only benefit medicinal products for human use, as defined by Directive 65/65/EEC. This is any medicinal product which is intended for the diagnosis, prevention or treatment of a human disease. This definition excludes medical devices and food supplements, for instance. I am not saying that there should not be a policy for medical devices and food supplements, but it would not be possible to cover these areas, which are useful in the prevention, treatment or diagnosis of rare diseases. It is just that they simply could not benefit from the clauses of this Regulation, due to the technicality of this Regulation being in the framework of pharmaceutical legislation.

It will not cover veterinary medicinal products; I think there would be a need to have an orphan drug policy for veterinary medicinal products, especially for the treatment of minor species. I hope that as soon as this draft is in Council and Parliament, my colleagues and I will be able to start working on the research and development of drugs for the treatment of minor species in the veterinary sector.

As Mr. Engelhorn quite rightly said, the Regulation is basically modeled on the US Orphan Drugs Act. We have taken the benefit of 15 years of experience in the United States, and one of the key lessons that we have learned is that the best way of describing, selecting and designating orphan drugs is to base oneself on the epidemiological criteria. In the early days, in 1982-1984, the criteria were economic, and there were very few – perhaps a couple – designations based on economic criteria. This prompted the FDA and Congress to change the emphasis and put it on prevalence. This is what we plan to do in Europe as well.

There is some explanation for choosing epidemiological criteria in the explanatory memorandum to the Regulation. It was obvious that we ought to be consistent with the Programme on Rare Diseases which colleagues from DG V had developed. In their proposal, which is currently being discussed by Council and Parliament, they have chosen a prevalence criterion of 5 in 10'000. If you relate that with the Orphan Drugs Act in the U.S., this would work out as 7.5 per 10'000, which means that we are slightly below the prevalence criterion that was selected in the United States.

Perhaps it would be interesting to see what diseases qualify under the Orphan Drugs Act in the U.S., but which would be left out under our proposal. This is something which perhaps would be useful for the debate in Parliament. It is quite obvious that Parliament and Council will have a debate on the prevalence, and they may revise this.

In Japan, as you know, the criterion is 1 in 50'000, which related to the population would mean 4 in 10'000. So with a criterion of 5 per 10'000, we are in-between the Japanese and the U.S. definition of orphan drugs. Again, as I have said, this is still open for discussion in Council and Parliament. I believe that the bulk of the rare diseases would be covered by any of the criteria, whether it is 4.5 or 7.5 per 10'000.
In response to a request from colleagues in DG XII, we have also elected to take into account life-threatening and seriously debilitating diseases, even when the prevalence is above 5 per 10'000. Obviously then you need to demonstrate that the product would be uneconomical to benefit from the qualification.

Again, this is something that we are prepared to discuss, provided that the discussion takes place in Council and Parliament and does not delay the passage of the proposal by the Commission.

The criteria will have to be used by a committee. In looking for a committee, we have thought to use the existing structure, which in the case of Europe is the European Agency for the Evaluation of Medicinal Products. The EMEA is currently running the scientific committees of medicinal products, the Committee for Proprietary Medicinal Products (CPMP), and in the veterinary sector, the Committee for Veterinary Medicinal Products (CVMP).

The first question we had to ask ourselves was whether we should use the CPMP for designation. I believe there are arguments both for and against using an existing committee. One strong argument against is that the CPMP is already overworked with its current tasks. Another one is that it would give a lot of power to a single committee, which would have to rule on the designation and then, later on, on the authorization to the market of the same product. This is a lot of power. I know that in the U.S. there has been a formal separation of the Office on Orphan Drugs and the Centers for Drug Evaluation and Biological Evaluation and Research, which are responsible for the drug approval.

The alternative is to create a new committee. I am afraid this is the usual response in the EU – when you have a new policy, you simply create a new committee. But I have explained the reason why we are moving in this direction. The committee would be composed of representatives from the Member States. I think this is important because the Regulation has taken away some competence from the Member States as regards market authorization through the market exclusivity clause. It is important to maintain a link with the Member States.

We also hope that the committee will have representatives from the patient organizations. This is a novel concept in the EU to have patients represented on a committee which does other things than advise the Commission. This committee will take decisions. There is no precedent, but why not create one? I think that the patient organizations have demonstrated, both in the U.S. and in Europe, their expertise in this matter. For institutional reasons, it looks as if Parliament could not possibly appoint these members, so they would be designated by the Commission.

We also propose that the Committee for Orphan Medicinal Products should consist of one member nominated by each Member State, three members nominated by the Commission to represent patient organizations and three members nominated by the Commission on the basis of a recommendation from the Agency.

The procedure should be flexible and speedy. The validation would be done by the EMEA Secretariat. An opinion would be given by the new committee within 60 days, and the Commission would have to transform that opinion into a decision. This is a mechanism which we are currently using for the marketing authorization; however, we propose to make it quicker and simpler than the current system of granting authorization.

What would be the benefits for products being designated? First, I think that designation, as has been demonstrated in the United States, is already a benefit in itself. If you get designated as an orphan medicinal product, irrespective of what will then happen, it looks as if this is already an incentive.

But, of course, there would be more than just that. There would be the availability of protocol assistance. We know that this has not been used very much in the United States, but we don't see why we should not try it in Europe. After all, Europe is different and we are told by patient groups that this would be important.

Another incentive would be direct access to the centralized procedure. Of course, most of these drugs would be innovative. Many of them would be biotech drugs because we talk to a large extent about genetic disorders. However, the company would not have to demonstrate that it qualifies for the centralized procedure; there would be immediate access.

We hope there will be a fee waiver; under the new Commission proposal for a centralized application the fee is currently 200'000 ECU. This is something which can be a problem, and therefore there would be a partial or total fee waiver to be administered by the EMEA with funds provided by the European Commission. But, as we know from U.S. experience, the main incentive would be the market exclusivity.

The conditions for benefiting from market exclusivity is that the drug must be designated as an orphan medicinal product, and it must have received an EU centralized authorization – this is very important. We are not closing access to the decentralized procedure on mutual recognition for orphan medicinal products, but the market exclusivity would only be granted to products going through the centralized procedure – there are technical and legal reasons for this restriction.

We propose that the market exclusivity would be ten years; in the United States it is currently 7 years, so let's do better!

The scope of the exclusivity would be limited to the same indication for a similar medicinal product. This is a technical matter, but a very important one.

Again, as we know from the experience in the United States, especially if you talk about complex proteins – we talk about a lot of biotech products –, and this is why we have asked the new Scientific Committee on Medicinal Products to draft guidelines for us on the notion of ”similarity” in medicinal products. Obviously we referred to that Committee as the equivalent FDA guidance on the notion of ”same drug”.

In response to a request by colleagues in DG XXIV, there would be a possibility of withdrawing the exclusivity after six years, but under very strict conditions. This would have to be requested by a Member State. The reasons for withdrawing the exclusivity would be that the prevalence criteria are no longer met, or that an excessive price is being charged or excessive profit is being made on the drug by the sponsor. This is a precaution to cope with the counter-argument that some blockbusters might go through. Again, experience in the United States shows that yes, there are a couple of them, but very few. At conferences and in literature in the U.S. the same product, EPO, and the new hormones, perhaps, are continually mentioned, but these are just 2 or 3 drugs out of around 800 designations. It does not seem to be a real problem. If there is a problem, the withdrawal clause will allow us to cope with it.

There would also be derogation to the exclusivity, notably when the second applicant has the authorization of the first company. This is called “informed consent”. If there is an insufficient supply, or if the second product is clinically superior, this would be a case for a Member State to grant a second authorization.

What are the time scales and procedure? Firstly, the Commission has to finalize its proposal. As I have already mentioned, the only problem left within the Commission is the financial statement, the budget, which we are proposing. We are still in discussion with colleagues in DG XIX. We hope that we will come to an agreement, and that we will be able to table the proposal for adaptation by the Commission perhaps at the end of May or in June. The good news is that Commissioner Cresson and Commissioner Flynn have accepted to be associated with this proposal from Commissioner Bangemann. It will then be for Council to reach a common position and the co-decision procedure after Parliament has delivered an opinion in the first reading. Parliament will have the ability to propose amendments in the second reading. My rough guess is that all of this procedure will take around 15 months, so that if the Commission can adopt its proposal in May or June, we can expect the Regulation to come into force at the beginning of the year 2000. This is why our financial statement starts in 2000. I think that if by June the Commission has not approved the proposal, some of us will have to sit together and look at strategies to make it tougher, because as we all know, this is a very important proposal. It is not just another piece of legislation which we are proposing to complete the Single Market; this is about patients getting access to drugs.

They are entitled to such treatment, and if the market is not providing the drugs for the patients, I think that it is for society to take the appropriate steps, and this is what we are trying to do with this proposal.

Giovanni N. FRACCHIA, Medical Research, European Commission DG XII

The Biomedicine and Health Programme; Development of orphan medicinal products and support of fundamental clinical and epidemiological research on rare diseases in the European Union.

First I would like to thank Mr. Engelhorn and Mr. Schiltz, the organizers of this meeting, for the invitation to this conference on rare diseases and orphan drugs.

It has been estimated that there are more than 5000 identified rare disorders affecting tens of millions of people throughout the world.

Personnel in primary health care are familiar with the clinical characteristics and morbidity of common diseases. And they are often supported in the management of these illnesses by structured care programmes issued by appropriate professional organizations, who provide standards of good care and treatment guidelines. However, most of the personnel in primary care will at some time become involved in the management of rare, often genetic illnesses with chronic nature, some of which may in fact be more common than generally known.

Several studies have demonstrated some of the current problems faced both by health professionals and patients with rare diseases. These include:

- major lack of information about the ongoing clinical research;
- limited knowledge of experts and support services;
- limited access to specialized health services or to approved therapies;
- greater cost of providing advice, diagnosis and health interventions for rare diseases;
- lack of national financial resources.

In addition, researchers and clinical investigators have acknowledged that research projects on the development of treatments for rare diseases are unlikely to be funded, due to their limited economic value. Therefore, it seems that the needs of patients are unlikely to be met, not only because of a lack of treatment, but also because a lack of knowledge concerning the causes, prevention and diagnosis of these diseases.

As Mr. Hansen has already mentioned, in 1995, on the initiative of the DG XII and DG III, an expert group was convened in Brussels with the objective of discussing issues related to rare diseases and orphan drugs. The group of experts succeeded in identifying a series of objectives to be considered as recommendations for action at Community level in the fields of research and development and regulation on rare diseases and orphan drugs.

The expert group recognized that in Europe the greatest obstacle for studies on rare diseases is the relative lack of knowledge about them. In addition, the treatments are often frequently inappropriate and ineffective, and may even in some cases be harmful. At the time of the meeting, neither a systematic review nor an orderly classification or identification of these diseases had been reported. Any evaluation of a therapy is almost impossible in a single country due to the rarity of the patients. The expert group also concluded that the present situation indicates that there is a need for developing randomized clinical trials to validate currently used therapies or to establish new therapeutic approaches.

According to the recommendations it would also be important to establish a European network of clinical trials on rare diseases with the collaboration of already existing centers. This kind of collaboration on rare diseases may have the additional advantages of helping patients with more common diseases. As a matter of fact, the investigation of rare diseases can sometimes shed light on the mechanisms behind more common chronic diseases and provide better opportunities to establish preventive measures.

Under the current Fourth Framework Programme for Research and Technological Development, research on rare diseases and orphan drugs has been supported under the Specific Programme on Biomedical and Health Research (Biomed 2). This is a medium-term planning instrument to support research at European level, and Biomed is part of the Life Sciences Programme, with a budget of some 1.5 billion ECU for the five-year period 1994–1998. So this Programme is now coming to an end. The aim of the research in the area of rare diseases, which is one of the objectives of the Biomed Programme, is to pool the knowledge on basic and clinical research into pathogenesis, genetic aspects and prevention of rare diseases in order to arrive at a critical mass of information. This supports the subsidiarity principle, which is a basis for the Programme, and also contributes to "European added value". Research in this field is also interlinked with other areas, such as human genome (e.g. inborn errors of metabolism, a major area of research), pharmaceutical research (e.g. orphan drugs development) and public health research for the inventory of rare diseases.

On the whole, 22 research projects on rare diseases are currently supported in the Programme. In addition, under the area of pharmaceutical research, there are two research projects related to the development of orphan drugs for rare disorders. The total financial support to all these research projects is estimated to be around 8 million ECU.

The projects are aimed at the development of basic and clinical research on rare diseases. Projects have participants from academia, research institutes, and national health undertakings, such as hospitals and clinics for specific rare disorders.

The mean duration of the projects is three years and the average financial support is about 250'000 ECU. On average, there are about ten participating teams in each project.

The general aims of the projects are:

- to promote collaboration between clinicians and basic researchers;
- to collect epidemiological, clinical and biological data on rare diseases;
- to establish inventories, databanks and registries of the disorders;
- to establish protocols for diagnostic and clinical practice;
- to support short-term visits of researchers to other laboratories working in the field.

The projects can be divided into three main categories, and I would like to give you just a few examples of success stories:

The first category would be standardizing clinical and genetic studies to collect European epidemiological data. This includes a very interesting study on fatal familial insomnia, which now seems to be a prion disease. There are also other examples, and I have a complete list including details of the project leaders, with full addresses and phone and fax numbers, for anyone who is interested in the specific pathologies.

The second category concerns projects putting special attention on severe childhood diseases or life-threatening diseases. The success story I have chosen here is Neuronal Ceroid Lipofuscinosis (NCL), whose prevalence is around 1 in 100'000, so it is a very rare disease. We are trying to define clinical criteria and accelerate genetic studies by mapping and cloning the genes.

The third category involves projects to improve the early diagnosis of the diseases, the detection of the weak signals in these pathologies which are so interesting in order to find out pathologies which in the end might prove to be even more frequent than we thought. My example here is Peroxisomal Leukodystrophy.

There are two projects in pharmaceutical research; one is on Von Willebrand Disease, and the other is on Polycythemia Rubra Vera, both blood disorders.

Research on rare diseases has also been proposed as a research task under the forthcoming Fifth Framework Programme for Research and Technological Development. The Fifth Framework Programme will run from the end of 1998 until 2002, so it will hopefully coincide with the Regulation which we are preparing coming into force. The research on rare diseases has been put under the generic technologies.

In the next Programme we have defined activities of a generic nature as being those research activities which are essential to achieve the objectives of the thematic programmes, which complement the more focused and programme-oriented key actions, and whose aim is to increase the scientific and technological capabilities in areas of research where it is really urgent to increase knowledge.

Theme 1 will be called “Improving the Quality of Life”, and we find here the rare and orphan diseases identified as a research priority, and we hope that the scientific community will take this opportunity and will present good research proposals when the next call will be opened.

Antonio LACERDA DE QUEIROZ, Health Promotion and Disease Surveillance, European Commission DG V

Programme of Community action (1999-2003) on rare diseases, including actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organizations.

First if you allow me I would like to congratulate the European Foundation for the Advancement of Medicine for this workshop. It is certainly very, very interesting. Before I start making my presentation, there is a personal matter I would like to mention. There is a very dear friend among the participants who worked at DG V and who had the present responsibilities which I now have relating to rare diseases, and he was, among other things, DG V's authority on rare diseases, and it is certainly quite a pleasure to have Professor Paul Peters among the participants.

The Treaty on the European Union provides the Community with an explicit competence in the field of public health. That competence is even expanded in the Amsterdam Treaty under ratification by EU Member States.

In order to reach the objectives on health protection laid down in articles 3(o) and 129, the Commission defined a framework for action in the field of public health, where rare diseases were identified as a priority topic to be covered by a Programme of Community action.

The Community actions on rare diseases are in line with ongoing activities in biomedical research and with a coming proposal for the development and marketing of orphan drugs, used for treatment, prevention or diagnosis of those rare diseases where the commercial return is insufficient.

A Communication and a proposal for a European Parliament and Council decision adopting a Programme of Community Action 1999-2003 on Rare Diseases was therefore adopted by the Commission in May 1997. It aims at defining a multi-annual set of objectives and priority areas of action for that five-year period.

For the purpose of the Programme, rare diseases are defined as life-threatening or chronically debilitating diseases, which are of such low prevalence that special combined efforts are needed to address them. They cover those diseases with a generally accepted prevalence in the Community's total population of less than 5 per 10'000.

The very fact of the rarity of the low-prevalence diseases and conditions, and the consequent lack of information about them, can lead to people affected by these conditions not receiving the health resources and services they need.

Because of the large population of the Community as a whole, individual cases will be aggregated to form larger groups sharing the same characteristics. This provides the opportunity to undertake a wider range of interventions and to initiate coordinated actions at national level, the dissemination of information and experiences and the joint establishment of priorities with respect to patients who might otherwise be isolated.

Moreover, the diseases to be specifically addressed will be those where special combined efforts are needed to ensure that there is no significant prenatal and premature morbidity or mortality, great loss of lives or significant socio-economic potential loss for the individual.

The Programme aims at facilitating an accelerated and effective sharing of information to provide knowledge about rare diseases, especially for patients, health professionals and researchers; to establish, foster and strengthen voluntary organizations involved in supporting people directly or indirectly affected by rare diseases; and to ensure an efficient handling of the problem of clusters, which is of key importance for rare diseases.

A cluster can be defined as an aggregation, in time and place, of occurrences of a rare disease. Another way to put it is that, in a defined area, during a defined period, conspicuously more cases of rare diseases occurred than what was predicted from the “base-line” or the expected number of this condition. A specific local factor might have contributed to the cause, and this has to be identified.

The Communication reviews the situation as regards the potential area of rare diseases, looks at measures taken in Member States and international organizations, and describes the current activities of the European Community. It explains the place and links of the Programme in relation to other public health activities, as well as other Community policies or instruments and the need for additional public health actions at Community level.

By developing actions complementary to existing Community programmes and actions, while avoiding unnecessary duplication, the action programme will concentrate on the following areas of activity:

1) To provide knowledge about rare diseases, especially for patients, health professionals and researchers, in particular by:

- Encouraging and supporting the establishment of a European rare diseases database, with entries listing the disease name, synonyms, a general description of the disorder, symptoms, causes, affected population, standard treatments, investigational treatments (when available), and a list of resources that can be contacted for further information about the condition;
- Promoting access to information and coordinating existing information systems and services by supporting the setting up and strengthening of networks at local, regional, national and community level;
- Organizing consensus meetings among health professionals in order to improve the early detection, recognition, intervention and prevention of rare diseases.

2) To establish, foster and strengthen voluntary organizations involved in supporting people directly or indirectly affected by rare diseases by:

- Promoting the establishment of groups of persons with the same rare conditions, or those professionally involved, in order to disseminate their experience, to facilitate training and coordinate their activities at national and Community level;
- Promoting the group’s cooperation and networking, and the setting up and fostering of umbrella bodies, focusing particularly on efforts to encourage the continuity of work and cross-national cooperation.

3) To ensure an efficient handling of the problem of clusters, which is of key importance for rare diseases, by:

- Supporting the monitoring of (sentinel) rare diseases, including birth defects, genetic disorders or organic diseases;
- Promoting the creation of rare diseases response teams and of specialized training courses for those investigating clusters;
- Supporting surveillance and early warning systems for clusters;
- Encouraging the exchange of expertise in the evaluation, assessment, communication and management of clusters of rare diseases that are associated with exogenic causes.

The Economic and Social Committee and the Committee of the Regions both adopted favourable opinions on the proposed Programme.

The European Parliament delivered its favourable opinion – first reading – on 11 March 1998, proposing a number of amendments, most of them being accepted by the Commission. On 30 April 1998, the Health Council held a meeting in Luxembourg, at which the common position was unanimously approved. So now I am in a position to announce something which you certainly know already, that is, that the legislative procedure will proceed with the second reading in the European Parliament.

Patrick LE COURTOIS, European Agency for the Evaluation of Medicinal Products (EMEA)

The criteria for the designation of orphan medicinal products and the Community marketing authorization. EMEA perspectives.

I want to thank the European Foundation for the Advancement of Medicine, Mr. Engelhorn and Mr. Schiltz, for the invitation to EMEA to present these perspectives. I will be giving some background information on the EMEA in general in dealing with orphan drugs, as well as our point of view on some challenges and some practical ideas as consequences of the Orphan Drugs Regulation. My presentation is based on draft VI of the Regulation.

The European Agency for the Evaluation of Medicinal Products (EMEA) was created in 1994 and is located in London. It started its activities with the implementation of the new system for marketing authorization in 1995. The main activities of the EMEA are centralized procedure and the coordination of scientific evaluation and control activities.

There are two scientific committees in the EMEA, one for human and one for veterinary products. In these committees there are two delegates of each Member State, who are in charge of the evaluation of scientific data for marketing authorization.

In the centralized system there are two kinds of products: biotech products which are named A products, for which the centralized system is mandatory, and products containing new chemical entities, as well as innovative products, which are called B products, for which the centralized system is optional. These products can also use the national and the mutual recognition routes.

The EMEA's centralized system has treated 148 products, which are now in the assessment phase; 74 products have received an opinion from the CPMP; and 56 products have received a decision for marketing authorization from the Commission. Some of these can be considered as orphan drugs.

How do we see the next system for the orphan drug products? For orphan drug products, the centralized procedure will be mandatory for A products, while for B products the CPMP agreement will not be necessary. These B products will also have the possibility of using national and mutual recognition procedures.

The EMEA Designation Committee and Commission will be the starting point of the procedure. When the product receives the designation as an orphan drug, Commission's grants will be allowed. EMEA/CPMP protocol assistance will be allowed, with a question mark relating to fees. There will be fee waivers for marketing authorization for products if they use a centralized procedure. The products will also be allowed to use the national way, and there are a lot of question marks concerning what will be done at national levels in terms of national incentives, national advice and fee waivers. There is also the question of pre-marketing authorization availability, where there is some discrepancy in the Member States. Of course, all these products will be listed on a register which I presume will also be shared with the Member States.

Now I would like to go into what we have done at EMEA level for all these incentives and what we anticipate doing in the coming years. One of the challenges concerning orphan drugs is that the same guarantee as for any product should be given for marketing authorization. Marketing authorization is based on a benefit risk ratio on pharmaceutical aspects, preclinical, and efficacy criteria, all based on good manufacturing, good laboratory and good clinical practice.

Even if, for orphan drugs, some adaptation is possible in terms of safety or efficacy, in no case should a discount be accepted for orphan drug diseases. This is one of the main ideas behind the policy, i.e. that the same guarantee should be given for all patients.

What regulatory tools are already applicable to orphan drugs? There is the marketing authorization under exceptional circumstances, which is already in the annex of Directive 75/318/EEC, point G, where it is possible to grant marketing authorization when it is not possible to provide comprehensive data because the indication for which the product is intended is rare. This Article has already been used, and so completion of the development Programme, together with annual re-assessment of the product, is necessary.

One other possibility which is not a regulatory tool but rather a practical aspect is the accelerated procedure. When, at the request of the CPMP, a product complies with certain criteria, it is possible to accelerate the process of assessment, which is normally 210 days. These criteria are seriousness of the disease, absence or insufficient alternative treatment and high therapeutical benefit. One example here are the anti-proteases, which were assessed under this accelerated procedure.

At EMEA level, we had already implemented regulatory advice, and have practical experience in this field with pre-submission meetings which also include inspectorate advice and logistic aspects. All these requirements will have to be further developed and adapted to orphan drugs.

As far as protocol assistance is concerned, we have already started with scientific advice, which is part of the EMEA mission. This scientific advice is given by the CPMP and is already in place. We can estimate that about 15 % of 54 advice given to medicinal products were for orphan drugs. We are aiming to develop a database, and to move from advice to protocol assistance and to follow-up. One question mark will be the problem of the fees, since the new regulation on fees foresees fees for scientific advice.

What are the major challenges? For designation and for market authorization, we will have two separate committees, and 15 Member States which will have to apply the same rules. At the level of designation, there will be a Designation Committee, and at the level of marketing authorization, there will be the CPMP, and in all cases the EMEA, the Commission and the Member States.

Regarding the major scientific issues, we need to be clear on what we understand by prevalence. It will probably be the number of patients to benefit from the treatment. The definition of diseases at the level of designations is that they are medically plausible, we will have to avoid artificial “salami slice”. For some products, such as gene therapy products, enough proof of potential efficacy, and the need to be sure that we are designing a medicinal product and not a concept. The problem of clinical superiority, the definition of life-threatening or seriously debilitating communicable disease, and the definition of same versus different medicinal products, which is so important for the breaking of exclusivity will have to be defined.

The risks comprise non-adequate designation and the breaking of exclusivity, knowing that even if exclusivity will only be granted for centralized products, there is always the possibility that at a national level there is breaking of this exclusivity.

As far as international cooperation is concerned, we will take advantage of the FDA’s experience and have already organized a mission in Washington. We will also have to further develop our contacts with the Office of Orphan Product Development (OOPD) and work on real situations.

As regards fee waivers, the EMEA took an initiative in 1995. The council regulation on fees states that the Executive Director may grant fee waivers in exceptional circumstances and for imperative reasons of public health. The EMEA Management Board has already taken practical measures in relation with orphan drugs in 1995 pending adoption of the future EU Regulation. An allocated amount is earmarked every year for fee waivers, and the decision is taken by the Executive Director after consultation of the CPMP.

To grant fee waivers, we use criteria defined in the draft regulation:

- the prevalence as in the draft regulation
- the availability of alternative treatment
- expectations as regards public health and we consider the international status of the product in terms of orphan drug status and marketing authorization

Until now, seven applications have received fee waivers with 100 % to 50 % exemption – 4 in 1996, 1 in 1997 and 2 in 1998. Three have already received a marketing authorization in 1997 - Cystagon, a product used for Nephropatic Cystinosis, Benefix, a recombinant factor IX used to treat Hemophilia B, and Cerezyme, a biotech product for Type I Gaucher Disease. All of these seven products which received fee waivers, except one, had U.S. orphan drug status, and the amount granted was 620'000 ECU.

Since the beginning of 1998, we have received several additional requests for fee waivers, and some are expected in the coming months. Unfortunately, however, the budget line is now exhausted. In fact, we have been blamed by the European Parliament for having taken this initiative without any regulation.

From the EMEA's point of view, the anticipated resource allocation will be for:

- staff, for managerial and scientific activities
- organizational supports, including the implementation of a database
- expertise for the Designation Committee and protocol assistance
- fee waivers for protocol assistance and marketing authorization
- the need to implement and develop the transparency policy which is already in place at EMEA level in favour of orphan drugs towards patients, health professionals and the industry.

The links with all the Commission Directorates and their scientific committees in charge of programs for orphan drugs will be something to further develop in the coming months and years.

To conclude, I just want to say that the success of a European policy on orphan medicinal products will depend on the means allocated.

Statements and comments on the European Commission's and EMEA's programmes by Patient Groups, Industry, Health Authorities and Médecins Sans Frontières

* PATIENT GROUPS:

Abbey S. MEYERS, President, National Organization for Rare Disorders, NORD®, USA.

When I thought about preparing my presentation today, I realized that it is impossible to prepare a speech about the Orphan Medicinal Products Regulation which technically does not yet exist. I had not seen the latest draft until this morning, so I didn't know for certain what it was going to look like. I had a sense of what the law might look like because I know that the initial drafts of the Regulation were firmly established on very sound principles – creation of financial incentives that would promote and entice private industry into developing new treatments for rare diseases. It is the talents, the expertise and the resources of industry that will bring these treatments to the European market, and ultimately to the rest of the world.

I also know that the Programme of Community Action on Rare Diseases is a wonderful plan, that Parliament has voted on it, and that the Council of Ministers is reviewing it. I want to congratulate all of those who were involved in its drafting, all of those who recognized the importance of quickly enacting it, and for assuring that appropriate funding is made available to guarantee the promise that the Programme represents for the entire European Community will indeed be realized.

I am especially impressed with the recognition that the Programme of Community Action gives to the rare disease patient organizations. In the United States, our politicians do not understand that the uniqueness of these diseases requires customized social services from knowledgeable agencies that have expertise on these conditions. Therefore, the European Programme will be a model for the rest of the world, and you can be very proud that Parliament has acted very wisely and quickly. We hope that the Council will reaffirm Parliament's wishes, because the importance of the Programme is profound and it will have worldwide implications.

On the other hand, the continued delays in action on the Orphan Medicinal Products Regulation have not been wise. Indeed, they have been very foolish. It is my understanding that the European regulatory authority approved 22 new medications last year, and eleven of them were biotechnology products. All eleven were developed by American biotechnology companies. In the absence of European orphan drug incentives, your biotechnology industry will remain years behind the American industry, your health authorities will have to pay any price the American companies ask, and orphan disease patients in Europe will find access to improved treatments greatly delayed.

Not all orphan drugs are biotechnology products. Many are ordinary chemical entities. Nevertheless, until Europe's orphan drug law is in place, you will continue to import these products from America and Japan. They will not create new jobs in Europe, they will not create new companies as they have in the United States, and the taxes they generate will go to Washington, DC, rather than London or Paris or Brussels.

So who is being helped by the delay in this important law? Not the patients, not the governments, not the physicians nor the hospitals. No one is being helped! But many people are being harmed.

The American Orphan Drug Act has spurred development of approximately 850 orphan drugs that have been designated by the FDA, and 170 of these have been approved for marketing in the United States. It has been estimated that these 170 products are saving the lives or diminishing pain for more than 7 million Americans. The European Union has approximately 100 million more residents than the United States. This means that probably more than 10 million Europeans are benefiting from the American orphan drugs. Europe has no choice but to import them from the United States.

It is important for the Commission to understand that orphan drug incentives are good for everyone. They will create jobs, they will create new companies, they will generate taxes, they will increase your exports, and most of all they will help patients. No one will lose, everyone will win. So why is the regulation delayed? Does anybody benefit from the delay?

Until the European Parliament acts on the Orphan Medicinal Products Regulation, European drug companies will continue to develop "me-too" diet pills, anti-depressants, anti-hypertension drugs, baldness medicines. This is where the pharmaceutical industry see the most profit, and this is where their resources are going to be invested. It is the small and medium sized companies that will be satisfied with the smaller markets that orphan drugs are aimed at. It is the innovative biotechnology companies that will develop the needed treatments for genetic diseases because they are willing to take higher risks, especially in areas where there are no satisfactory existing therapies. Give them the incentives that will attract them to Europe and they will flourish here, and we in the patient community will be the beneficiaries.

The orphan medicinal products legislation won't cost your government any money. It will save you money! It doesn't call for government funds to build factories or hire workers. It simply sets the incentives in place to create lifesaving medicines with private investment capital, not public funds. It is very troubling that Europe is taking so long to do the right thing. The orphan disease community is one family throughout the world, and we do not care where our treatments and cures come from.

Now they are coming from the United States and Japan because Europe has not acted; but when you do, the world's orphan drug development could easily double or triple very quickly. Selfishly, we want this to happen because too many of our loved ones have no time to spare. So I urge the Commission and Parliament to expedite the regulation for the sake of your governments, your economy, but most of all, for the sake of the rare disease patients and families whose future is intricately tied to the enactment of this law.

NORD® Web page: http://www.rarediseases.org/

Stéphane KORSIA, Executive Director, European Organization for Rare Disorders, EURORDIS, France

First of all, I would like to thank the European Foundation for the Advancement of Medicine for organizing this seminar, and for allowing me to present the point of view of families affected by rare disorders in Europe.

EURORDIS is a coalition of 103 patient organizations in 12 European countries which is geared toward improving the quality of life of those affected by rare disorders throughout Europe. It was created over a year ago to carry the voice of patient organizations at the European level, to coordinate their actions in this domain, and to facilitate exchange of information between them. The idea for this coalition was born at a September 1996 meeting in Paris, where patient organizations were presented a draft of the European Regulation on Orphan Medicinal Products by a representative of the Commission.

Concerning the Programme of Community Actions on Rare Diseases, we think this is a very good Programme which has a real potential for truly improving the availability of information on rare diseases, and for increasing the collaboration between the European patient organizations. Regarding the European Database Initiative, EURORDIS has been working for the past year to bring together all those involved in providing information on rare diseases throughout Europe to prepare a project to be submitted to the Commission which will avoid redundancy and make the best possible use of what is available today in Europe in terms of information for patients. Since, in this age of the Internet, a European database will have to be a world-wide one, we are in the process of discussing with NORD® to be able to benefit from their several impressive databases as a basis for this European project.

The Parliament added two excellent amendments to this Programme, one asking for patients' involvement in the implementation of the Programme of Action, the other increasing its budget to 14 million ECU for 5 years, instead of the 6.5 million ECU proposed by the Commission. Considering the price of a national database, such as Orphanet in France (half a million ECU in the first year only), it is obvious that 1.3 million ECU per year is grossly inadequate for a Programme of which the database is only one of three items. We urge the Commission and the Council to put money where their mouth is, and to realize that the Parliament budgetary amendment is a reasonable one, if we want this Programme to really have a positive impact on the life of those affected by rare disorders.

Regarding the Fifth Framework Programme on Research and Technological Development by the Council and Commission, we are concerned about the fact that rare diseases have not been considered worth being a *bona fide* "key action", as the Parliament had requested in an amendment. We understand that it comes under "research activities of a generic nature", which, as we have seen this morning, are complementary to the key actions, but they are there along with cancer, diabetes and cardiovascular diseases, and we think that rare diseases have been denied their specificity and the fact that they, in the words of the Programme of Action, require "special combined efforts to address them". Combined efforts are indeed what is needed, and a solid Community-funded research programme must be seen as the necessary element of a coherent European policy on rare diseases. Without a substantial commitment from the Fifth Framework Programme, research on rare pathologies will severely suffer from money shortage. Development of medicinal products against rare diseases may, in the proper economical context, be ensured by the pharmaceutical industry. However, basic research on these pathologies relies almost completely on public funding of research centers and universities. If the Fifth Framework Programme does not allocate enough money to do research on rare diseases, we will lose many therapeutic opportunities.

Now to the Regulation.

I already mentioned the September 1996 meeting in Paris. After this meeting and the September 1997 meeting of the European Platform for Patient Organizations, Science and Industry on a similar topic in Brussels, today's seminar may seem like another party thrown for a guest who never shows up! Like Samuel Beckett in his play, "Waiting for Godot", we could also say, "He will surely show up tomorrow," and leave it at that. For the past year and a half, we have been shown a quite satisfying draft of a much awaited Regulation, but after all the continuing delay, we are left like the proverbial donkey with a carrot hanging in front of it, without knowing if he is going to ever be able to eat it.

To support this feeling, let me read a few excerpts of the activity reports I have been submitting to EURORDIS Board of Directors over the past 15 months. They will show you what sort of roller coaster the families have been going through.

March 1997
We are assured that the Regulation will be filed early July (1997).

April 1997
Work on the Regulation has not progressed, but should move ahead in the coming weeks.

May 1997
The Regulation should be written for mid-June, then it will be translated and submitted to other services. This means that the document will be filed with the Parliament in September.

June 1997
Nothing new.

July 1997
The final version is said to be presented to the Council and Parliament at best in October.

August 1997
The orphan drugs document, as well as the financial notes, have been finished and proof-read. Translations should be finalized and the document should go through Commission approval around mid-September. If these delays are respected, the document should be officially submitted to both Council and Parliament around mid-October.

September 1997
Everything seems on schedule.

October 1997
Patrick Deboyser mentioned the existence of problems with the Regulations in some DGs, especially about the creation of a Committee for Orphan Drugs. There is resistance about the costs associated with waiving new drug application fees for orphan medicinal products.

November 1997
Things seem to be stalled for good at DG III.

December 1997
The Regulation should be finished by the end of January, if DG XXIV still agrees not to give comments about it.

January 1998
The Regulation has been modified following a meeting of the FDA.

April 1998
The Regulation is still within the Commission.

So where does that leave us today?

For the past year, the patient organizations which are involved in EURORDIS have trusted the Commission to do all it could to help them obtain the treatments they need. After over one year of delays and unexpected hassles, the mood of our members is starting to become one of distrust and anger. Already, some members are asking us to be louder in denouncing the situation. Although we have always preferred to bring constructive criticisms to the table and to be supportive of the Commission's work, these unacceptable delays may force us to radicalize our speech. Our members have had their hopes raised, and this makes the delays feel even more humiliating.

As an organization advocating on behalf of families affected by rare diseases, EURORDIS is reaching a point where its own credibility and power might be questioned as a result of its lack of ability to make things budge within the Commission. Consequently, louder activist-like actions which so far did not get our preference may become more of a necessity, and those of us who have had long experience with these means of action may have to feel again the bittersweet taste of spectacular actions aimed at drawing the attention of the media to an unacceptable situation.

So we urge the Commission to find NOW a solution to the current obstacles, and to move forward the Regulation. The public journey of this proposal has not started yet, and it will be a long one. There will be many opportunities to discuss each nook and cranny of it, including its budgetary impact. We need the Regulation to be published now, so that we can start the momentous task of preserving and improving what is already a very good text.

In conclusion, I would like to remind you that, as the Programme of Action justly defines, rare diseases are in need of concerted efforts. Today, the Community policy on rare diseases is like a three-legged stool: the Regulation, the Programme of Action and the Fifth Framework Programme. If any of these complementary three legs were too short or not sturdy enough, the whole Community policy would fall over and become ineffective, mere good intentions to pave further the Hell of those living with rare disorders today and tomorrow. On the contrary, the more legs this policy has, the deeper the impact it will have on the quality of life of these families.

We need concerted efforts between DGs, and between the Parliament and the Council. We need both political commitment and financial commitment. We need swiftness, because we cannot wait any longer. And we will NOT wait much longer.

* INDUSTRY:

Erik TAMBUYZER, Vice President, Genzyme NV/SA, Belgium

I want to thank the organizers for taking this splendid initiative. It is the first time since September 1997 that we have come together with the group that is discussing this topic in a more public forum, to talk about orphan drugs and rare diseases, and therefore I would like to start by taking one of the slides that I presented at the September meeting.

As regards the role of industry in this process, we want to stress over and over again that industry is not an island. Industry is part of society, so it has an important societal role to play, perhaps even more so in the case of rare diseases and orphan drugs. We, as industry, help academia in funding and technology platforms. We have to develop, manufacture, market, distribute, QC, etc. the products that result. Ethics are a long-term strategic requirement, also for industry. If we know beforehand that we cannot pursue a certain road, then we do not do it. That is why we want clarification on that, too.

I am not just talking on behalf of Genzyme, but also of the whole of the bio industry in Europe, which has been discussing such topics for a long time, not just among itself and with its colleagues, but also with the patients, the Commission and everyone concerned.

What can we learn from the U.S. experience on orphan drugs? I don't want to repeat what has already been said by the previous speakers, but one point I would like to stress is that prevalence is not really a very critical criterion for the designation of an orphan drug. In most cases, prevalence for a rare disease is not even known very well before a treatment exists. Most orphan drugs cover rare diseases with a prevalence which is far below the limits that are set, and the treatment itself is creating a sudden jump in the statistics of patients that can be cured with it because there is a real incentive to identify them.

A point that Abbey Meyers has raised very strongly is that treatment is much less costly in economic and in human terms than no cure at all.

Another point, which has also been raised by Patrick Deboyser and Patrick Le Courtois, is that clinic trials have to be tailored for orphan drugs in specific cases, but that the safety and efficacy of the drug should not be compromised.

Another point that has been mentioned is that most orphan drugs are developed and marketed by small or medium-sized companies, and I believe that we have missed such opportunity in Europe for the development of the biotechnology so far, and this is something we have to catch up on.

Of course, biotechnology itself plays an important role, and perhaps the development of genomics technologies in the larger companies will also lead to more orphan drug spin-offs from those companies' research, but so far it is mostly the small or medium-sized companies that have developed orphan drugs.

Academia – and here the Fifth Framework Programme comes in – really carry out discovery research, and play a key role in bringing products to a certain level from where they can be further developed. And in this regard it is worthwhile to stress – and this also relates to the Patenting Directive –, most complete genes are patented by academia, not by industry.

Just as a reminder, the clinical success rate of drug development: out of 1000 drugs, about five are marketed in the end.

For orphan drugs, some extra activities are required (compared to other medicinal products), which concern, for example, patient identification. These include physician education, because most physicians have never seen patients with a specific rare disease, or maybe only once in a lifetime, and patient education, because the patients themselves need to be educated about the available therapy. So the contact between the supplier of a product, the medical doctor treating a patient and the patient is much stronger than in the case of a classical drug.

As far as the European orphan drug legislation is concerned, from the industry side we would like to congratulate the Commission that we are really getting somewhere now, and we hope that it will continue at a speedy rate. However, looking at all the signs, not only from the patients' side, but also from that of EMEA, for example, where the budget for fee waivers for 1998 was already exhausted in April, it is time for this process to move on and for legislation to be passed. Of course, in order to have real impact this European legislation should be more attractive than the US legislation, because otherwise the process as it is today will still continue.

In this regard, I would like to stress a couple of further points. We need an orphan drug legislation and not an orphan disease legislation in Europe, and this no matter what the budgetary impact might be, because otherwise there will only be one therapeutic possibility for each disease and there will be no opportunity for improvement of the medication of a certain disease. I hope that this is taken into account in the definition of the clinic superiority.

Secondly – and this, I think, is the largest question mark for industry –, is the implementation in the Member States. When legislation is provided and an act passed in the U.S., I believe it is easier to implement it in the different states than it will be in Europe.

So there are a number of important points relating to the availability of the drug, because that can only come after price issues have been resolved, legislation implemented, and so on.

Market exclusivity is, of course, the most important attraction point of the legislation, but the secondary measures are also very important. Fast track provisions have been described; fee waivers have been discussed; clinical trial protocol assistance; the competence of the special committee which will be installed is of very high importance; the definition of a similar product in practice (how did it work out?); transparency on how industry can dialogue with the competent authorities regarding the process and its various steps; and then of course, perhaps other tax credit measures and so on are needed later on, but that can be done at a review stage.

Finally, some spin-off effects: The orphan drug legislation should form a stable and foreseeable part of a stable and foreseeable environment for pharmaceutical and biotechnological research in Europe. We believe it should also form the basis for support for the patient organizations, because in Europe, all too often they hear that they are depending on industry for survival, and perhaps there is a better way to go forward thanks to this legislation.

Retesting upon importation is an important point for orphan drugs coming in from other countries, because today they need to be fully retested at the first country of importation.

Health care costs should decrease, but more importantly, lives will be saved or their quality improved thanks to this new orphan drug legislation.

* HEALTH AUTHORITIES:

Annie WOLF, Ministère de l'Emploi et de la Solidarité, Mission des Médicaments Orphelins, France

As you know, the United States were the pioneers in the field of orphan drugs. It should be said that the Orphan Drug Act came about due to the determination of a handful of individuals and in particular, Abbey Meyers, who presides over NORD®, a consortium of American associations for patients.

After Japan, Europe took a long time in realizing the importance of this challenge in terms of public health. In fact, it was essentially upon the presentation of an official report to the French government that the Health Minister at the time – in 1995 –, Mrs. Simone Veil, decided to integrate this priority subject within the Cabinet programme of the European Union.

In 1994, when I started my preliminary research report on rare diseases to be remitted to the French authorities, I had the opportunity of meeting several members responsible for the Commission. Most of them are here today in this room and I would like to say that, without the warm welcome and advice they extended to me at the time, our ideas would no doubt not have progressed in the same way.

In parallel, Simone Veil established a ministerial mission in France responsible for orphan drugs. This mission, which I have been coordinating for three years now, has enabled the necessary expertise to be gathered for French participation within the European bodies and groups that have worked on this subject. It should be said that the French government has been arguing in favour of a European policy on rare diseases and orphan drugs since 1995.

Why has this choice been made, and what room does it leave for national action? This European choice was necessary because of the size of the population and therefore the market, the creation of the European Drug Agency, a certain harmonization of regulations and the importance of conducting epidemiological studies on rare diseases on a European scale.

However, given the extent of work to be accomplished on a European level, there is certainly room for considerable national action. I would like to mention just three:
- informing the public as a whole
- establishing tax incentives for manufacturers, and
- acting with the aim of making treatments developed as a result of this new policy accessible to all patients.

Here I would like to develop the first theme: informing the public as a whole. The associations for patients or families affected by these diseases all convey, of course, their anxiousness to have rapid access to new treatments. But they also express with insistence the absolute necessity to be directed from the outset towards consultation centers that are specialized and expert in this field to avoid losing months and even years before a precise diagnosis is made.

They express the need to be informed as soon as there is a development in these diseases that are often very disabling, to be given genetic advice that is understandable since these diseases are frequently of genetic origin, and to be informed of the therapeutic possibilities, thus enabling them to make their choice with a full understanding of what is involved and in complete freedom.

To break with the impression they have of isolation, the Orphan Drug Mission, along with others, has aimed at encouraging a consortium of patient associations. This was firstly achieved in France on the initiative of four large associations, which are: the Muscular Distrophy Association, the Cystic Fibrosis Association, the National Cancer League and the National AIDS Federation. Numerous associations from all European countries rapidly joined them within a European federation called EURORDIS, one of its main assignments being precisely to see that European legislation on orphan drugs is rapidly established.

From the outset, the Mission also organized a work group to create a database on rare diseases and orphan drugs, which has now come to fruition thanks to the French Health Ministry, INSERM, the Social Security and EURORDIS. This database, called ORPHANET, is already accessible on the Internet and should soon serve as a starting point for the establishment of a European database.

This mobilization of the patient associations has been accompanied by action undertaken by the Mission for a greater awareness among drug manufacturers. And like others, I can vouch for the great interest they have shown regarding the perspective of future European regulation.

By way of conclusion, I would like to mention the French government's satisfaction with the work that has been accomplished, its confidence in overcoming the remaining steps to be taken, and its expectation of seeing regulation coming into force that fully satisfy the requirements for the development of orphan drugs.

* MEDECINS SANS FRONTIERES:

Patrice TROUILLER, Centre Hospitalier Universitaire, Grenoble, France

Despite recent advances in the research and drug discovery, the drug development pipeline for tropical diseases is drying up and by their nature and prevalence, tropical diseases are low-priority for private industry.

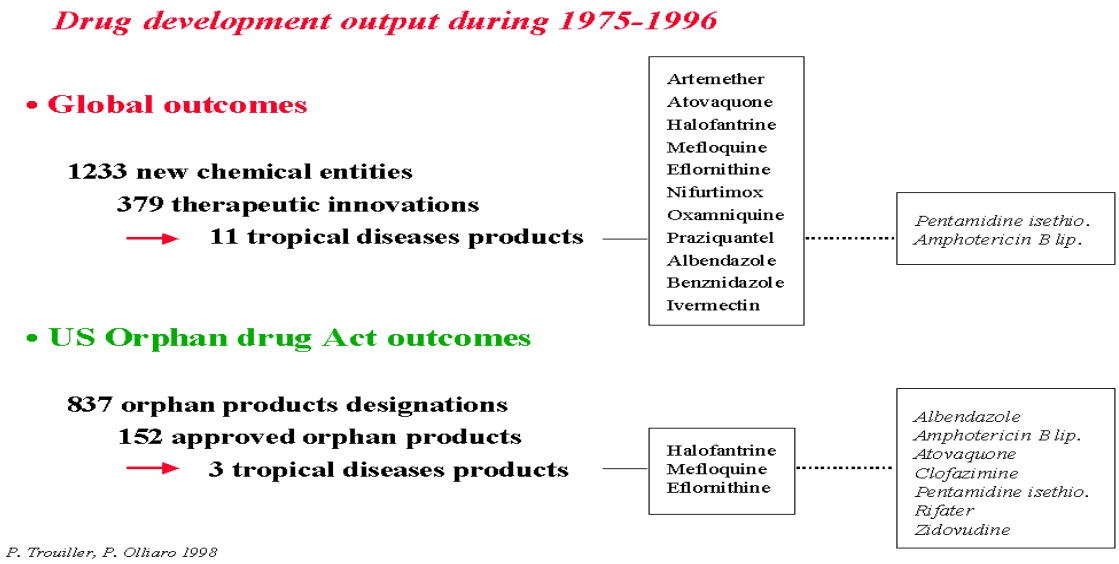
If we analyze the outcome of 22 years of pharmaceutical research, we observe that:

- of the 1223 new chemical entities that were commercialized worldwide during the period 1975–1996, 379 products were real therapeutical innovations, all from Western pharmaceutical companies

- less than one percent, that is 11 products plus 2 new products for the reformulation of known chemical entities, were destined for tropical diseases

- of the 837 orphan product designations and the 152 approved orphan products from the period 1983–1997, 3 were tropical disease products (Halofantrine, Mefloquine and Eflornithine). The other 7 products used in tropical infections – ranging from Albendazole to Zidovudine – had got an orphan designation or approval for another indication.

  For instance, both Pentamidine isethionate and Atovaquone have been approved for the treatment of *Pneumocystis carinii* pneumonia, relating to HIV/AIDS and not for sleeping sickness or malaria.



If we analyze the pharmaceutical development context of these three orphan products, we can see that

- firstly, the two antimalarials – Halofantrine and Mefloquine – have been discovered and mainly developed by government institutions (for instance, the US Walter Reed Army Institute of Research) and anyway, with or without an orphan designation, they would have been developed because of military necessities and moreover, producer price is still an obstacle for their accessibility and availability in most developing countries.

- The second important point is that Eflornithine or DFMO used as the only second-line treatment of human African trypanosomiasis (sleeping sickness), designated in 1986 and approved in 1990, is no longer commercialized and has been totally abandoned by Marion Merrell Dow company.

So, what prevents the pharmaceutical companies from conducting research and development (R&D) for tropical diseases?

- Firstly, the cost/risk ratio of drug R&D, compounded with the low purchasing power of the developing countries

- Secondly, the protection of intellectual property rights (IPR) – that is, product and process patents –, and the return on investment. In the context of an extensive use of generic products, and because unfair competition and counterfeit products are not uncommon, as was the case with praziquantel for the treatment of Bilharziosis

- Lastly, because of the impact of regulatory requirements and the length and the costs of the process, which increases the ultimate market price of the product. This favours pricing strategy of pharmaceutical companies in setting single global prices for new products and denies access to new ones, as was the case for Atovaquone and HZT

Finally, we come to the conclusion that orphan drug legislation is only shaped and sized for rare diseases, and not at all for tropical and assimilated diseases. The original intention of legislators, politicians and patient organizations was focused strictly on rare diseases. All regulatory or financial provisions for rare diseases can push and speed up drug development. They impact on R&D process at a upstream level with different needs, such as tax credits, grants and, above all, market exclusivity. And downstream, the social and economic context is favourable for pharmaceutical companies. Consumers are able to buy directly or indirectly, thus completing the loop.

At the other end, the development for tropical diseases needs not only a push, but a pull to be efficient, and there must clearly be room for newer and specific approaches. The framework fixed on for rare diseases – as is the case for the US Orphan Drug Act and the future European Regulation on Orphan Medicinal Products – is not adapted to tropical diseases, and these diseases would probably not benefit from the future European legislation. This and prior analyses call for broader debate on proper drug development strategies for tropical diseases.

Open Discussion, Part 1

BRUNO HANSEN, European Commission DG VII

Ladies and Gentlemen: we now have an open discussion. I do not believe that the European Foundation for the Advancement of Medicine is organizing this meeting in order to write history. I have the idea that you are organizing this meeting to have the different players come together, and to try to identify what kind of actions might be taken in order to move this field in an appropriate way. So I would like to divide this discussion session into two parts. The first part will comprise questions and answers, because we need to be sure that we are all operating on the same knowledge level and have the same information; then in the second part, we will need to discuss what kind of measures might be taken to move the field and generate the next step in the public debate to make sure everyone understands what needs to be done.

As you know, funding for research at European level comes from some Member States who have some constraints on how much they want to send to Brussels.

There are many other areas which are important for research, too, so we need to profile it in the right way. Not overbetting, because that would not be appropriate, but finding the ultimate actions. I really liked Abbey Meyers' comments which will actually both provide the basis for appropriate treatment, but which she linked not to a carrot, but to employment, job creation, which is, of course, important.
I am often saying that, when we address this area in the Commission's services, we have the responsibility for the quality of life.

There is frequently this distinction between competitiveness and quality of life. Competitiveness is something bad, something negative for society, while quality of life is the right thing. I am always trying to argue that these two things go hand in hand. You are not competitive if you do not address quality of life.

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ABBEY S. MEYERS, National Organization for Rare Disorders NORD®: During the coffee break, somebody told me that if a manufacturer asks for a centralized approval through EMEA, they get 10 years' exclusivity on any drug. Is that true?

PATRICK DEBOYSER, European Commission DG III: It is correct in one way. Through the centralized organization you get 10 years data exclusivity. A generic manufacturer cannot use the dossier to file a generic application, an abridged application, for a new drug approval with the EMEA. You cannot use the data generated and submit them in the application file to file a generic application to the EMEA within ten years. But you also get ten years in seven Member States, and six years in the others. It is the equivalent of the five years' data exclusivity in the United States. In this respect, Europe is doing better already.

ABBEY S. MEYERS: But then there is no advantage to a manufacturer to ask for drug exclusivity under this law. It is ten years, and it could possibly be withdrawn within 6 years.

PATRICK DEBOYSER: Yes, there is, because of course the protection given by the data exclusivity is only against someone filing an abridged application, but if someone was filing a whole dossier he would not have exclusivity. I think it is explained in the explanatory memorandum that the protection by the market exclusivity as an orphan drug is in fact a new intellectual property right which we are creating. This is not as good as a patent (a patent is stronger – if you can have a patent you should go for it because it is stronger protection), but it is better than data exclusivity, because data exclusivity does not provide you with protection against another company which would be prepared to develop its own data for the same substance.

ABBEY S. MEYERS: So a second manufacturer would have to submit a whole new drug application, not an abbreviated one.

PATRICK DEBOYSER: Yes, and have generated its own data. So in fact the orphan drug protection exclusivity is stronger protection than data exclusivity, but is not as strong as a patent.

ABBEY S. MEYERS: It just seems that a better exclusivity would be a longer exclusivity than the ten years.

PATRICK DEBOYSER: Fifteen would be better than ten, that is correct. And twenty would be better than fifteen.

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LESLEY GREENE, Research Trust for Metabolic Diseases in Children: I would like to congratulate EMEA on the moving ahead of the Regulation, having the courage to set things up. It is obviously dismaying that the budget for this year is already exhausted. I would like to know what criteria were used for setting the budget and what the plans are for replenishing it now?

PATRICK LE COURTOIS, EMEA: For 1998, an amount was earmarked for fee waivers and there was no possibility to allow any extra amount for fee waivers, unless we receive extra funds from the Commission.

PATRICK DEBOYSER: Actually, the possibility for the EMEA to give a fee waiver for orphan drugs is written in the Regulation 267 of 1995 on the fees to be paid to the EMEA. There the possibility of granting fee waivers is already foreseen. The problem has been that there was no budget allocation. So the way it has been done from 1995 on, is that in 1995 – which was the first year of operation of the EMEA – there was, as Patrick has shown, only a couple of requests and it was quite clear that especially for an agency which would basically deal with biotech products, potentially a lot of products – perhaps half of those going through the EMEA – would qualify for orphan drugs designation if one was using the criteria used in the U.S., for instance. If you look at the first drugs which were approved by the EMEA, Epivir and the like, were orphan drugs in the United States. So it was quite clear that it was not possible to use designations in the U.S. to grant the fee waivers in the EMEA. The criteria that were used are described in the EMEA's standard operating procedures. For the following years, we have used the surplus in the EMEA budget. So far, in 1995, 1996 and 1997, the EMEA has made a surplus, that is, it did not use the entire subsidy that had been voted by the European Parliament. So there has been a carry-over of surplus from one year to the next, which has been used for orphan drugs. This is what has recently been criticized by the European Parliament. The Rapporteur from the European Parliament criticized the fact that the EMEA was creating reserves, carrying them over from one year to the next and using them for orphan drugs. I believe it was just that the MEP was badly informed, because the possibility of granting fee waivers is in the regulation on fees.

Secondly, the carrying over of surpluses is entirely coherent with the policy upheld by institutions – of carrying over excess revenues from one year to another – provided that they are used for a specific purpose. I believe that until the Regulation on Orphan Drugs is adopted, it will be possible to continue the current procedure being consistent both with the regulation on fees and the financial regulations of the institutions.

BRUNO HANSEN: But that leaves the question that once you have the Regulation in place, how do you make sure that you have the right amount of money to do the waiving there?

PATRICK DEBOYSER: When the Regulation is in place, the criteria will have been adopted. However, we do not propose to grant a total fee waiver for every drug that has been designated as an orphan drug. We know that some are more orphan than others. If we only have, say, half a million a year, which is what we plan for the year 2000, I do not think that that should go to products like Betaferon, for instance. Betaferon has been developed in the United States, it is available and making money on the market in Europe, and I don't think that that would have needed a fee waiver. However, the Gaucher Disease drug, which I understand did get a fee waiver, that is the sort of drug which will qualify for a fee waiver. What we have in mind is that every year Parliament would vote a budget for the following year. Let's say there is one million next year for fee waivers; in that case the EMEA would set up a procedure and say that by 31 March 2000 we need to have all the applications of those companies which plan to file with the EMEA a product which has been designated, and then whatever funding is available will be split amongst the applications. This should, however, not be on a pro rata basis; I think there ought to be some judgement as to which drugs deserve the fee waiver. Again, this should also be an indicated judgement by the director subject to the Council of the management board of the EMEA as to whether he wants to use the fee waiver for the scientific advice or the protocol assistance, or more for the new drug applications. But according to the Regulation, there is no right to a fee waiver, and the fee waiver can be anything between 0 % and 100 %. So there is a possibility of giving a 100 % fee waiver for some drugs, as well as giving very little, or nothing at all, to others, depending on the case which is being made for a fee waiver.

BRUNO HANSEN: So the main message here is that in this interim period there has been a maybe not totally clarified, not agreed activity from the Parliament but actually had work taken from other activities and ploughed into this one. When the Regulation is in place, there will be a budget line?

PATRICK DEBOYSER: I think there will still be a budget line for 1998. I am surprised that that Member of Parliament made the remark that he did, and I am surprised that the EMEA accepts the remark. I am prepared to raise that at the next meeting of the management board. I think that this is a misunderstanding. It is legally possible to grant fee waivers, and the question is, what are the possibilities for this year. But if you want to know what is the real possibility, I think Patrick said 7 fee waivers granted, 620'000 ECU, so that is an average of 90'000 ECU per fee waiver granted out of a fee of currently 140'000 ECU. So there have been 7 cases where on average a waiver of two-thirds of the fee was granted. So this is what I think you could expect through 1998 and 1999 until the Regulation comes into force.

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PAUL W.J. PETERS, Professor of Teratology, University of Utrecht, Netherlands: We have here three programmes (or regulations); they all started or will start at a different time, the budgets are limited and this is a fast-moving area. What are the possibilities for the Commission, and what is the attitude of the various Directors-General, to put all that money to the best use and to ensure a high level of coherence between the various regulations, actions and proposals? This could be linked with a second question: What about the coherence between the different programme committees? Is there a possibility of collaboration of these advisory committees to strengthen the various programmes?

BRUNO HANSEN: I don't know if the Chairman is allowed to speak, but I hope you will allow me to say a few words because this is a very important point.

I think it was Stéphane Korsia who mentioned about the three-legged stool. If one leg is too low, the whole thing will tip over. There is a clear intention to work together. We need to understand that at different levels:

- First of all, there is the research level; then the health policy part already needs to be part of the research level in order to benefit the most in their aim of surveillance, information distribution, and so on. So there is a very good relationship here, and you know that we have worked very well together on a pilot experiment on the TSE, where again we are supporting research. The Framework Programme is at the same time very closely related to the activities on the house in order to provide for surveillance that will be in place afterwards.

- Secondly, we need in this specific case to ensure that lines exist between research and the whole procedure of the authorization. I do hope we are encouraging the best experts to embark on this field, and we need to make sure that we have the right relationship and connections, so that the expertise available is utilized to the maximum. By that I mean avoiding fragmentation, avoiding creating an expertise network to do the research and then at the end of the day it is another body that sits down and decides whether it is any good or not. We have to be careful not to have any vested interest. We have already discussed with EMEA the fact that we need to make sure that we have the right network and expertise and that we work together on this. So from the research point of view, there is a clear intention to provide the basis for a good network in Europe, to make sure that there is liaison between both the health part follow-up and the authorization follow-up.

This also gives me the opportunity to comment on Stéphane Korsia's comments on the Framework Programme.

- Firstly, it is not with great pleasure that I saw the common position of the Council on the Framework Programme Five. When we know that the Commission suggested for the Framework Programme Five a total budget of 16.3 billion ECU, that the Parliament in its first reading suggested an increase to 16.7 because the Commission proposal was very conservative, reflecting the same percentage of GDP for research, and inflation, nothing more, so not a general increase. So the 16.3 was calculated that way and the common position of the Council was saying 14 billion ECU. This is a reduction compared with what we have for research today.

- Secondly, it looks as if the agreement between Council and Parliament is a very good one. There will be four themes, so it will be a much more coherent programme than the present Framework Programme. You don't have an isolated or fragmented biomedical and health research programme which is underfunded as is the Fourth Framework Programme; 336 million ECU was the decision, and then addressing all issues, where the Member States want the Commission to do the same as NIH (National Institutes of Health, USA) are doing with $ 12 billion, which of course is impossible. But now there is a more coherent programme. It looks like theme one is a very good agreement, concerning quality of life and management of living resources.

You were also talking about key actions in our activities. Part of the Programme will address specific key actions, where we are trying to bring together different players to answer questions for the good of society. The generic part is meant to bring the parties together to make sure that we have the right knowledge and to increase knowledge at a European level by means of a network.

- And thirdly, we have infrastructures, to make sure that we are optimally utilizing the infrastructures in Europe. Here we have added clinical research and clinical trials.

So it is not our intention for the money to be only ploughed into the key actions. We need to have the right balance.

So to be proactive, I think in the Fifth Framework Programme we will have a much more coherent structure, we will make sure that those actions needed to promote the area of rare diseases and orphan drug developments will be taken care of. The first input from Parliament to put rare diseases in a key action was not a key action for rare diseases; I think it was just thrown into the rare and infectious diseases at the end. This is, of course, not the appropriate way of doing things. For that reason we have put it in the generic part in its own right, to make sure that it is addressed appropriately.

PATRICK DEBOYSER: I am not sure I want to add much to that. Of course it would have been better to present Council and Parliament with one coherent policy on rare diseases, which would have included the communication, the draft regulation on exclusivity, and perhaps the Fifth Framework Research Programme. That would have been ideal, but I already feel so guilty for not delivering the Regulation that to be guilty of blocking the communication on rare diseases just to be coherent would be even worse! I think we should progress with some elements of that policy. I am very glad Council has agreed on the common position on the Communication decision on rare diseases, and let's hope we can make some progress with the others. Coherence will come as it always does in Commission work from inter-service consultation and discussion. Maybe one day when all the pieces are in place there will be a need for a task force on rare diseases. But I am not sure this is the priority. I was struck by the remark by Patrice Trouiller. You can often get drug designation for a tropical disease because the prevalence is the prevalence in the Community. I believe that malaria is a rare disease in the Community. If you believe this is not clear enough, or we should address it, we can still do this in Draft 8.

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ANNIE WOLF, Ministère de l'Emploi et de la Solidarité, Mission des Médicaments Orphelins, France: Patrick Deboyser presented a very good proposal for a Regulation on Orphan Drugs, good for both patients and industry. We would like this proposal to be adopted as soon as possible by the Commission before passing through the Parliament and the Council. What can we do for you, Patrick, to help you drive this proposal forward so that it is adopted as soon as possible?

PATRICK DEBOYSER: Keep on doing what you are doing so well!!

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N. BAUDRIHAYE, S*A*Ph*I*R Europe: I consider that important features of the presentations put in evidence that the different programmes, whatever origin they have (DG XII or DG V)as well as the draft of the Regulation, are highly appreciated. I also think that the participation of senior representatives of the Commission here is a clear sign of the interest granted to the topic. However the delays and successive postponements encountered are creating problems. Would it be wise to analyze a little more in depth the possibilities which Patrick mentioned earlier, that is, if after a normal delay, the release of the Regulation is not allowed, to have a few people meeting again and trying to develop another strategy or a different approach? I think it would be important and useful, because the problem is the same everywhere –and that is "insufficient funds". These are insufficient within the DG V programme and that is also the reason why the Regulation is blocked.

I also have a few more technical questions. If I have properly understood, you have specified that the market exclusivity is linked to the centralized authorization. But in Article 8, it is stated that Community and Member States shall not give an agreement to other applications for a period of ten years. What is the difference?

I would also like to ask Mr. Le Courtois a question regarding waiving of fees. We know how it is now, and we know what is in the draft Regulation. But if I have understood correctly, the protocol assistance would be subject to fees, even for orphan drugs. Is that the case? It is clear that some fees are planned for protocol assistance operation, and I would like to know if that also affects orphan drugs, assuming that the Regulation has come into force?

It is also evident that there are some words in the legislation which are difficult to define, especially "similar products", "excessive profits", etc. Do you intend later on to think about guidelines by appropriate committees, or is it something which, as was the case in the US, has to be developed year after year following experience gradually gained by the authorities?

BRUNO HANSEN: This a very important issue that you have raised here. Patrick Deboyser was also saying that it might perhaps have made more sense to try to carry over the common plan – the health, the research and the authorization. If I have understood you correctly, you think that this might not be helpful. Sometimes by wanting to accomplish everything, you end up accomplishing nothing. So if something is happening, you need to act immediately and make a strategy. Could I also mention here that the Research Framework Programme contains other things as well as rare diseases. So I don't think that we could hold up the Research Framework Programme in order to get a complete plan.

The first reading in Parliament started in December 1997, the second proposal was made by the Commission on 14 January 1998, to show that we could accommodate some of the amendments from the Parliament. We had a political agreement on a common position in the Council on 12 February, followed by comments on that common position from the Commission on 13 March, and we could not do that until it was a written common position on 24 March.

The second reading in Parliament has now started, with a Council meeting for planning on 22 June. The Fourth Framework Programme covers the period until 1998, so we need to have a new Framework Programme in place in order to sponsor research in 1999. So we are aiming at making a call for proposal at the end of 1998, and start sponsoring research in 1999 under the Fifth Framework Programme. There are many hurdles to overcome, because after the Framework Programme you need to have a Council decision on the specific programme having heard the Parliament, and you need to have a work programme agreed by the Member States programme committees before you can make your call. You must also remember that this is a high-speed area, and there is no way that we can hold back on the research area and not do our best we can to get the money working. At the same time, we have to make sure that we have the right links between the "chair legs", making sure that we have the right expertise needed for further actions, whether as regards surveillance or authorization.

PATRICK LE COURTOIS: As far as the fee waivers are concerned, in the new regulation which is under discussion for new fees for the EMEA, there is a fee anticipated for scientific advice. So the waiver could also apply to this area. The problem here is that scientific advice is quite a punctual activity, and the protocol assistance will be much more important in terms of workload for the experts from the national regulatory authorities and the EMEA. The only thing we know is that the amount for fee waivers will have to be used for marketing authorization fees and for scientific advice of protocol assistance fees. So the only question is: Is the amount proposed too conservative in view of the number of requests which we receive as regards marketing authorization and protocol assistance for orphan drugs?

PATRICK DEBOYSER: I am not sure that I agree with that. In my view, there can be no fee for protocol assistance. Protocol assistance can only go to products which have been designated as orphan drugs and the EMEA will not be allowed to charge a fee for the protocol assistance. This is because the cost of the protocol assistance will be covered by the Community budget. There will be a specific subsidy paid to the EMEA to operate the protocol assistance, so if the EMEA was to levy a fee for that, it would not make sense, because protocol assistance can only go to orphan drugs. In fact, this was one of the criticisms that DG IXX made of our earlier proposal, and we accept that, on that at least, they were right, and we have changed it.

As far as market exclusivity is concerned, to obtain ten years' market exclusivity you will need to have obtained a) orphan drug designation by the Community and b) a centralized authorization from the Community. Then you are granted exclusivity against any other authorization in the Community, granted either by the Community or by a Member State. So the Member States cannot deliver an authorization. What I said is that there would be no exclusivity if a company which has got orphan drug designation was going to a Member State to obtain a national authorization. That national authorization for an orphan drug product would not trigger an exclusivity within the Community. I don't even think it would be feasible. You might say that the two procedures would balance each other out, but I don't think it would, because in the decentralized procedures there is no obligation to go to all the Member States. So the company could just go to one Member State and have exclusivity in the Community. The product would not be on the market in the other Member States. So for technical reasons, I don't think that we could give the exclusivity in the Community for a product going to the decentralized procedures.

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SILVIO GARATTINI, Istituto de Ricerche Farmacologiche "Mario Negri": What will the Community provide to help studies of rare diseases? I understand that the Fifth Framework Programme will essentially provide money for basic research, or in any case, research which is not for a competitive type of activity. This is fine, because we can only get an idea by studying a disease, and it is only by knowing more about the disease that we can learn how to develop new drugs for it.

In my opinion, in the Fifth Framework Programme the position of rare diseases is not well established. It should be a key position, because if there is one area in the Community that requires collaboration, it is rare diseases. If you look at all the other areas of health, there are very few where it is so important to have close collaboration. So if we look at the Community's philosophy for supporting research before it becomes a real entity, there is only one area, and that is rare diseases. Perhaps we have failed to convey the message to Parliament that rare diseases is an area where national activities alone are never sufficient. It is impossible to solve this problem on a national scale, so European collaboration is needed.

BRUNO HANSEN: In the field of rare diseases, as in any other field, you need to have the rules in place as a first step. I could describe a comparable situation, where we actually set up a task force on vaccine and viral diseases, because there was the need to bring the actors together. Who were the actors? Government, industry, science. Then you can say, yes, but that's too slow. But I can tell you that after that task force report which came out in January 1996, we are now sponsoring 34 projects for 26.8 million ECU, in a scenario which is as competitive as orphan drugs. Of course there were great difficulties with the European vaccine manufacturers as regards the way in which they could work together as they were also competitors, and allowing new companies coming in. 21 companies are participating in these 34 projects. Time has shown me that if you discuss things with the right participants, you create a network that will move. There is no way you can hold back because you have the resources.

If you say it is too late, yes, maybe it was too late in the past, but in the Fifth Framework Programme we are going to operate very quickly. We want to have money out in 1999, we want to make rolling work programmes and adapt them every year. So I think that what needs to be done, and there I agree with you, we need to establish some sort of grouping, that will take up the different issues and therefore know exactly what to do. Then you can respond quickly to the research framework programme, whether it is a demonstration project or research, and then you can also act on the others. But maybe you would like to hear the point of view of the industry.

ERIK TAMBUYZER, Genzyme S.A.: I think from the industry side we are really willing to play a role in the debate, and I am of the opinion that we should create some kind of platform with the patient alliances, the Commission and the industry to discuss the speed and transparency of the process, which is then something that can raise flags when problems emerge. I think that from the industry point of view, the most important thing now is to get the legislation in operation and make sure that it can get criticized or can prove itself, because time is of key importance.

I totally agree with your point about the need for speed and transparency, and that is perhaps something that that same platform can look at.

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ERIK TAMBUYZER: At the same time, I have a question. Many people have already pointed to the stalling of the present process of the legislation approval for budgetary reasons. We are all talking about the text, but there is no presentation by someone who has budgetary approval authority for this. I would like to see a possibility to shed some transparency on that part of the process to make sure that this is not further delaying the on-going process.

PATRICK DEBOYSER: The discussions on the budget are very much linked with the discussions on the subsidy to the EMEA. The Commission services in charge of budget are trying to reduce the Committee subsidy to the EMEA and they suspect DG III from trying to fire the EMEA through the back door. I believe Professor Garattini is right to detect that whatever budgetary dispositions are contained in this Regulation are to support a system which will be built on the EMEA. So it is true that there is a link. I have already said and accepted that some of the criticism made by the people in charge of the budget is correct, and this is why we have re-written the financial statement and our request is now more than half of what it was before.

But if I might address the question by Professor Garattini. I think you are right that this Regulation does not give direct incentives to companies in terms of research. The concept is a very simple one, and one which has been inspired by US experiences. A company can obtain orphan drug designation at a very early stage of the research, maybe ten years in advance of even looking at marketing authorization. You can be granted designation by the Community that no one can challenge. From that day on when you have got orphan drug designation you can start looking for grants, from Mr. Hansen, or from the Member States. You can apply for tax credits.

As you know, all of the Japanese system of orphan drugs is based on tax credits, tax credits because fiscality is a national competence and can only come from the Member States. But the Member States will not be able to challenge the status as an orphan drug. In terms of developing the drug, after research has been completed, we know that that is a cost. The logic of this Regulation is that the companies will be willing to support the funding of the development of the drug if they have reason to expect that they will be able to recoup that money over a long period, and this is the exclusivity bargain that we are offering with this Regulation.

In addition, developing the clinical products is very important; this is why we have built in protocol assistance, which is going to be entirely free, financed again through the Community budget. We know that many products which have been designated as orphan drugs in the US do not even reach the Community market. Forget about researching them, they have been researched and are being marketed in the US, yet they don't reach the Community, simply because paying for the regulatory process of having the drug approved is too expensive for the expected return. We hope to cover this with the fee waiver and the prospect of exclusivity in the Community.

So yes, this is a modest proposal, but we know that it is one that companies and patients are waiting for. When this is done, there will still be many other things to do. I hope that the next step will be that, in cooperation with colleagues from DG V and DG XII, we will be able to convene meetings with the Member States to ask them what their policy is in developing tax credits for the drugs which will have been designated as orphan drugs. But as far as I am concerned, the first step is to progress that Regulation, establish the system for designation and for market exclusivity. And then we can see what else needs to be done in terms of having the Member States contributing by means of their own resources, tax credits, or direct drug state aids, as well as looking at such issues as tropical diseases.

We know it is just one part of a bigger project, but is it the part we want to do now. But I entirely agree that this will not fuel any direct support to companies for the development of their drugs. They will probably want to do that themselves if they can obtain exclusivity at the end.

SILVIO GARATTINI: You are looking at the companies, but in future it may not be the only ones who want to develop some of these orphan drugs. There may be non-profit organizations, or groups that are not interested in exclusivity, but want to develop drugs that are useful to patients. So you also have to take into account this part of the European population, who is willing to do something in the interest of these patients, not only industry.

BRUNO HANSEN: You have heard Patrick Deboyser say that you are right. This is an authorization model, it is modest, built on the experience of the United States. I have already said, in a more optimistic way, that I believe you have done the best you could under the present legislation to create the tools. Of course this also invites participation not only from the industry, but also from the academic side. There need to be some specific actions taken in order to explore the possibilities in a discussion between companies and non-profit organizations, academia, etc.

MARLENE E. HAFFNER, Food and Drug Administration (FDA): I think, that at the present time, the most important thing is to get started and to get a Regulation through. I suspect that once the Regulation is out of the Commission and is submitted to the Parliament, some of the fun has just begun. At least, if your Parliament has anything relative to our Congress, then God help you!

I also think that Dr. Garattini has a very important point, and that is that our grants programme does not go to the companies at all. It does in the Japanese model, at least as originally passed. They support companies, for the most part we do not. Maybe 10 % of our grants funds go to only very small companies that do not yet have anything available on the market.

But what has been really exciting and delightful about our grants programme is that it does give money to academia, and when those academic people have developed a product to a stage that is a little bit further along that a gleam in somebody's eye, then the industrial side is willing to pick it up. But they simply cannot afford to pick it up before then.

I think that is important, and when, Professor Garattini, you say that the US is talking about increasing Biotech by 100 %, and they are, regrettably none of that is coming to me, and if you could talk to them about that, I will help you if you will help me!

BRUNO HANSEN: This reflects exactly what I was trying to say. You have a process, in which you start up research discoveries, and I mentioned the tools available in the research programme, even demonstration projects. That should bring the products through the first, difficult steps which no one from the commercial area would embark upon. But once healthy, they should not continue with subsidiaries, but it should be taken over by industry. And that was my point in creating the grouping I mentioned, that would assist in that process. I think that is exactly what we can do: "to press the orange the best we can"; we can support that on the research and demonstration side. And then we can make the links to what is needed further on to move it through. This is the only way we can start the fun.

ABBEY S. MEYERS: I also agree with Dr. Garattini. A very important part of the Orphan Drug Act in America is the orphan drug research grants. It is a very tiny amount of money; for the last few years, it has been about US$ 12 million if Dr. Haffner can hold on to it – sometimes other FDA departments try to take parts of it away. It has been critically important. I believe that 21 products have reached the US market with support from that research fund, including Ceredace for Gaucher's disease. The critical part is that if it supports an academic researcher and is solely for clinical trials, most academic researchers are able to get money from elsewhere for basic research. It is clinical research that is so difficult to find funding for. So they turn to that FDA programme, and if they can get a small grant and get the clinical data together, they can use that to attract a company. On the other hand, when a small company gets it – there was one company that just got approved last year for a drug to treat cystic fibrosis – it was only about US$ 100'000 a year that they got for this clinical trial, but they were able to go to Wall St. and say, "My drug must be better than everyone else's because the Federal Government, the FDA, is paying me to do this study", and they used that to leverage investment on Wall Street. So those few dollars and that programme have turned out to be extraordinarily important! I think it would be very wise for the European Union to put aside some money just for the small clinical trials that can be used for companies as well as academic researchers. Many of the 21 products that were developed out of that money are life-saving, they've been very important, and they just would not exist without that little bit of money.

With reference to the tropical disease question that came up before, if you look at tropical diseases which are basically forgotten – it is like the Western world doesn't care about them at all – it is the orphan diseases in Europe that are the tropical diseases of Europe. People living here who have rare diseases tend to feel that they are expendable, that they don't matter because there are not a lot of them and their problems are too unique, and I think that what we have got here is a Third World medical problem without a programme that really focuses on it. A number of tropical disease drugs have been approved in the United States; the latest is thalidomide for leprosy. We only have 8'000 cases, but this drug has been approved for leprosy. So you have to examine the drugs that have come through the American orphan drug programme for tropical diseases. One of them, I believe, was a disease that only had one American suffering from it. They would never get the attention of the world if they didn't get approval in the United States.

BRUNO HANSEN: The two messages we have received here are extremely important. Firstly, that you need to stimulate during the first part of the whole process to bring it to a certain stage in which it is natural that the conversation process starts. Secondly, your grant programme does not involve billions of dollars, it is actually a reasonable amount of money. Mr. Fracchia, how much do we spend in the present Framework Programme on rare diseases?

GIOVANNI N. FRACCHIA, European Commission DG XII: 8 million ECU, around US$ 9-10 millions.

ABBEY S. MEYERS: Has it occurred to anyone that Mad Cow Disease is an orphan disease? How much are you spending on it?

BRUNO HANSEN: This is interesting. I don't know how many of you here today know that the origin of the discovery of Mad Cow Disease was actually a concerted action sponsored by the Commission, with the participation from the UK, the Netherlands, France, Germany and Italy.

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LARS-UNO LARSSON, Swedish Orphan AB: I have a practical question. I always like to look ahead in time. If we look into the year 2000, this proposal will be in effect. Have there been any approaches to the Commission from non-Member States, such as the Baltic States or Norway? Have they approached you to be part of what you are doing? I cannot see that as individual countries they will do it all over again, and there are patients in these countries with orphan diseases and the same needs as in the Member States who can benefit a lot from this good proposal.

GIOVANNI N. FRACCHIA: The only country of which I am aware of has a strong interest is Norway. We have not received any suggestion or expression of interest from the Baltic States.

LARS-UNO LARSSON: The Australian Government has taken a very practical approach. They have gone to the US Government and asked: "Can we use your evaluation protocols?", "Can we use your know-how in evaluating and approving products?", and I think that some of the non-Member States should approach Patrick Deboyser's proposal, and maybe have it included that non-Member States should be able to get the evaluation protocols and benefit from them and have the product approved in a very short period of time in these countries without having to do it all over again with a lot of expensse and delay for the patients, and so on.

PATRICK DEBOYSER: Norway and Iceland will join the regulatory system this year. So when there is an orphan drugs policy it will automatically apply to these two countries. As far as the Baltic States are concerned – as you know, one of them, Estonia, is in the front row for enlargement – yes, one day they will be part of the overall system, including the EMEA. We are already working on them for recognition of the centralized authorization, for instance, but there is no specific project to associate them more quickly as regards the orphan drugs policy than the rest of the regulatory policy for pharmaceuticals. So they will benefit with the rest of the system. Again, the main priority for my unit this month, this week, is to get this project approved by the European Commission. When that is done we can look at some of these other issues, but clearly the priority is to get rid of that one and then we can move to other issues.

ANTONIO LACERDA DE QUEIROZ, European Commission DG V: As far as public health programmes are concerned, including that on rare diseases, they are open to cooperation both with international organizations and certain countries. These countries include EFTA/EEA countries, that is Norway, Iceland and Liechtenstein, but also all Central and Eastern European countries, all those countries which have an association agreement with the Community. At the present time, of the ten, we already have six Central and Eastern European countries. With the exception of Slovenia, all the nine remaining states are already participating in Community action programmes at a different level.

The reason Slovenia is not yet participating is that after the association agreement there is the need for additional protocol, as well as an internal procedure that takes up to 6 months – Parliament, Council, Commission – before they are able to participate. Due to procedural reasons, only six countries will so far be participating in Community action programmes, and certainly in public health programmes, including this one on rare diseases. But we expect that in the end, all ten countries will take part in the programmes.

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Afternoon Session

Experience with Orphan Drugs

Marlene E. HAFFNER, Director, U.S. Food and Drug Administration, Office of Orphan Product Development

Managing Orphan Drug Programs

I was saying to François Schiltz just before lunch that I come to many of these meetings, maybe not all with the EU, but I end up going to many meetings where I get the opportunity to talk about the Orphan Drug Act, and for the most part they become very routine for me. This is a most exciting meeting, and I am enjoying every moment of it. So I just want to thank you for permitting me the opportunity to come and to listen.

As I listen today, I have been struck by the frequency that the U.S. Orphan Drug Act is referred to. As we might say in the U.S., we are the best game in town. However, we have had more than 200 years now of independent states coming together and figuring out how to do things. We have involved our own culture and one cannot just pick up what we do and set it down here any more than one can pick up what you do and set it down in the United States. Were one to serve two wines in the United States for lunch, one would be just severely frowned at – I might say not by me, but perhaps by other people! We don't always do things the same, and we have to learn how to build on our own experiences and carry that forward. As I already said, I think the important thing is that one is moving forward, and that soon we will see a program here in the EU.

The unique thing about the Orphan Drug Act for the U.S. is that it did establish the public policy that the Federal Government must be involved in the development of treatment for rare diseases. This is something truly unique, unusual, different and something that had not been done before. I think most of you have seen in writing many times the definition of what an orphan drug is: "A drug intended to treat a condition affecting fewer than 200'000 persons in the U.S., or which will not be profitable within 7 years following FDA approval". This actually came about as an amendment to the Orphan Drug Act, because the first law had an economic definitions that was too difficult to implement; and so the figure of 200'000 was used as a surrogate for profitability. Clearly this definition is not perfect, but is one that I think, at least for us, has worked very, very well. I think that the population figures which the EU have determined are fine and will work extraordinarily well too.

I do want to point out that it is for a disease affecting fewer than 200'000 people in the United States, because it was already anticipated at that time that we did have a responsibility to countries where products could not necessarily be developed, and that we would assume that responsibility. And so today – unless they have done something to me since I left Washington on Sunday –, we have 168 orphan products approved for treatment of rare diseases. If you add up the population of each of those, you come up with 7'862'136 people in the U.S. who are potentially being treated for their orphan disease with an orphan product. If you look at figures in a somewhat different way there are now 711 active designations. We have granted more designations than that, but some have been withdrawn as products have been approved and a company developing the same product has withdrawn their designation.

Some designations have been withdrawn as companies have determined that a particular product simply is not going to work for that disease. Periodically, a company decides that they are no longer interested in developing a useful product; then we go about finding a firm interested in doing so.

We have awarded 350 grants, and from those, 21 products have been approved through the Grants Program and there are many, many more approaching the approval stage.

When I talk about the Grants Program, many times drugs get used in rare diseases in an anecdotal fashion – it helped Auntie Nelly, so probably it will help Uncle Paul. Good clinical trials are hard to do. Many of our grants have been awarded to those kinds of clinical trials where there is only anecdotal evidence. Sometimes we find out from those clinical trials that the product doesn't work on that disease; that is extremely important data as well. We don't want people exposed to a drug that is not going to help them, and may be detrimental. Virtually every drug that we know has some less than beneficial side effects.

In the Research Grants Program we look only at clinical trials. We would love to do basic research, but we don't have the money for it. I depend on Abbey [S. Meyers] for getting us more money, but even Abbey has been unable recently, and she has tried very hard!

Orphan drugs are important drugs. It is nice to be able to look at things through the "retrospectroscope", and we have discovered all sorts of things that were not anticipated. Nobody thought that there would be 63 new molecular entities developed through the Orphan Drugs Program, and we also have 52 new uses for products that were already on the market. Both of these are important bits of information.

Our mission, then, is to assist and encourage the identification, development and availability of safe and effective products. I heard, I think it was Patrick Deboyser, talk about the fact that there might be occasions where it was too difficult to do a clinical trial because of the size of the population, and we thought the same at the time the Orphan Drug Act was passed. But since PEG-ADA was approved for a population of twelve in the U.S., we have decided that we can find a way – if the drug works well enough – to approve just about any drug for the rarest of all diseases.

The incentives. One of the incentives, quite frankly is the assistance of my Office, and I think that you all will find that as well. Now, it could be that that translates into your protocol assistance, which, as has been mentioned, we don't use in a formal way; we use it informally in a tremendous amount, but formally it is almost not used any more. Our Office works with the companies, with the rare diseases communities and with the FDA, so we are quite a valuable broker. We inform the FDA that, you know, "You would like a second clinical trial, but you have got a population out there of 500 people, so there is no way you are going to do another clinical trial!" At the same time, we will be sitting down and working with the company and saying, "I know you say you cannot do another clinical trial, but your population is not 1'000 people, your population is 20 or 30'000 people, now just go find them!". Or, "How about if you cannot do a second clinical trial, you agree to do a post marketing trial?" And so we are working back and forth in complete openness, but still helping each other understand what the other is doing. Then when we get really frustrated, we talk to the rare disease community; we call Abbey, and she acts as a communicator as well. But the name of what we are doing is communication.

Marketing exclusivity, as you have already heard, has been a very important incentive.

Tax credits for clinical research are just beginning to become important. For a long time these credits would expire every year and a half to two years, and companies could not count on them. But within the last year, they have been made permanent with a 15 year carry-forward and a three year look-back provision, and that has made them very, very valuable, especially to small and medium-sized enterprises.

User fee waiver. This is brand new for us. In the original FDA user fee legislation, orphan drugs were not written as being waived from user fees. Indeed, most that applied received waivers, but they had to go to the trouble of putting the application together. Now orphans are automatically exempt from application fees, and we have seen our workload go up more than 20 % since November when this law was passed. So we think that user fee waivers are having a major impact.

And then another very real incentive, as has been already discussed today, has been our grant funding for clinical trials.

What do orphan drugs need? They need enthusiasm; they need someone to fight for; to be their defender. These are products that only those with the disease are really interested in – and not everyone has a family member with Adrenoleukodystrophy, or with Maple Syrup Urine Disease, or with Amyotrophic Lateral Sclerosis – so they need a champion. They need to be effective and safe. They need the same approval requirements as non-orphan drugs. You do not want a second-class citizen, and I think you all have acknowledged this loud and clear, but you need to repeat it to yourself frequently. I still get asked, “Orphan drugs, you run orphan drugs, those are experimental things, aren’t they?”. And I say, “No, no, no, those are drugs that treat rare diseases, but they indeed have been shown to be as safe and as effective”.

Now in truth, they are probably less safe and more effective. Less safe, only because if you are giving a product to 1'000 people in your clinical trial, or let’s say 500 people in your clinical trial, you are not going to know all the side effects that might occur. On the other hand, in order to show efficacy in a clinical trial, you have to have a product that works fairly well, otherwise it is going to take a really creative statistician to show that it does work. You need, as I said, a dedicated physician or researcher, and clearly one needs a sponsor. Virtually all of our products that have been approved have been adopted by a firm prior to approval. I say virtually, because there is one researcher in Dallas, Dr. Charles Pak, and he has – on his own – written four NDAs. But he is a most unusual guy, coupled with a committed sponsor so that they can jointly use resources.

In studying and assessing orphan products it has already been mentioned that among the problems we have with rare diseases is the real aetiology of the disease, the science behind the disease. All diseases have some degree of heterogeneity, and so orphan diseases do as well. We now have three drugs approved for Wilson’s Disease, which is indeed a rare disease in the United States, and we find that some patients are benefited by each of these drugs, and there may still be some patients that are not benefited completely by any of them. So one always has additional needs; you need more than one anti-hypertensive and you probably need more than one product to treat many of the rare diseases. At least as long as we are treating, and not curing.

We need novel study designs. You need to know that your product works, and there is a variety of ways of finding that out, all of which require clinical trials. But, for instance, in one situation we found that virtually all the patients with a particular disease were already being treated by the drug, but we really could not establish efficacy. So we went to withdrawal trials, where everybody on the drug would continue taking their pills, but a certain number then would be randomized to placebo, and they didn’t know who they were. They had to agree to participate in the trial, but they didn’t know who was continuing to take placebo versus who was taking what was considered to be the active ingredient. Then, if the disease reappeared, we had some idea that the drug did work.

You have to have a disease that is readily treatable again by the drug; you have to have a drug whose half-life activity is short enough that it can be used in the situation described; and, clearly, you have to have willing patients. There are unique study designs that have been developed around orphan drug treatment or orphan drug use; many of the standard double-blind clinical trials are not easy to carry out in these populations.

We need creative statistical methods. Now, I don't mean we need to lie – we always say that figures don't lie, but liars figure! I don't want liars figuring here, but one has to look creatively statistically, because there are plausible sub-sets of patients with a particular disease that may be helped by a drug, and so it is very important to be able to evaluate creatively, and flexibly. Clearly one needs flexibility in studying orphan drugs.

If you have holes in your data – and you will have holes – you must look at risk benefit, and be flexible. You have got to look at how much and how adequate that data is. Is it reasonable to make exceptions in this instance? Or do you have to say, "You know this is great, but it is not great enough and we have got to have more data". You don't want to compromise the health of the patient, nor do you want to hold the requirements too stringent. It is possible that a drug will be approved that you find out later does not work well. You can remove it from the market, or at a later time, you can publish the pitfalls of using the product. If the drug has what appears to be a good enough safety profile, it may be worthwhile to make that product available for patients, so that you can either look at it as far as a larger trial is concerned, or continue to evaluate it and see how well it might work.

I have already mentioned that as far as safety is concerned, rare events – and probably even fairly common events – may not show up in a clinical trial for an orphan drug. One always has to emphasize and be aware of risk-to-benefit ratios. We talked earlier about the fact that orphan products have the same review standards as do non-orphans. However, traditionally orphan products have received a faster approval than have non-orphans. Right now, with user fee resources, they are about the same, but the reason for the faster approval time is that usually there is not any other drug available for this usually serious and life-threatening condition; you have fewer data points to evaluate; and you have a product that probably works very, very well because you have been able to show that it works. So you have got four things going for you. There is no automatic fast-track for orphans. FDA has recently passed in the FDA Modernization Act fast-track provisions which will look at surrogate end points as to their acceptability for drug approval.

We have looked at surrogate end points for a long time in orphan diseases. Sometimes, using surrogates works – sometimes, not always. But fast-track, per se, will be available to all clinical drug trials, not just trials for rare diseases.

What if we approve a drug that we determine is not effective or is not safe? As far as effectiveness is concerned, you are talking about a small number of people. But sometimes you may pop up with some safety parameters that are absolutely frightening when they make themselves manifest. These were not visible during your clinical trial of 32 people. Most likely, during research, patients have not taken it long enough to be certain without a doubt. You have a responsibility to take corrective action. On the other hand, you cannot wait forever to get a drug into the market-place – until, and if, it is proven completely safe. That just won't work. In many instances, you have to evaluate the risk benefit.

Some time ago, we evaluated PEG-ADA. PEG-ADA is a fairly famous orphan. Its approval was based on a study of six patients. Historical controls were used rather than any kind of blinded study, and we did use a clinical end-point. So the clinical end-point was that these kids could lead a more normal life. They were no longer confined to a bubble, and indeed we discovered during the trial that they could even get chicken pox and stay home from school for a few days and then go back to school – something that was absolutely unknown in the days before PEG-ADA.

These children would have died from chicken pox. We found that the drug was measurable in the blood and that the red cell metabolites did imply activity of the product itself, and that was the basis upon which this drug was approved. The data that we had was not as in-depth as we have had for other products, but it was in-depth enough, and some more than five years later the drug is still actively treating these kids, not just in the U.S., but now in a worldwide fashion. The drug has been a life saver for children with PEG-ADA deficiency.

We have had some issues and debate. Same vs. different keeps challenging us. And, Patrick, I look forward to working with your group on defining same drug vs. different drug.

Medically plausible subsets. A question that came to me just before we began this afternoon as to what is a medically plausible subset and what is not. Medically plausible subsets is a nice way of talking about “salami slicing”. Is a subset of disease legitimate or is it simply a way for a sponsor to define his disease as an orphan disease? We have written a position paper on medically plausible subsets. Development of the document began with a request for designation of a product for end-stage colon cancer. Colon cancer is fairly common in the U.S., affecting more than 200'000 people, so we said, “Why are you requesting for end-stage?”. They said, “Well, because any wider population description would be over 200'000”. I said, “You must have a better reason. Why medically are you requesting that?”. Well, they didn’t really have any answers, so we sat down and thought about it, and we said, “Well, if a drug is too toxic to be given at an earlier phase of disease, we will take a look at it.” In other words, if there is something about that particular subset that is indeed different, for instance: you find out later on that a disease is really quite heterogeneous and maybe more than one gene is affecting the disease process, such as occurs in Maple Syrup Urine Disease where there may be different gene loci that cause the disease. That is a legitimate subset. There are other similar kinds of explanations as well, but in general we look at treating the entire disease process.

There are situations where a drug may treat more than one disease. One disease may be an orphan disease, and another may not. In this situation, each disease will require its own clinical trials to determine safety and efficacy of the drug in that disease process. Then the multiple designations and approvals are not salami slicing, but rather are legitimate disease entities entitled to individual designation and approval, and exclusivity. This situation is well explained in our Regulations.

We have had some profitable orphans – or those we presume to be profitable orphans – but the numbers have been very, very small. We have 168 approved products and there may be four or five drugs over which there has been controversy surrounding profitability – hardly a majority. We have had discussions about the advancement of science that ties back into same vs. different. You always want to be able to approve a new product where science will be advanced. You don’t want to hold something back because it is just the same as the previous product. On the other hand, the initiating sponsor has done the major amount of work, and so you want to protect the innovator.

Once again, there are delicate scales to balance. I sometimes wonder whether it should not be medicine that has the scales as its symbol rather than justice!

Typically an orphan drug treatment is a therapy for which there is no other treatment available. I mentioned three treatments for Wilson’s Disease, but that is indeed an unusual circumstance. Wilson's Disease has a dedicated researcher who develops excellent new ideas for treatment. Orphan diseases are frequently bad; about 90 % of orphan diseases are serious or life-threatening.

Bigger and better clinical trials than what you have sitting in front of you to evaluate are probably not going to happen, so do the best with what you’ve got! A bigger and better clinical trial would both delay the availability of the product and cost huge amounts of money that may not be reasonably spent. There are times when it is necessary to spend money. But there are other times when a delay is only costing money and lives, which is unacceptable.

I have put together a few of our famous orphan drugs: Both Pentamidine and Zidovudine originally were orphan drugs. Pentamidine was long off patent; the IND had long been held by the Centers for Disease Control for use with the occasional patient with chemotherapy that got Pneumocystis pneumonia. Then, suddenly, the drug was needed. It took us some time to find a sponsor. At the time Pentamidine was approved, there were fewer than 500 cases of Pneumocystis pneumonia described. It seems impossible today!

AZT was developed in 1961 at the University of Wisconsin for use in certain malignancies, but it was believed too toxic to be used; there were better drugs around. In 1981, when the first AIDS cases were described, Zidovudine had been around for 20 years, so the patent was long gone. Were it not for the Orphan Drug Act, both of these drugs would have taken a lot longer to be developed.

AZT ultimately got a use patent; I am not sure that Pentamidine ever received any personal property protection. So, the orphan products program is rather proud of this service to the public health. The population of patients obviously grew too large for the disease to be an orphan disease; but, the Orphan Drug Act significantly assisted the patients that had and have HIV disease.

Interferon for MS has been mentioned today. This is a product where exclusivity was broken for approval of a second product. The second Interferon seemed to have a significantly better safety profile. We have not broken exclusivity for efficacy. We have done it several times – several meaning maybe four – for safety, but we have never done it for efficacy. People have come in to us and argued efficacy, but they have never been able to prove it to us.

These are some statistics that I am sure were not really contemplated at the time the Orphan Drugs Act was passed. 82 % of orphan products are for serious or life-threatening diseases. Of the drugs approved, 29 % have been for pediatric indications. 25 % for oncology products, 18 % for infectious diseases and that includes some of the diseases for developing nations' Malaria, Leprosy and Filariasis in addition to HIV. 13 % have been replacement therapy, such as growth hormone for dwarfism, PEG-ADA for ADA deficiency, and the like.

What are some of the barriers to developing and approving orphan products? There is a small market obviously – after all, they are rare diseases. It is a chronic market for the most part. If you look at the list of drugs for rare diseases in the U.S., there are very few of them that are given for 7-10 days. Most of them are given for a lifetime, and some for 3-5 years. That is significant for manufacturers to consider as they are looking at an orphan drug. You can clearly realize more return on income from a product, even if your population is very small, if it is given for a very long period of time.

The patients are of course widely dispersed – they don't all occur in Brussels, they don't all occur in Paris. They know no state or national boundaries, but as individual researchers begin to make a name for themselves in a particular disease, patients do flock to that center, and I think that one thing that hopefully you will be able to do is to develop centers without regard to national boundaries. So that France will become the place to go, let's say, for Amyotrophic Lateral Sclerosis, and Luxembourg for inherited metabolic diseases. I don't mean those specifically, but that kind of situation, so that you can afford to have a concentration of interest and patients know the best place to be referred for a particular illness. The products are frequently not patentable, that is why they were not being developed in the first place, and the only personal property protection that you are able to offer them is the protection of exclusivity, which is important.

Heterogeneity of disease and orphan diseases are no different from any other diseases. They are extremely heterogeneous and we know less about them than we do about more common diseases.

Our Program has now been in existence for 15 years. I have been there for almost 11 of those 15 years, which seems totally amazing to me! I don't believe in staying in jobs for more than 5-7 years, but this has not been the same job, and I am going to stay until it gets boring. Abbey, don't kick me out yet!! It is a lot of fun and to see a program develop and expand the way our Program has done makes you feel good at night. So I can only encourage you to move forward with due diligence and get something started. We found early in our time that our Act was amended three or four times. It has been fairly quiet recently and I hope it stays that way – other than getting more grants money! It has done a tremendous amount of good for more than 7 million people in the U.S.

Lars-Uno LARSSON, President, Swedish Orphan AB

Practical experience in developing and marketing orphan medicinal products

I would like to share with you not only my experience of being involved in orphan drugs, but also my experience of forming a company 120 % devoted to the orphan drug cause. I hope to be able to share with you our experience in the distribution, marketing and development of orphan drugs. I also would like to touch on what is going on in this room, i.e. professional relations, which over the past ten years I have learned to appreciate and found very important in the area of orphan drugs. I will then like to close my presentation by commenting on some few issues which I think we feel are important in the world of orphan drugs.

Eleven years ago, working for a major pharmaceutical company, I found on my desk a report of an orphan drug conference here in Brussels. Some of you here today, I believe, attended this conference. The report made me very interested and I decided to look into this area to find out whether it would be worthwhile devoting time and energy to work on orphan drugs. After some market research we found out that there were actually quite a number of orphan drugs in late stage development and/or approved in the USA. However, most of them were not available in Europe, neither for clinical research, nor for introduction to the market.

With this background we decided on a short term strategy, i.e. to try to find a way to bring these products to the attention of scientists and regulators in the Nordic area, which by that time could have been labeled as ”Orphan territory”.

On a long term perspective, we decided to find a way to develop orphan drugs through in-house programs – but the short term objective had to take priority. Thus, we decided to broaden our market research by visiting health care providers, governments, the pharmaceutical industry and patient support groups in Sweden, France, the UK and the USA. We were overwhelmed by the interest we received. So we decided to form a company called Swedish Orphan AB. We had a long discussion regarding the name, but we felt strongly that the name “Orphan” had to be part of any activity we were planning to be involved in – we were convinced that one day this name would be well recognized in the world-wide health care industry. We also had several discussions regarding the funding of this company. We decided initially that the company should be a ”non-public” company; we wanted to have the freedom to work with any orphan drug, no matter how small it was. To finance the start-up of the company we – in addition to the investment made by the original share holders – approached the banks and the Swedish Development Foundation, but also the Wallenberg Foundation. All of them found the mission of our company very interesting and decided to support us. To travel to the USA for our initial contacts with the FDA, PMA, NORD, etc. we received a travel grant from the Wallenberg Foundation, and as Abbey Meyers said, ”the first grant makes people very excited”, and this is what happened to us – we were extremely encouraged that this prestige foundation supported us.

An important part of forming the company was to find the right partners. We engaged in looking for the ideal partners with long international experience in the industry, but also partners who where prepared to take long term view. We were successful in finding these partners, who still are with us, 10 years later.

With this background, we formed Swedish Orphan AB in 1988. At that time, Sweden was not a member of the European Community, and after two years, we decided that we should do something similar within the European Community. Thus an affiliated company was formed in France – basically due to the fact that the French Government seemed very committed to Orphan drugs and after a stimulating discussion with Annie Wolf.

This was followed by the formation of an affiliated company in the USA, Orphan Pharmaceuticals, with the objective to bring orphan products being developed in Europe to the U.S. Today, there are affiliated companies being formed in Japan and Australia. We also made a first initial grant to start up the Orphan Foundation, a non-profit foundation, to support research and development in the orphan disease area. The objective is that sometime this year, this foundation will be in the hands of some Swedish scientists dedicated to the cause of orphan diseases.

So what have we achieved so far? Well, we feel that in some way we have been pioneers in identifying orphan drugs and bringing them to the Nordic area, Europe and later on also to Australia, Japan and the USA. Today, the pharmaceutical and biotech industry regularly contacts us to discuss collaboration in the orphan drugs area.

We believe that the network of Orphan Pharmaceutical Companies makes available around 40 orphan drugs around the world. Approximately 40 employees are involved in the network, and we strongly believe these employees represent 40 ambassadors of the orphan drug cause.

The organization could be said to be a mini-version of a traditional pharmaceutical company, with a smaller and sometimes more devoted staff with experience in regulatory affairs, clinical and medical affairs, marketing and distribution. One product, Cystagon, which is made available by the MA holder Orphan Europe and Swedish Orphan AB, was mentioned this morning by Dr. Le Courtois. Cystagon recently received an approval through the centralized procedure with a full waiver of the application fee, which has served as an important encouragement in our day to day work.

When it comes to the marketing of orphan drugs, we feel that the most important to work with is what we call medical marketing, realizing that these products and this disease area are handled by the specialists of the specialists. Thus, we are very much involved in clinical research programs, we have participated in several publications and consensus reports as well as chapters in medical text books on rare diseases with diagnostic and therapeutic guidelines. We believe this to be one of the most important part of our daily activities.

A first example is a clinical research program designed to confirm the development of a novel antivenom therapy for the treatment of Viper bites in Sweden. Here we coordinated a clinical research program regarding a four-year study in 18 hospitals. The study is completed, published, the results have led to new guidelines on how to treat Viper bites in Sweden. The experience with this technology in Sweden has resulted in similar programs sponsored in other parts of the world.

A second example is Kaposi's Sarcomas, with approximately 15 cases in the Nordic area. Here we have been part of a Scandinavian Consensus Study Group, which resulted in therapeutic guidelines for the treatment of Kaposi's Sarcomas.

We have also been engaged in several pivotal studies in the treatment of systemic fungal infections with liposomal amphotericin B. Also here, the studies have resulted in several publications in leading journals – to the benefit of those 300–400 patients with immuno-compromised host.

Let's now move forward to another area which we are involved in, i.e. an in-house development project: Tyrosinemia I, a life-threatening disease. It is an acute liver failure disease and the only treatment until several years ago had been diet and liver transplantation. Swedish Orphan together with Swedish scientists is developing a Dioxigenase Inhibitor for this disease with the assumption that the compound could improve liver and kidney function, neuropathy and quality of life. 200 cases of Tyrosinemia I have been diagnosed worldwide. The ultimate goal is to file for a marketing authorization in Europe, USA and Canada in a few years. The Dioxigenase Inhibitor has initially been discovered by Zeneca and licensed for worldwide development to Swedish Orphan. The funding of the project is a "joint-venture" between Swedish Orphan, its affiliated companies and the Swedish Development Foundation.

As a small company, one has to be very creative in maximizing one's resources. Thus this exciting project is driven by a Project leader from Swedish Orphan together with European and USA project team members, a Swedish Research Group and in close collaboration with CRO's, tox experts and a contract manufacturer.

For the last 10 years, we have had the pleasure to get invited to meetings like this one in Japan, the USA and Europe. We think this is the most important way to make public relations and create good will for orphan drug regulations, orphan drugs and orphan diseases.

As a part of our mission, we have been very active in promoting this by, above all, providing free of charge the NORD Database on Rare Diseases to the medical and patient support community in Scandinavia. As a matter of fact, we promote the concept of orphan drugs and orphan diseases every time we participate in medical meetings or conferences. A year ago, we had been invited to participate in and speak at the European Pharmacy Students Association meeting where we encountered great interest and approval on the part of the students. We really feel it is important to bring the concept of orphan drugs and rare diseases to the attention of medical and pharmacy schools, and to get them involved as early as possible.

Some final comments: Whatever we do in making orphan drugs available or developing orphan drugs – there is always the issue of reimbursement. So, in meetings like this one, it would be excellent to have participants from social security and insurance companies in order to avoid misunderstandings at the time the products enter the market place. Another issue, as discussed earlier, is the waiving of application fees, but also of annual fees and fees for clinical research programs.

Over the years, the Swedish Medical Product Agency has been very receptive and waived annual fees as well as fees for clinical research. We believe this should be part of the European program. As mentioned by Marlene Haffner, grant programs can represent a great encouragement for the development of orphan drugs. In the USA, a research group recently got a grant for clinical research related to the Dioxigenase Inhibitor compound discussed earlier. Marlene Haffner also mentioned a US scientist, Dr. Charles Pak, who has developed several orphan drugs in the kidney stone area. Swedish Orphan is making these products available in the Nordic area and the Danish Board of Health has recently made available a major research grant to a Nordic cooperative group in urology with the objective to confirm some of Dr. Pak's hypothesis. Thus, we feel a continuos excitement and encouragement in our day to day activities.

Let me just finish by making public relations regarding the First Workshop on Orphan Drugs to take place on 22 August of this year at the Karolinska Hospital in Stockholm, Sweden. This meeting coincides with the tenth Anniversary of Swedish Orphan. The workshop at Karolinska will be preceded by the First Nordic Forum on Rare Diseases, with the objective to familiarize clinical specialists with the world of Orphan drugs regulations.

Open Discussion, Part 2

LESLEY GREENE: I just want to make a couple of quick comments in support of Mr. Larsson's presentation. Firstly, earlier this year, our organization received three different inquiries from families whose babies were newly diagnosed with Tyrosinemia. I am pleased to say that all those babies were already on the product that Mr. Larsson has been describing, so those babies' lives are being saved.

The second quick illustration is of a typical Sunday morning. My husband, Peter, is washing the car, I am out taking the kids to judo. There is a phone call on our helpline. My husband has to take it, after wiping the soap off his hands. It is a doctor in an emergency room down in Surrey. She has a patient with Acute Intermittent Porphyria, realizes that this patient needs Haem Arginate but doesn't know where to get it. I get home and phone one of Larsson's UK pioneers on his mobile, he phones a hospital in Cardiff that has the Haem Arginate available, which is then transferred from Cardiff to Surrey. It is administered to the patient, and the patient comes out of the emergency room. I think that is enough said.

BRUNO HANSEN: This underpins what we have been saying about the importance of information, the importance of making sure you are early and have an information network so that the information is available, because it is needed very fast. What is your experience in the United States?

MARLENE E. HAFFNER: I think our information system is two-fold. One is that NORD® gets a tremendous amount of phone calls from patients and parents when they are in trouble. We get phone calls from both our patients and our pharmacies. None of them come before 4.30 in the afternoon – 4.30 on a Friday afternoon is the most common time for the phone to ring, and since I cannot abide a phone ringing, I am always the one to pick it up after everyone else has gone home! But we always manage to find a way for people to get the product – well, almost always.

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PAUL W.J. PETERS: Apart from the activities and actions at the FDA, there is also the Office of Rare Diseases in the National Institutes of Health (NIH). Can you elaborate a little bit on what their responsibilities are, and what their budget is? What is the "added value" of the National Institutes of Health, with their activities in the area of rare diseases?

I have a second question to you: What about privacy? The number of patients is small, they might be all known to the pharmaceutical industry. Is this a problem or not?

Before I forget, I appreciated your lecture very much, because it was not only clear and open, but also showed how involved you are yourself. The clearness of your presentations can also be seen on your homepage on the Internet, and I would advise everybody to check regularly not only the homepages of the FDA, but also of NORD® and the National Institutes of Health, because the enormous wealth of information is very useful.

MARLENE E. HAFFNER: First of all, as to the National Institutes of Health, which as everyone knows, is a major research arm in the United States. They carry out a tremendous amount of basic research. They now have an Office of Rare Diseases, headed by Steve Groft. They have put together a database on what grants exist throughout the US as far as rare diseases are concerned. And we rely on NIH for a lot of the work that comes afterwards. As I mentioned our grants programme is very small; it can afford to be so small because the basic research is being done at NIH. As far as privacy is concerned, it is not an issue that comes up. There are times when a firm has difficulty finding patients with a disease. We send them to Abbey [Meyers], Abbey then queries the patients and says, "If you are interested, contact so and so". She would never give a company a name, because that **is** a privacy issue. Patients are very anxious to get therapy for their disease. Where we have had privacy problems, and I am sure this is as true with rare diseases as with more common diseases, but as we are beginning to find out more about the genetic origin of certain diseases, and the genetic basis of certain diseases, people are afraid to be tested because if their employer or insurance company find out they will lose their employment or their insurance. I have heard a lot of people discussing this as far as the BRAC 1 and 2 genes are involved in breast cancer and I can imagine that Huntingdon's Disease would have the same problem – the list could go on in that regard. But from what we have seen, it has not been a problem.

I do want to thank you for mentioning our Web page. Our address is: www.fda.gov/orphan. If you forget all that, just type in "fda" and put it on a search engine and it will eventually get to us – we have a hot key on the FDA homepage.

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MICHAELA REHBERG, PhD, Medac Gesellschaft für klinische Spezialpräparate mbH: With reference to Mr. Larsson's speech, when he pointed out a long tradition of developing orphan drugs, I would like to know if a procedure has been discussed yet as to how to deal with orphan drugs that are already on the market in Europe?

LARS-UNO LARSSON: That is a very, very good question. We have seen over the years that now companies are taking products off the market which have a small volume. We have been approached on several occasions over the last year about the possibility of looking after this kind of products. That is something we are very positive towards, and I think any pharmaceutical company has to at least try to find another supplier or someone else who could take care of those products because they could be very instrumental for those few patients who need them.

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STEPHANE KORSIA, EURORDIS: The theme of Marlene Haffner's presentation was clinical trials and the methodology of design and analysis of clinical trials. Nowadays in the Community there is an attempt to harmonize the good clinical practices for human clinical trials. It is one of our concerns that this harmonization is only done for large trials, and for small trials for rare diseases we are going to run into cost problems due to all the constraints imposed on the sponsors. I would like to know what, in your opinion, is a good environment to do a clinical trial on rare diseases, in terms of ethics and regulatory affairs?

MARLENE E. HAFFNER: The best clinical trials are double-blinded, controlled trials. You get your fastest answer that way. It is not always possible to do, but when patient groups don't want to get involved in a placebo-controlled or even an active-controlled trial, they are always assuming that the product works. They are forgetting that you are trialing the drug because you don't know whether it works. So all the good clinical practices that are being discussed, do apply to orphans. You just have to be flexible and creative. I have not seen recently the various guidelines, so I cannot critique them, but very few are made to be followed absolutely rigidly, under any circumstances. We just have to be perhaps a little more flexible in the orphan disease situation.

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BRUNO HANSEN: Stéphane Korsia, I would like to ask you why you suspect that orphans will be forgotten?

STEPHANE KORSIA: I could give you a simple answer, and say that it is because they have been neglected for so many years. But beyond that, it is because the Community is a multi-state environment, and because some domains, such as tax, and in the case of clinical trials, ethics, are national issues, we are going to have to deal with each individual Member State on some level. In particular for Ethics Committees, if we follow the new, Good Clinical Practices, we would have to have one opinion per State participating in the trial, plus one eventually per site. Now, if you have 50 patients with a rare disease, you may have one patient per site, which means you have 50 different sites.

PATRICK DEBOYSER: With all due respect, that doesn't make sense to me. We are promoting the Clinical Trials Directive. I can accept that you say that in the Clinical Trials Directive there is no specific mechanism to address clinical trials and orphan drugs. That is correct. But to state that the Clinical Trials Directive is going to make clinical trials for orphan drugs more difficult than they are at present, that is totally wrong. Because you have an orphan drug, it is likely that the population will be suppressed. This is the situation that we are addressing in the Clinical Trials Directive. It is true that you will still need one ethics opinion per country. The current situation is that you will need several per country, so one per country is an improvement. However, I am prepared to discuss this with you. The Directive is currently before the Parliament. If you have an amendment in mind which could improve it, then I am open to discussion. But I believe that you have to be more specific in what you would like to see in the Directive. Just to state that as usual, it will make things more difficult for orphan drugs clinical trials, is wrong.

STEPHANE KORSIA: No, I am not saying that it is going to make things more difficult than it is today – I don't think that that is possible! I am just trying to foresee difficulties that could arise, and try to find creative solutions that might make things even easier.

PATRICK DEBOYSER: What I mean is that you are launching an unfair attack against the Directive. I believe that it is a very important piece of legislation. It will do a lot for the information of patients in clinical trials, speed up multicenter-clinical trials, and I don't think you are doing any good by saying that it is not specifically addressing clinical trials in orphan drugs.

BRUNO HANSEN: I am sorry to have provoked this matter, but it was intentional. I think that it is important that we put this matter on the table, that we attack it and get to grips with it. Can I say that as regards clinical research, the new Framework Programme actually foresees supporting Centers of Excellence. This is, of course, not because we want to substitute what companies should normally be doing, but because we want to actually get to the surface how we, at a European level, can promote the science base and how to come to grips with doing clinical research. It is evident that this requires that you set up, let's say, Centers of Excellence with specific knowledge, that you link them together and discuss rare diseases and orphan drugs.

GIOVANNI N. FRACCHIA: I have a point to add to this. To come back to the draft Directive on GCP, the spirit of the Directive was the protection of the individual as a part of an experimentation – protection not only in ethical terms, but also in terms of the quality of the product which is administered in the trial. Why should a patient, who is suffering from a rare disease, be discriminated against and not have the same high standards of quality as other patients? This applies equally well to rare diseases as to other kinds of diseases. So one should actually congratulate the Commission services for having produced such a proposal.

MARLENE E. HAFFNER: I just wanted to make one comment. We have had one experience in a grant for infant Botulism, where there were 60 different sites that were used. We funded all of it. The cost over six years has been about US$ 500'000, which I think is a nominal cost. We have saved the State of California US$ 4 million. The product works – and works well – and has reduced the length of stay in hospital of patients with Botulism from 68 days to 21 days maximum. That includes both those who got the drug and those who got the placebo. So I think that the cost of the clinical trial has not been excessive in this situation. It took that long to do the trial because we needed 120 patients to determine efficacy; at least, that what our statisticians told us, so that we had 60 with placebo and 60 with active product. The researcher is, I suspect, one who has never gone to bed – he is always busy! He had to go to all 60 hospitals, discuss the protocol and get the approval from their institutional review board. So it was a lot of work, but it was do-able, and when he gets the NDA written and submitted, we will have a product that is going to be very worthwhile. So that is our one major experience with something like that. We have lots of drugs that are trialed in more than one site, but 60 sites for an orphan with a total of 120 patients means a potential of two patients in one facility; some, of course, had none and some had more.

SILVIO GARATTINI: In relation to the question of clinical trials, which are particularly difficult for rare diseases – because of the difficulty of collecting patients –, I believe that the standard should be randomized controlled clinical trials. But there might be other possibilities: for instance, the development of the so-called ”N of 1” trial, where you do studies in a single patient and you alternate various treatments, and then you can use the method in other schemes in order to convert it to a ”control” trial. I am saying this only because I believe that there should be more interest in this topic which is not discussed enough. I have never seen a workshop that brought together people who are interested and knowledgeable in this field. If we could do this, perhaps we could find new ways to produce schemes for treatments and new statistical designs, and so on. I think we need to adapt the clinical trials to the fact that in some cases we have very few patients.

ABBEY S. MEYERS: Somebody asked what evidence we have regarding the problems of rare diseases having very unique problems that are related to research. The report of the National Commission on Orphan Diseases has a lot of this evidence. In one questionnaire, the Commission had surveyed research scientists, asking them if they studied rare diseases, or if they didn’t study rare diseases, why not. More than 70 % said that studying a rare disease was very difficult because you could never find enough patients. But when we questioned the patient community and asked them whether, if there was a research project on their particular disease, would they participate, over 80 % of them said yes. So it is easy to see that the patients who wanted to participate in research could not locate the doctors, and the doctors could not locate the patients. And so it is a big communication problem, and much of what you are trying to do will solve it, because you will have that patient network set up. At NORD®, we maintain a mailing list, which includes the diagnosis of the person’s disease. So anyone writing to us about studying Menkes' Disease, for example, we will send a letter to everyone who has inquired about this disease. It might not be just a parent, it may be a teacher or a physiotherapist, but these people are in touch with these families, and the message gets through to them. We have had occasion where scientists or companies have called us and said, okay, stop, we have got too many patients. So if you do it properly, you are not going to have a problem here.

The other very unique thing that is going to happen is because there is a transportation problem with rare diseases. You are not going to find – in the States, anyway – more than two or three experts who really know how to diagnose and treat a specific disease. So it is not unusual for us to have to find a way to get a patient from Florida to Minnesota, because the only doctor who knows anything about it is in Minnesota. And this has turned into a truly major problem. We have had to work very closely with groups of volunteer pilots with their own planes, who are willing to put in some extra time to fly patients from place to place.

In one case, when NORD® funded a clinical study of a doctor who was building an artificial rib for babies who were born without ribs, we found it was much better to fly him around than to fly the baby and its parents down to his hospital in Texas. So a lot of this is going to have to be coordinated, and a lot is unique and you are not going to find it in any other type of clinical research circumstances.

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FRANÇOIS MEYER, French Medicines Agency: I have a question for Marlene Haffner, concerning orphan drugs in the U.S. and the amount of pre-clinical data that is available for these drugs. You mentioned that there was no possibility of grants for pre-clinical research, and I guess that if we want products for rare diseases of the same quality as for non-orphan drugs, we need to have the right amount of pre-clinical data. They are expensive and take time, so how do you deal with this problem in the States?

MARLENE E. HAFFNER: We deal with it creatively, with a lot of prayer, and a lot of hope, and a lot of jawboning, and a lot of saying to people, “Please do it”! Many of these diseases are serious and life-threatening, and for them sub-part e) of the FDA Regulations comes into effect. That says – I don’t administer it so I don’t know it exactly – that you can do some of the pre-clinical studies after the product has been approved, if it appears to be a generally safe product. So the sponsor can have some money coming in to be able to pay for the tox studies. But we do require toxicity pre-clinical studies on orphan drugs, similar if not the same as non-orphan drugs. Again, it just requires more creativity and figuring out the money to get them done. For a long time, I have said I would love to have some money for that, but it is not feasible in today’s environment. So we have to work with the sponsors in finding the best way to get it done. You are right, they are expensive.

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FRANÇOIS MEYER: I have another question. You mentioned that you operate separately from the FDA reviewers, but when it comes to giving advice on the clinical development of a drug, I guess you have some contact with the reviewers at the FDA?

MARLENE E. HAFFNER: Absolutely! It is the FDA Review Divisions that do the approval of the actual products. I didn’t mention that, so thank you for bringing it up. So since they do the review for actual approval, they provide the primary advice as regards exactly how clinic trial designs should proceed. We always are a part of that discussion, but it is not what we say, it is what the Review Divisions say. Now, a company is not bound by that, and if a company decides they don’t want to follow FDA advice, they don’t have to. Sometimes they can get into the marketplace more quickly, because clearly we will describe the perfect trial. Most of the time, though, companies take our advice, but not always.

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Summary and wind-up of the meeting by Jack BARNES, Rapporteur Général, Head of International and Industry Division, Department of Health, United Kingdom

BRUNO HANSEN:

I think we have had a good debate, and I have the pleasure now to hand over the microphone to Jack Barnes to act as Rapporteur. Jack, what have you got out of this meeting?

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JACK BARNES:

Today's meeting has been a very rich occasion, and one which, I think, is impossible to do justice to in a short summary. I have two general points, followed by eight action points for the future.

- The first general point is to thank Curt Engelhorn and the European Foundation for the Advancement of Medicine and congratulate them on a timely and well-focused occasion.

- The second thing is to say that it seems to me from today's discussion that there is a huge consensus as to the aim: to open access within Europe for its citizens to have their rare diseases treated effectively through our arrangements for medical care. Most of the discussion is not really around that consensus but is about what is involved in achieving the aim in practice.

Looking to the future, the key issues seem to be as follows:

1. In a complicated and mature democracy, change is a difficult, complex and often a protracted process. We need to gather the attention of a large range of institutions and individuals, often people whose attention is elsewhere. The action point here is that while the time may be coming for orphan drugs, we are not there yet. We may be moving into the next stage with DG III's proposed communication, but that will not be the end of the matter.

2. The second point follows directly. I was very impressed with Lesley Greene's cameo of how effective networking can be across Europe, as well as Abbey Meyers' account of the networks across the United States. But I suspect that in the next stage one needs to involve not only the networks of enthusiasts but to be prepared to engage with those whose attention and priorities are elsewhere, particularly as the Commission take their proposals to the Parliament and to the Council.

3. The third point is about the relationship between knowledge and organization. We began this morning with the observation that we need more knowledge about what to do within Europe. It was clear from what was said this afternoon that we can learn a great deal by tapping into the knowledge base and by networking with colleagues in the United States. But we also need organization at the level of Europe. It is clear that if we are to be effective in Europe, we need to establish ways to channel relevant knowledge adapting and developing our own institutions. The action point here is to influence European institutions, not only those which are kindly disposed to our purpose.

4. The fourth point is about the starting position for moving forward in Europe, because there are already elements in place which are growth points for the future. First of all, we have the R&D programmes orchestrated through DG XII. There was an extended discussion of those today, a discussion that focused particularly on how the science base within Europe, and small organizations within Europe, might be put together in more imaginative ways in future. But there is still some way to go to achieving this. There was a response from DG XII that this programme was maturing and in its next phases would be more focused, more developed, and more able to cope with the demands made of it. My own sense is that there was an open question there in the minds of the seminar, and the action point is with DG XII to bring the Fifth Framework Programme into the kind of focus with clearly visible and accountable programme management that can address the concerns of people evident from today's discussion.

   At the same time we have the Rare Diseases Programme agreed in the Health Council on 13 April of this year, which has the potential for supporting data development and European networks of patients, clinicians and others. The action point there seems to be to publicize that programme more effectively now that it is moving to be part of European law, so that people who are currently not sighted on the potential that is being created there can engage with it.

5. The fifth point concerns the critical next steps that will be taken by DG III and Patrick Deboyser. The distinctive features of the emerging proposal were, I thought, captured very well almost immediately after Patrick's presentation by Abbey Meyers: incentives for companies to apply themselves with greater commercial certainty through the arrangements for market exclusivity which are being proposed; institutions within the European Union to facilitate, resource and regulate those arrangements through the EMEA, and thirdly, the involvement both of Member States and of patient groups in the oversight and governance of those institutions. The action point here is for Patrick to help the Commission to get that Communication into the public domain, into the Parliament and the Council, and the debate really can then move into the next phase.

6. The sixth point concerns the discussion in the first open session of this morning, which was, as I interpret it, a discussion about the politics of change. A series of questions were raised about what precisely was going on, who was involved in the process, and where exactly we were at different parts of the action. It revealed a paradox to me about how complex organizations can be transparent to those who depend on them for effective administration. In a sense, the more you tell the story as it goes along the less coherent you may be in giving an account of precisely what is happening next, and the more uncertainty can develop. So transparency doesn't always lead, during the course of the process, to coherent understanding.

   I thought the most interesting part of that discussion was the question about whether we should be trying to make progress on the key strategic issues through the channels available, or whether we should, as Paul Peters observed, think more about whether we had the balance correct across all the actions that were achievable. There were discussions about whether we should have tropical diseases as well as orphan medicines included in a programme. There were discussions about whether we could include the candidate countries for accession; about whether we should develop guidelines rather than allowing the case law to develop ad hoc until we had got sufficient case law to build guidelines. It seems to me that the key strategic step there was to take action, given the opportunities that were available, and to codify, clarify and coordinate later. That I thought was the Chairman's clear lead through the majority of that discussion.

7. The seventh point was about the next steps that DG III will take, and the proposal for regulation. Four sub-themes came through to me from the Deboyser discussion:

a) The fact that an enormous amount of detail will need to be taken on board, accommodated, argued over and understood, and the need for the enthusiasts to be prepared for those detailed arguments and for a great deal of confusion and potentially for misunderstanding. There is a need for a group, to be able to address this confusion with clear and rational arguments and, where possible, with the evidence.

b) The second step that DG III is proposing is the development in important ways of regulatory principles at the level of Europe. This includes the market exclusivity guarantee, the proposed new committee, which will include patient groups, the levels of expertise that that committee will be required to marshal, not only expertise in epidemiology and medicine, but some financial or economic expertise too – they are expected to form a view about whether excess profits are being taken by companies at the level of Europe. Each of those three areas – exclusivity, what kind of new committee and how it fits into the developing European structure, and what kind of expertise will be brought to bear – will need to be debated. As will be the budget issues, where orphan medicines will be just one of an enormous range of budget issues that will need to be resolved through the Parliament and in dialogue with the Commission.

c) Lastly, the feed-through of an orphan drugs regime into health services will need to be thought through. My colleague from the industry made some interesting points about the need for patients and doctors to be educated and the need for some important reimbursement decisions to be addressed as the benefit of a Community regime feeds through into the – at the moment – 15 health care systems.

8. Lastly, how to prepare for all this. I think that the workshop thus far has been a good example of how to extend and build the network; that obviously needs to continue. I think that our colleague from the industry made some interesting points about the possibility of finding allies in diverse quarters – in the science programme itself, among the clinical fraternity, among the industry – to extend the network of friends so that the choir is even larger as the song is sung. But also, it seems to me, to be prepared to have a discussion with those whose priorities are elsewhere, as well as those who have the priorities of the enthusiasts.

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BRUNO HANSEN:

Thank you very much, Jack Barnes, for a very elegant summing up of what happened here today. It just leaves me to say that I have enjoyed the meeting, I think it has been a good one because, as you pointed out, it has initiated thinking for the future. It might not write history, but should initiate actions. I would like to invite everyone of you to start thinking about how one can create the right networks and platforms. You already need to do that now, so that once the research programmes are in place you are prepared to act immediately. So there need to be some activities, some forms created to get the discussion going and not to lose the momentum.

I would also like to thank once again the organizers, the newly established European Foundation for the Advancement of Medicine, and again congratulate Mr. Engelhorn and Mr. Schiltz for the very timely choice of this subject.

Last but not least, I would like to thank all of you for your really active participation.

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CURT ENGELHORN:

Thank you very much to all of you for your kind words. I have followed the procedures here in this room with great interest. I had the feeling that the meeting gathered momentum as it went on, and that it has been a valuable exchange of thoughts and ideas, and a valuable analysis of the existing problems. There is always one thing in the background: let us act! We have discussed things, we have analyzed things, and now that should form the basis for action to take a step forward in order to work on these interesting and important problems relating to rare diseases and orphan drugs.

I would like to take this opportunity to thank Bruno Hansen for chairing this meeting so capably, Jack Barnes for the excellent summary which we have just heard, and all of you for your participation. It was a lively meeting, and I hope you go home with many not only good memories, but also good ideas for continuing your work.

Notes