

## EBE and EuropaBio White Paper “Towards an optimal Orphan Medicinal Products (OMP) Framework in Europe”

### EXECUTIVE SUMMARY

The European Orphan Medicinal Products Regulation has been a remarkable piece of legislation, approved unanimously by the European Parliament in 1999 to provide timely access to therapies for patients with rare diseases and to encourage industry by giving it incentives to develop these therapies.

EBE and EuropaBio members strongly support this Regulation, but upon analysis of the current situation, put forward **9 suggestions to optimise the framework around it**. The suggestions are summarised below.

The overarching principle is that the European Commission should take the initiative for a **full application** of Regulation 141/2000, in a spirit of co-operation between all the interested parties.

This application of the system should also include Member States resolving the issues related to **access**, and the creation of a more **predictable orphan medicines environment** that would foster further R&D in the field.

Specifically, EBE and EuropaBio members would like to ask the European Commission to:

1. Undertake an educational programme to build **awareness about rare diseases** in Europe, which should target the European level as well as the national level.
2. Establish a **EU-wide network for diagnostic testing for rare diseases**, in order to ensure timely intervention for the patients.
3. Promote a Europe-wide compassionate use system for the **provision of orphan medicines** to patients in need.
4. Increase **understanding of the Regulation in Member States** in order to eliminate conflicts of understanding in national legislation.
5. Undertake a review of the **incentives** for Orphan medicine development in the Member States, focusing on the provisions of Article 9 of the Regulation.
6. To **eliminate the confusion** created around the potential reduction of the 10-year market exclusivity laid down in Article 8(2) and to ensure that incorrect translations are corrected.
7. Undertake a **review of the disincentives** to orphan drug development at the national level, such as additional requirements for **clinical and cost-effectiveness data** before reimbursement or at launch.
8. Ensure that **clinical trials in the field of rare diseases**, under the EU’s “Clinical Trials Directive,” are facilitated and that the cost implications of post-marketing commitments are reviewed.
9. **Coordinate and streamline EU** rare disease research and therapy development between DG Research, DG Enterprise & Industry and DG SanCo as well as with the EMEA and the FDA.

EBE and EuropaBio members want to help reach this optimal legislative, as well as psychological climate for the development of rare disease therapies in Europe in a proactive way, for the benefit of the patients. At the same time, they want a competitive application of the OMP Regulation in Europe, even in the absence – as practised in the US – of incentives such as tax credits. Weakening of the OMP Regulation, which is not yet fully applied in Europe today, would carry a substantial risk that research and clinical trials for medicines to treat rare diseases will be carried out outside Europe. This would be counter to both the letter and the spirit of the Orphan Medicinal Products Regulation and would not reflect those very reasons for its introduction by the European Commission and its unanimous approval by the European Parliament.

## OVERVIEW OF CONTENTS

This White Paper examines the Orphan Medicinal Products Regulation from different viewpoints and covers the following aspects. The paper has also been reviewed and commented by other stakeholders and their comments have been taken into account in the final version of this paper.

### INTRODUCTION

1. **The European Parliament and European Commission Goals for the OMP Regulation**
2. **The current situation**
3. **Industry’s proposal for a partnership with the other stakeholders**

### THE FRAMEWORK FOR IMPROVING ORPHAN MEDICINE DEVELOPMENT AND ACCESS IN EUROPE

1. **The need for Europe to address orphan medicinal products issues at a European level**
2. **The need for accurate diagnosis and early treatment**
3. **Compassionate use and responsibility**
4. **The myth of “market exclusivity”**
5. **Market exclusivity for orphan medicines does not lead to higher prices**
6. **The rarity of the disease**

### THE OMP REGULATION AND ITS APPLICATION IN PRACTICE

1. **Application in the Member States and their accountability**
  - a. Access
  - b. Health economics for OMPs
  - c. Member States’ incentives for orphan medicine development?
2. **Applying the Regulation**
  - a. The significant benefit clause in Article 3 of the OMP Regulation
  - b. The confusion surrounding Article 8(2) regarding reduction of Market Exclusivity
3. **Developing rare disease therapies and the Clinical Trials Directive**
4. **Working with the EMEA, the COMP and the CHMP**
  - a. Designation
  - b. Scientific Advice
  - c. Transparency
  - d. The COMP and its Working Group for Interested Parties
5. **Linking the OMP Regulation and the newly proposed Paediatrics Regulation**

### EU COORDINATION AND RESEARCH PRIORITIES FOR RARE DISEASES

### CONCLUSION

## INTRODUCTION

### 1. THE EUROPEAN PARLIAMENT AND EUROPEAN COMMISSION GOALS FOR THE OMP REGULATION

The *EU Orphan Medicinal Products Regulation No. 141/2000* entered into force in April 2000 with unanimous approval of the European Parliament. The European Commission has reconfirmed, on several occasions, that the purpose of the Orphan Medicinal Products Regulation is to provide incentives to industry to develop therapies for rare diseases so that European patients in need would get the necessary treatments. The European Commission and other authorities recognise that, without these incentives, companies would not be easily able to invest in research, development and marketing of therapies for rare diseases.

The European Commission's goals are identified in the OMP Regulation – some key goals, as stated in the text of the Regulation, are:

- *In the European Union, only limited action has been taken so far, whether at national or at Community level, to stimulate the development of orphan medicinal products; such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited resources;*
- *Patients with rare conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process;*
- *Experience in the United States and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered; and*
- *Rare diseases have been identified as a priority area for Community action within the Framework for Action in the field of public health.*

### 2. CURRENT SITUATION

In its first 5 years, the Regulation has had a successful start. It has attracted quite a lot of companies to apply for designation of their product as Orphan, compared to the situation before the Regulation was enacted, when there was almost no development activity in this field in Europe. However, we need to recognise that some of the orphan drugs developed and approved in the USA have reached European patients before the Regulation.

As of January 2005, there were 254 orphan designations granted by the European Commission. On the other hand, 20 Orphan Medicinal Products have been granted Marketing Authorisation in the EU and, therefore, it is arguably early days to judge the real impact of the Regulation in fostering the development of therapies for rare diseases in Europe.

EBE and EuropaBio members therefore believe that it is **important now to ensure not only the continuation of the Regulation, but also its full application, and the necessary framework to support it.**

EBE and EuropaBio members are also concerned about the confusion surrounding the incentives of the Regulation, and especially regarding a potential reduction of the market exclusivity (which lacks, in our opinion, legal foundation where the reduction is based on sufficient profitability but is applied to products that received orphan designation based on prevalence criteria). This confusion should be avoided because it may negatively affect orphan medicine development in Europe by removing the incentives needed to foster investment and potentially creating a less supportive climate in the field.

### 3. INDUSTRY PROPOSAL FOR PARTNERSHIP WITH OTHER STAKEHOLDERS

EBE and EuropaBio members propose, first of all, a full application of Regulation 141/2000 and the creation of supporting measures for a framework supporting it. **The European Commission should take the initiative for this, and, in doing so, approach this in a spirit of co-operation between all the interested parties** – including the patients, researchers, clinicians, the Member States as well as industry – in order to achieve all of the objectives set out for in the Regulation.

The elements of this co-operation should include improving education of healthcare professionals and especially clinicians about rare diseases, research into rare diseases, diagnosis and awareness about rare diseases in all aspects, access for patients to approved orphan medicines in all Member States, more sustainable solutions for so-called “compassionate use” programmes, and providing better overall care for those people suffering from rare conditions. Providing clarity on the issues concerning market exclusivity and about the pricing of Orphan Medicinal Products should also be part of this programme.

EBE and EuropaBio members want to contribute to the debate on the optimisation of the legislative, as well as psychological climate for the development of rare disease therapies in Europe, beyond what is already available today, for the benefit of the patients and our society. We have, therefore, made the analysis and have formulated additional proposals in this paper.

<b>THE FRAMEWORK: IMPROVING ORPHAN MEDICINE DEVELOPMENT &amp; ACCESS IN EUROPE</b>
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In the Foreword, page 9, of the “*Report on the first 3-year mandate of the COMP April 2000-April 2003*”, Françoise Grossetête, MEP and *Rapporteur* of the OMP Regulation, writes:

*“This Regulation is fundamental for ethical, economic and scientific reasons. We cannot tolerate patients suffering without a remedy at the beginning of the 21<sup>st</sup> Century only because their disease is rare. The economic aspect is crucial for the competitiveness of the pharmaceutical sector in Europe.”*

In this section, we outline some of the basic elements and some of the misconceptions related to the field of rare diseases.

#### 1. THE NEED TO ADDRESS ISSUES RELATING TO ORPHAN MEDICINES AT THE EUROPEAN LEVEL

**Much more work on the awareness about rare diseases in Europe should be undertaken. In particular, it should be underlined that – because of the rarity of the diseases – there is the need to work at a European level for some aspects, and at the national level for other aspects and why, in order to solve current issues, such as access, in a coordinated way.**

The simple fact that the OMP Regulation is a European Regulation underlines that the issue of rare diseases needs to be tackled at the European level. Europe needed the EMEA, the European

Medicines Agency, to be created before it could create its own Orphan Medicines legislation, 17 years after the US had already done so. The rarity of the diseases concerned made it impossible to set up an appropriate incentive system to foster the development of therapies for them at the EU Member State level. The unanimous approval of the Regulation by the European Parliament is a clear indication that Europe wanted to take the issue of rare diseases seriously, and that there was a high political support for the Regulation and its goals.

However, the rarity of the individual diseases and their varying incidence across European countries – and even regions – continues to create strong regional differences, including inequalities in information and in research, in diagnosis and access for patients to approved therapies. The regional and national differences in tackling availability, reimbursement and access in the EU Member States are clear, but the reasons for them are complex, and relate to the differences in health care systems as well as to other factors as outlined below.

## 2. THE NEED FOR ACCURATE DIAGNOSIS AND EARLY TREATMENT

Much work on diagnosing rare diseases is still needed in the EU. Most patients suffering from rare diseases are diagnosed late in the course of the disease, because of their rarity. Many clinicians do not know about rare diseases, which leads us to conclude that there is a lack of clinical and academic education and also capacity to identify and meet patients' needs in Europe. This apparent gap is made even more complex because of the high heterogeneity in phenotype and in clinical symptoms of each genetic rare disease. Rare diseases are for 70%-80% genetic in origin.

Diagnosis for a rare disease can only be confirmed by a biological test for a small percentage of all rare diseases. As a consequence, even if for some conditions, well-established and clinically effective medicines are available now individuals cannot always be treated, because diagnosis is not accurate and even less timely. Therefore, it should be a priority to develop diagnostic tools and programmes for the accurate and, possibly, early diagnosis of the disease. Companies developing orphan medicines must often also undertake the task to develop a diagnostic method on the way to a therapy.

**EBE and EuropaBio members support the call for an EU-wide network for diagnostic testing of rare diseases, as late diagnosis resulting from the rarity of the disease is often associated with poor prognosis.**

EBE and EuropaBio members also believe that the supply and organisation of diagnostic and, in some cases, population and/or neonatal screening services should be considered part of the health care system services and be offered to clinicians and patients, because they are an integral part of a patient's access to a needed treatment. In a recent report published by the European Commission's DG Research, an expert group working on recommendations related to the *“Ethical, legal, social issues of genetic testing: research, development and clinical applications”* made the following recommendations (STRATA group, May 2004 – the R number relates to the number of the Recommendation in the report):

- R6a: medically relevant genetic testing be considered an integral part of health service provision;
- R6d: national healthcare systems ensure that genetic testing will be accessible equitably to all who need it;
- R17d: the EC takes measures to facilitate the availability of genetic testing for rare diseases as well as for more common diseases;
- R18a: an EU-wide network for diagnostic testing of rare genetic diseases be created and financially supported as a matter of urgency;

- R18b: an EU-level incentive system for the systematic development of genetic tests for rare diseases be created and financially supported; and
- R18c: for rare but serious diseases for which treatment is available, Member States should introduce universal neonatal screening as a priority.

These are all very relevant issues for rare disease patient care and they should be discussed in the context of and as support for the OMP Regulation and be evaluated how they can be integrated into a comprehensive package for the management and care of rare diseases in the EU.

### 3. COMPASSIONATE USE AND RESPONSIBILITY

Most rare diseases *are severe, life-threatening or otherwise chronically debilitating conditions*. Compassionate use is the provision of medicinal products free of charge to patients, because of a high medical need. Such compassionate use may happen either during clinical development (either for patients taking part in a trial or in an expanded access programme), after clinical development but before approval – for example, to allow the continuation of a successful treatment for patients who have participated in clinical trials – or after approval, while waiting for third party payment. It should, however, be recognised that compassionate use programmes can create very difficult dilemmas for manufacturers, patients and for healthcare systems, especially when a potentially beneficial product to treat a life-threatening disease is in development but the quantities that can be produced are not sufficient to meet demands for clinical research and for all patients requiring compassionate use.

The supply of therapies for compassionate use to the patients in need should be a shared responsibility between the clinician, the developer of the product and the authorities. In developing and supplying products to treat rare diseases, companies assume a significant responsibility in educating the physician and patient communities, as well as the responsible payment authorities, on why this is a product of high clinical benefit. Companies also devote resources to increasing awareness, increasing the availability of diagnostic tools, etc. In short, they help to build up the health care infrastructure to care for patients with rare diseases.

A company embarking on the development of therapies for rare diseases assumes also a significant ethical responsibility to society: it is not ethically possible to stop supplying a life-saving medication to clinical trial participants before approval or payment coverage, or if profits are not at an acceptable level, because the life or, minimally, the quality of life of the participating patients will depend on such supply.

Some countries, such as France (ATU system), Italy and Belgium (Special Solidarity Fund) pay for the supply of Orphan Medicinal Products to patients in high need before the regulatory approval of the product and/or before reimbursement if approved. It would be recommendable that similar systems are set up in all European Member States, to allow treatment of those with a very high medical need – in many cases saving patients' lives – before a medicine is finally approved or reimbursed. This was also proposed by the European Platform for Patients' Organisations, Science & Industry (**EPPOSI**) in **the report of its 2001 Barcelona Workshop on Access**.

It can also be argued that, for patients with serious and life-threatening diseases, the question of the risk/benefit equation on which products are approved takes on a different aspect than it may do for members of the wider public, since for such patients, life may depend on the availability of a medicine at a particular time. Given this, and the fact that most rare diseases are serious or chronic, life-threatening conditions, the patients' views should also be sought in the evaluation of this risk/benefit profile and, therefore, about the early availability of medicines, even if a fully developed safety profile is not yet available.

Finally, it is also important to bear in mind that many Orphan Medicinal Products are developed by Small and Medium-sized Enterprises, which cannot support long-term compassionate use programmes without government intervention and financial support.

**Based on the above, we propose the promotion of a sustainable, appropriate Europe-wide system for the provision of medicines to patients with the highest medical needs before approval and/or reimbursement.** This system should, however, not eliminate current compassionate use programmes, which are helping patients.

#### 4. THE MYTH OF “MARKET EXCLUSIVITY” LEADING TO MONOPOLIES

The OMP Regulation was created to increase the availability of Orphan Medicinal Products for rare disease patients, meaning that their availability was minimal before the Regulation entered into force. This necessitated the development of incentives for industry to invest in the field, a drive based on the experience of similar legislation in the US. Nevertheless, the very first approvals for Orphan Medicinal Products in the EU under the new Regulation split the exclusivity between two products, giving them co-exclusivity.

It is sometimes stated that the market exclusivity granted by the OMP Regulation may lead to a lack of competition. EBE and EuropaBio members do not support this statement, for the several reasons outlined below. But first and foremost, there is a range of competitive developments ongoing for most of the marketed orphan medicines, while at the same time, it must be remembered that, as in any new field, competition will take some time to catch up with innovation. In addition, the EU’s OMP Regulation has carefully provided for a balanced system as innovations, or very different products, would always be allowed on the market.

We further explain these points as follows:

1. The OMP Regulation provides only for partial market exclusivity, and does so “*in respect of a similar medicinal product*” (Article 8(1) of the Regulation). A “similar product” is unambiguously and scientifically defined in a separate Commission Implementing Regulation. This Implementing Regulation needs to be regularly updated in the light of current scientific knowledge, but this has been foreseen in the text of the Regulation itself. The term “similar product” was clearly defined with the specific aim of not limiting innovation but, rather, of allowing progress in this field, while providing a (*be it partial*) market exclusivity incentive to the innovators. The two, non-similar Orphan Medicinal Products approved to treat pulmonary arterial hypertension, originating from two different companies, are a good example of how the system works in practice. The two products belong to different drug classes and act through different mechanisms, therefore, they are not considered to be similar and, therefore, demonstration of clinical superiority was not required for the approval of the second product. This is also reflected in the fact that, although both products were approved for the same disease, they have different efficacy and one is only indicated for treating a subgroup of patients (with primary pulmonary hypertension). The market exclusivity protection also applies for biosimilar copies.

Clarification is needed, to ensure that the scope is broad enough, for the assessment of similarity for products that belong to the same class and act through the same principal mechanism of action, do not have a similar chemical structure but are “smart copies” acting on the same target, e.g., blocking of a receptor or active site of an enzyme, using a different chemical structure. Market exclusivity, both for innovative biologics and new chemicals, is important because a number of these products to treat rare diseases are not patentable or their patent has expired,

meaning that they would be highly unlikely to be developed without the market exclusivity protecting them against copies.

2. There is a derogation from the market exclusivity protection if a second applicant can establish in its application that its own medicinal product, although similar to an already authorised Orphan Medicinal Product, *is safer, more effective or otherwise “clinically superior”* (Article 8(3) (c) of the Regulation). The “clinical superiority” is, again, defined in the separate Commission Implementing Regulation, and is an important additional assurance for patients, that – in spite of existing market exclusivity – access to the best possible treatment will still be guaranteed. The European OMP Regulation is too young to provide European examples of how this works in practice; therefore we can take an example from the US. It should be noted, however, that a treatment for Multiple Sclerosis (MS) would not be considered an Orphan Medicinal Product under the EU’s OMP Regulation because such treatment would be over the slightly lower EU prevalence cut-off compared to the US legislation. This *caveat*, however, does not undermine the value of the example in the context of this text.

Schering received marketing approval for Betaseron as an orphan drug to treat Multiple Sclerosis in the US. Biogen, on grounds of clinical superiority, was subsequently able to receive approval for Avonex (which, under the European OMP Regulation, would be a similar product for the same therapeutic indication), effectively breaking Schering’s market exclusivity for Betaseron in MS. Even further on, Serono was, again, able to show clinical superiority over Avonex with their “similar product” to treat MS, Rebif, thereby bringing the number of “similar” orphan drugs to treat MS in the US under co-exclusivity to three. This example clearly demonstrates that the provisions within the legislation function correctly and allow competition, as the EU Regulation would function in the same way on this point as the US one did.

## 5. “MARKET EXCLUSIVITY” FOR ORPHAN MEDICINAL PRODUCTS DOES NOT LEAD TO HIGHER PRICES

In some instances, it has been stated that the reason why Orphan medicines are highly priced is because the “market exclusivity” granted by the OMP Regulation provides companies with a monopoly to treat a specific rare disease. While we have argued on the relativity of the market exclusivity above, we must also explain that the reason prices for most orphan medicines are high is precisely because of the rarity of the treated disease. This has recently also been found by the consultancy Alcimed in its recently published *Study on the Prices of Orphan Drugs – November 2004* ([www.pharmacos.eudra.org](http://www.pharmacos.eudra.org)). For, while costs for Orphan Medicinal Products are in reality similar in research and development (R&D) terms, process scale-up, manufacturing and other costs as those for treatments against common disorders, they relate to a product that is destined for a small group of people, meaning that all these costs need to be recuperated from a small market with a small number of patients, many of whom were not even identified at the time of the clinical trials. This means that, for products being developed specifically for a new therapeutic indication (as opposed to those that are a spin-off from other development programmes), the same level of costs and investments as those for therapies destined for a large patient population need to be shared between a much smaller number of people.

There is also a misunderstanding about the relationship between the rarity of the disease and the need for the company concerned to have a return on investment. Because the prices of orphan medicines may be higher, the perception exists that this price automatically must also lead to high profits. In reality, there is no intrinsic relationship between high prices and high profits, while on the other hand, there is a strong relationship between the price of a product and the rarity of the disease it treats, as shown by the Alcimed study referred to above. Carbaglu, currently used for treatment of just 25

patients in the EU, may be a good example to illustrate this. For, while it needed to go through all of the tests, development costs, evaluations and, eventually, approval on the basis of the established Quality, Safety and Efficacy criteria, it is used by a tiny number of patients. An additional complication is the fact that the number of potential patients to be treated for most rare diseases in a given country – especially those for which no satisfactory treatment currently exists – is very much an unknown factor at the time of clinical trials and even at the time of launch.

Furthermore, speaking in more general terms, profit for a specific product may be an artificial concept, because profits need to be considered in the context of a total company within a certain accounting year. The distribution of costs between different products will vary substantially between companies and will, among other things, depend on their development stage, the strategic plan of the company, and the number of projects they manage. And, while one individual product or project within a company may be successful, many others within the portfolio may only generate costs. For one Orphan Medicinal Product successfully developed by a company, it is possible that many programmes – and investments – have been unsuccessful, within the same company or by other companies, targeting the same disease and have been abandoned without returns.

Examining Annual Reports of those companies that are listed on a stock market may provide a good insight in the profits, if any, generated, as well as the use of these companies' profits, either to fund further R&D and growth or to provide dividends to shareholders, or both.

## 6. THE RARITY OF THE DISEASE

The European OMP Regulation defines Orphan Medicinal Products as therapies for diseases with a prevalence of less than 5 in 10,000 in the EU population. The difficulty of obtaining a return on investment increases (as does the price of a product) in accordance with the increasing rarity of the disease. The UK National Institute for Clinical Excellence has already also defined “ultra-orphan” diseases as those with a prevalence of just 1 in 50,000, or 25 times less prevalent than an orphan disease under the EU’s OMP Regulation’s prevalence limits. The largely increased difficulty in obtaining a return on investment from such “ultra-orphan” disease populations is not yet fully discussed. But it must be clear that it is much more difficult than in the case of more common diseases, or even of more frequent rare disease therapies. Such “ultra-orphan” diseases account for an important segment of the rare diseases, and account for a significant part of the discussion on the prices of therapies for such diseases. However, it is clear that a concept such as ultra-orphan should only be discussed with those who have a thorough understanding of the concept of an orphan drug, since ultra-orphan only means that all complexities and difficulties are magnified and amplified. The concept should be used with care in order to avoid confusing authorities and non-specialists. As we said above in relation to the market exclusivity confusion, confusion endangers the implementation and understanding of the OMP Regulation and should be avoided at all cost.

However, between specialists, we believe that the concept of ultra-orphan is not a gimmick and merits further discussion at the European level, in particular with a focus on the special considerations for health economic assessments of such products.

## THE OMP REGULATION AND ITS APPLICATION IN PRACTICE

### 1. APPLICATION IN THE MEMBER STATES AND THEIR ACCOUNTABILITY

**Work should be carried out to increase understanding of the OMP Regulation in the Member States and to draw up a list of areas of potential conflict with national legislations.**

Much work needs to be done to better involve relevant stakeholders in the Member States to increase awareness of the Regulation and its intention and to create an appropriate framework for the diagnosis and treatment of rare diseases. It would be important, for example, to draw up a list of potential areas of misunderstanding and how they should be handled.

Furthermore, we want to discuss in here a number of other elements of importance.

#### A. Access

As we already said above herein, the European Commission should take the initiative for a **full application** of Regulation 141/2000, in a spirit of co-operation between all the interested parties. **This should include the resolution of issues related to access, and the creation of a more predictable orphan medicines environment** that would foster further R&D in the field.

After nearly 5 years of implementation of the OMP Regulation, there is still a serious lack of timely and equitable patient access to orphan medicinal products in the EU (see page 24 of the European Commission's "*Study on the Price of Orphan Medicinal Products: an open invitation to tender*" August 2003). This is a key issue. It has also been recognised by the Alcimed Study referred to above. Clearly, pricing is a component of "access", but it is certainly not the most important one. The different systems of delivering healthcare in EU Member States, the lack of awareness about rare diseases and the needs of the affected patients in the EU Member States, the rarity of the disease and the geographic distribution of patients, the need for better and earlier diagnosis, the need for screening programmes, the inapplicability of standard payment and coverage schemes, all represent major hurdles to effective and timely patient access to approved orphan medicinal products. Earlier access may mean a world of difference for the affected individual.

There is a difference in prescription patterns and in requests for payment for Orphan Medicinal Products between different Member States and even between different regions in Europe. How can this be better handled, perhaps with help from policies at the European level? Can the European Commission offer support for driving the local agencies and payers to establish better local systems for Orphan Medicinal Products, which would allow rapid reimbursement and ensure availability of funds? At the very minimum, national, but even better EU-wide access criteria would be preferable.

Since for many orphan medicines ex-factory prices are similar throughout the European Union, differences in prices from one Member State to another appear to be caused by differences in taxation and distribution, and perhaps other country-specific elements. If we aim to drastically improve the early access of patients to approved Orphan Medicinal Products, we should find ways to organise pricing discussions for Orphan Medicinal Products at the European level, according to expert patients' representatives.

From the companies' standpoint, a system leading to earlier access for patients by reducing pricing and reimbursement negotiation times in individual Member States would be an incentive of high interest. This may turn out to be an interesting thought path for the development of future meaningful incentives in the field. However, this is complex matter and will take time. Nevertheless before we are there, much work can and should already be done today at the national level.

Two examples: firstly, in the UK, which organises its healthcare on a regional or even sub-regional (Primary Care Trust) level, the lack of national coverage for most orphan medicines creates unequal access for patients suffering from severe and life-threatening rare diseases. This leads to what is known as "postcode prescriptions", meaning that patient access depends on where a person lives rather than their medical need, despite the fact that the products are approved at the EU level, which

should ensure uniform access to all European patients in need. The NHS has now proposed, for some “ultra-orphan” medicines, a national reimbursement with national criteria.

Secondly, in the Netherlands, the “stuurgroep weesgeneesmiddelen”, a multi-stakeholder group set up and chaired by the authorities, has been alerted by the proposal of the current Minister of Health to require payment for new orphan medicines “for which the clinical effectiveness is unproven, but which are still approved by EMEA” out of individual hospitals’ research budgets. The “stuurgroep” advocates a national approach to this issue. The Minister is now talking with the patient groups to find a solution.

The patients’ advocacy group Eurordis discovered in its survey of the first 10 Orphan Medicinal Products approved in Europe, that only 50% are available in the 15 “old EU” Member States, and that the situation is much worse in the new Member States. And, even when official reimbursement is obtained, getting access to orphan medicines may be further hampered by the lack of authorised treatment centres or prescribers.

Another factor which should be streamlined is the “double work” which occurs when, after approval of an Orphan Medicinal Product by the European Commission (on the recommendation of the EMEA/CHMP), Member States ask for further clinical evidence before allowing access by the patient, leading not only to double work of the applicant company, but also to long delays in access for patients. It is not possible to supply long-term evidence in the early stages of the lifecycle of a new medicine. This issue must be re-addressed because when a therapy is a first breakthrough for a previously untreatable, serious or life-threatening rare disease, this fact should not interfere with access. One approach might be conditional reimbursement agreements.

## ***B. Health Economics for OMPs***

Health economic evaluation of the cost-effectiveness of Orphan Medicinal Products is another factor that is starting to play a role in delaying access for patients. While the question of health economics does not only apply to orphan medicinal products, given their higher prices (the reasons for which have been outlined above) and the smaller patient population, these products may come under intense scrutiny to prove that the patients “deserve” to have money spent on their treatment. And whereas for more mainstream products, there exists the possibility to compare between one treatment and another, the very fact that an orphan medicinal product is intended to treat severe and, often, life-threatening diseases where no other treatment exists, means that in reality, health economics may end up measuring the right of patients to have access to treatment or not.

Furthermore, criteria for cost-effectiveness for such rare disease therapies, and especially so in the case of “ultra-orphan” medicines, cannot be developed on the same basis as those for more common diseases. As quoted earlier from the OMP Regulation, patients affected by such rare diseases have the same right to treatment as other patients, in spite of the rarity of the disease.

The core of the OMP Regulation consists of non-economic societal values representing the desire for equitable access to therapies for European patients and a fair and just distribution of resources. Considering economic efficiency on an individual patient level is inconsistent with the value basis on which the EU OMP Regulation was founded. Furthermore, current health economic analyses are most probably not able to evaluate the cost effectiveness of OMPs or “ultra-orphan” medicines because of the rarity of the treated disorders and their high heterogeneity and variability in clinical symptoms. The lack of data may undermine the integrity and usefulness of any cost-effectiveness analysis because it eliminates the untreated comparator group based on natural history data. It has to be noted that the knowledge and understanding of rare diseases and the clinical sophistication

typically and dramatically increases with the advent of effective therapy. This leads to an incomplete assessment of natural history in the pre-treatment era, and one that inevitably underestimates the burden of untreated disease and the cost-effectiveness of a therapy. Future health gains are also heavily discounted, while, for genetic diseases, therapies may have most effect on children. It is not expected that therapies for orphan populations meet current standards of cost-effectiveness.

**More effort on the understanding that current demands in the Member States for additional clinical and cost-effectiveness data for innovative OMPs before their reimbursement or at their launch are contrary to the intrinsic rarity of the treated diseases and / or the spirit of the OMP Regulation should be carried out.**

### *C. What about the Member State Incentives for Orphan Medicinal Products?*

**EBE and EuropaBio members would fully support a new impetus by the European Commission on the subject of incentives for orphan medicine development in the Member States, focussing on the provisions of Article 9 of the OMP Regulation.**

The US Orphan Drug Act provides, amongst other provisions, tax credits for clinical research costs (a later addition to the original Act, to increase its effectiveness). This is an important difference between the US and European systems, because it is the lack of such equivalent tax incentives which makes the EU incentive system for OMPs rather weaker than its US equivalent. The EU lacks the ability to match some of the incentives available in the US, including these tax credits or research grants, because most of this competence remains in the hands of the Member States. This is also why the European Commission provided for a 10-year market exclusivity period in the European OMP Regulation compared to 7 years in the US.

Although the OMP Regulation stipulates that Member States should develop further supporting measures and incentives, in reality, few European countries have made any efforts in this field, in spite of the priority given to the field of rare diseases at EU level. The European Commission should not give up on stimulating the Member States to work on such incentives, as appears to be the case since it is not visibly following up on the Inventory of Measures. **Working on a European system for earlier access in all Member States would be a suggested way forward.**

## **2. APPLYING THE REGULATION**

### *A. The “Significant Benefit” Clause in Article 3 of the OMP Regulation*

One of the important objectives of the OMP Regulation is to stimulate research on rare diseases and to be open and transparent about the rules applied. Some of these rules need clarification.

In Article 3(1) of the OMP Regulation, it is defined that a sponsor can obtain orphan designation for a product based on the prevalence criterion or the financial criterion. *De facto*, however, the prevalence criterion has been used to date in the majority of the cases (only 2 very recent designations seem to be based on financial criteria in Europe). Furthermore, among other things, in order to obtain orphan medicine designation the sponsor must demonstrate at the time of filing either the absence of a satisfactory approved treatment in the EU, or, if there is such a treatment, that the anticipated orphan medicine will provide a significant benefit. In practice, if this clause is applied very strictly, meaning that clinical trial data are available, companies will have to wait until they can clinically prove that this is the case. This would hamper innovation by making companies wait for designation – or may even put them off applying for designation. Designation does not mean marketing approval and awarding designation for a product does not mean that it will reach the market.

For the moment, the practice of the COMP and the Commission is not too demanding with regard to the significant benefit requirement. There is, however, no guarantee that this administrative practice will be continued. We would, therefore, plead for a clear guideline on the application of the significant benefit criteria and to provide a workable definition of what significant benefit is. This definition should not be too strong in order not to undermine the objective to stimulate research in rare diseases in Europe.

### ***B. The Confusion surrounding Article 8(2) on Reduction of Market Exclusivity***

**The confusion created around the potential reduction of the 10-year market exclusivity laid down in Article 8(2) should be eliminated as it potentially damages the psychological climate to support the development by industry of rare disease therapies.**

Already, the possibility that the OMP market exclusivity can be shortened in a way that was not anticipated based on the legal text of the Regulation confuses companies and undermines this incentive, in creating doubt about whether rare diseases really are considered a public health priority in the EU. Although the safeguard aspect is understandable, on balance, for the good of European patients, it would be preferable, as a “carrot”, to allow some companies to make significant profits with a few successful products, which, in turn, could act as a strong incentive and, thus, a booster for more companies to invest in many more treatments. A success with one product does not necessarily translate into company profitability, since the income generated may be needed to finance failure in other development projects.

EBE and EuropaBio members are of the opinion that, according to the legal wording of Article 8(2), profitability can only be a criterion to consider reduction of market exclusivity for those companies that have been awarded designation on the basis of that criterion. That means that, for products that obtained OMP designation on the basis of prevalence, market exclusivity should not be reduced based on financial criteria, be it on profitability or another financial one. However, these products may of course have their market exclusivity reduced if the prevalence on which they received designation is no longer below the prevalence upper limit as defined in the Regulation.

Indeed, Article 8(2) of the OMP Regulation clearly states that: “This (market exclusivity) period *may however be reduced* to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that *the criteria laid down in Article 3* are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, *a Member State shall* inform the Agency that *the criterion on the basis of which market exclusivity was granted* may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.” Thus, Article 8.2 allows for a reduction of the market exclusivity period, upon the request of a Member State, from 10 to 6 years for any Orphan Medicinal Product if, after 5 years, the criterion of designation is no longer met. If the designation was based on prevalence, the decision for reducing the market exclusivity should also be prevalence, meaning that the criterion of sufficient profitability does, therefore, not constitute a basis for a review of market exclusivity as it was not a criterion for designation in the case of these products. Independent expert legal opinions support this view. **We also recommend that the current confusion caused by some incorrect translations be corrected.**

EBE and EuropaBio members would recommend not including profitability as a criterion to reduce market exclusivity for prevalence-designated orphan medicines. Instead, it is important to create trust,

confidence and the ability to plan for the longer term, to increase investments in the field in the EU, since this is the real purpose of the Regulation.

### **3. DEVELOPING RARE DISEASE THERAPIES AND THE CLINICAL TRIALS DIRECTIVE**

**Clinical trials for rare diseases, now also to be carried out under the EU’s “Clinical Trials Directive” should be made less complex and a review of the level, or cost implications, of post-marketing commitments should be carried out.**

The EU’s “Clinical Trials Directive”, which was to be implemented as of 1 May 2004 in all Member States, may have a considerable effect on the practical clinical development of orphan medicines. In spite of its main aims to protect individual patients in clinical trials and to increase harmonisation of clinical trials across the EU, the flexibility required to handle clinical trials for the affected patient groups may be challenged by the rigour of the Directive. Clinical trials with Orphan Medicinal Products within the EU are already a particularly difficult undertaking. One of the difficulties encountered in designing clinical trials for rare diseases is that affected patients, who are being treated with new investigational products, may survive longer than their peers. This means that no natural history data for such surviving patients exist, resulting in studying “uncharted territory”. This, in turn, means that responses to treatment cannot easily be predicted. Actions of individual clinicians often lead to breakthroughs in this field. Moreover, it is unclear if and how compassionate use programmes, which allow access to products after trial completion but prior to market authorisation, are covered by this Directive, since this will depend on how the programme is structured.

Post-approval clinical trials in the areas of rare diseases should preferably be set up in such a way that companies can recover their costs in that process. An EU Guideline for medicines used in post-approval clinical trials for rare diseases and cancer should be envisaged. A continuous dialogue with a sponsor during the design of clinical trials and during the discussion of the post-approval commitments, especially for orphan medicinal products (as many of these are approved under exceptional circumstances), should be established.

Consultation between Member States and the CHMP should be established to verify that post-approval commitments and additional trial requests are both ethical and feasible under the national rules. A working group to discuss and avoid excessive bureaucracy on the already very difficult and complex process of organising and conducting cross-border clinical trials for orphan medicines should be set up. For amendments to protocols (unavoidable for trials with medicines to treat rare diseases) bureaucracy needs to be minimised, and increases of costs for clinical trials that are unnecessary should be avoided.

### **4. WORKING WITH EMEA, THE COMP AND THE CHMP**

Given the nature of rare diseases and Orphan Medicinal Products, in terms of both the small numbers of patients concerned, the relative scarcity of expertise in any given field and the often urgent need for treatments to save lives, a partnership approach is arguably more important in this field than in any other.

#### ***A. Designation***

Currently, and perhaps also influenced by the conditions stipulated in Article 3 of the OMP Regulation (see above), most orphan designations are for projects in advanced stages of clinical development. As mentioned in 2 A above, this is because a sponsor has to prove either that there is no

existing therapy or that the therapy it proposes to develop has significant benefit for the affected persons at the time of designation, which is very difficult to demonstrate without any clinical data, meaning that designations are unlikely to be granted early on in the development phase. Furthermore, this can also lead to the perception that gaining orphan designation brings more work than it does benefit.

In the US, orphan designations can be filed for at any stage of the development since these requirements are not necessary there. As receiving orphan designation does not cost society anything, it would be better to encourage more companies to receive orphan designation, since they are still required to make the investments to prove Quality, Safety and Efficacy before a marketing authorisation is granted. It would also be important to document, in relation also to the provided Scientific Advice and Protocol Assistance, whether receiving an orphan designation does actually in practice either speed up or improve the quality of the development of an Orphan Medicinal Product.

### ***B. Scientific Advice***

Further improving the informal dialogue with a sponsor during the development phase of a medicine will help to address the issue of requests for additional data and regulatory questions during or following submission and allow for better planning of resources, particularly in the case of smaller sponsors. The aim should be to reach a scientific consensus between the Agency and the company. Increasing opportunities for interaction of assessors with practising physicians in the specific field and/or, for example, patients in the case of rare diseases, would also improve the quality of assessments.

### ***C. Transparency***

Allowing informal direct discussions between the assessors and the applicant without the need for a formal meeting within the EMEA premises at every stage would help transparency and process. A partnership approach should be favoured, without changing the responsibilities of the involved parties, and access for the sponsors/applicants to relevant assessment documents will help to ensure transparency of the process and build understanding and predictability of the system. Open and rapid discussion of issues raised by the sponsor/applicant with the EMEA and the *Rapporteurs* should be allowed.

### ***D. The COMP and its Working Group for Interested Parties***

The COMP, with its positive approach to applications for designation, its patient group representation and its member state advocacy people for the OMP Regulation has played a key role in the field since its creation in April 2000. EBE and EuropaBio members recognise the genuine interest of the COMP and the EMEA to create a robust and appropriate regime for OMPs in Europe.

Since its inception in 2001, also the COMP Working Group for Interested Parties (COMP WGIP) has been a unique platform for dialogue between the COMP, the EMEA and patients, learned societies and industry about issues relating to orphan medicinal products. The experience of the group has translated into some successful projects, one of which was the “***Joint Meeting with all Interested Parties – A Continuity Policy for Orphan Medicinal Products in the European Union***”, held in December 2002 in London.

Building on its successful beginnings, we now suggest that the COMP WGIP becomes a multi-stakeholder think-tank, which provides input on policies to the COMP within the mandate defined in

Article 4(2)(b) of the OMP Regulation as being “to advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union.”

## **5. LINKING THE OMP REGULATION WITH THE NEWLY PROPOSED PAEDIATRICS REGULATION**

We applaud that the Commission in its “*Proposal for a Regulation on Medicinal Products for Paediatric Use*” wants to provide incentives for sponsors to study paediatric use of newly developed Orphan Medicinal Products, by granting a potential 2-year additional market exclusivity. However, we believe that such paediatric data should not be a requirement at time of filing for a marketing authorisation, as this may unnecessarily delay therapy access for some patients. Also we propose that ongoing paediatric studies are allowed the same benefits retroactively as soon as this new Regulation is approved in order not to delay paediatric work in Europe.

We suggest that this proposed Regulation and its impact on Orphan Medicinal Products be carefully studied and evaluated on its impact on development of rare disease therapies.

### **EU COORDINATION AND RESEARCH PRIORITIES FOR RARE DISEASES**

**The coordination and streamlining in the EU of rare disease research and therapy development between DG Research, DG Enterprise & Industry, DG SanCo as well as the EMEA and the OMP Regulation, and with the FDA is highly needed.**

The minutes of the last meeting of the European Commission DG SanCo’s Task Force on Rare Diseases in January 2004 reconfirmed that rare diseases are one of the important priorities in the new Programme of EU Community Action in the field of Public Health (2003-2008), and are now classified under “Health Information” instead of “Health Threats”.

The European Commission has also taken the initiative of organising a conference on Rare Diseases during in June 2005 in Luxembourg, during the Luxembourg Presidency of the EU, in order to publicise the European achievements in the field. At the same Task Force meeting, the strategy of DG Research on rare diseases was discussed and it became clear that only very large projects will be the hallmark for the Framework 7 programme. Close collaboration with stakeholders in the field of Rare Diseases in order to increase the available budgets was proposed.

There is also a need for more cooperation in the field of rare disease research, as indicated during several conferences (EPPOSI, Eurordis, EMEA with stakeholders) in the recent past. Such cooperation should more seamlessly link research activities in Europe to the reality of the OMP Regulation and the potential to convert research into accessible therapies for patients. Moreover, it has been recognised that research into the underlying mechanisms causing rare diseases reveals and uncovers important information that, in turn, also helps to develop therapies for more common diseases. This is another aspect that should be embraced by DG Research in order to lead the world’s efforts in this field.

### **CONCLUSIONS**

Europe cannot expect its patients to benefit from the innovation and research into medicines for rare diseases without making appropriate incentives available. It cannot expect other parts of the world to create and supply incentives for the development of rare diseases while at the same time getting the

benefit from the availability of therapies for such diseases at low prices. Europe has understood this and has first worked on the OMP Regulation that now needs to be put in a comprehensive framework of further measures to educate the health professionals, stimulate research on rare diseases and to help the affected patients.

Industry is ready to cooperate with the authorities and other stakeholders to establish this framework. Reducing incentives to develop orphan medicinal products would be against both the spirit and the intent of the OMP Regulation, and would be in contradiction with the priority status given by the EU to rare diseases as a public health issue. It would also undermine the policy continuity needed for long-term planning by companies.

EBE and EuropaBio members believe that, while it is too early to draw conclusions from the results obtained by the OMP Regulation in the EU, it is important to ensure further adequate and full application of this important and ground-breaking Regulation by appropriate supporting measures, which include all aspects of education, research coordination, diagnosis, epidemiology, registries, Member States' incentives, access, reimbursement and care.

As the Regulation is very new, being only operative since 2000 and yielding so far 20 approved Orphan Medicinal Products in the EU, some more time is needed to see how it pans out. Nevertheless, Europe should take this field very seriously and should actively seek further ways to promote research and development for such therapies. It should certainly avoid the risk that the research and clinical trial work for medicines for rare diseases would largely be carried out somewhere other than in Europe.

Working on a fully fledged framework would be an example of positive long-term policy making, since rare disease research leads not only to treatments for patients with rare diseases, but ultimately also to a better understanding of (related) common diseases. Further, it would support the objectives of the Lisbon treaty. As Dr. Peter Liese, a well-known member of the European Parliament, stated: *“for orphan medicines we need tax cuts, not price cuts”*.

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