Improving access to orphan medicines for all affected EU citizens

The overall objective of this document is to promote the sustainable development of valuable orphan medicines and to improve sustainable access to these medicines for all affected citizens in the EU.

It is in particular a valuable exercise for the Working Group on Pricing of the Pharmaceutical Forum to address the area of orphan medicines, as these medicines amplify strongly the common tensions we have found in the field of pricing and reimbursement: assessing and rewarding innovation is difficult, budget optimisation is challenged and access for patients is limited in several countries.

Introduction

Orphan diseases are life-threatening or chronically debilitating diseases that affect less than 5 out of 10.000 citizens. Although each of the orphan diseases only concerns a limited number of patients, rare diseases are socially and ethically relevant. In the EU, about 6% of the population is expected to be affected by one of 5,000-8,000 orphan diseases at one point in their life-time[1]. The low number of potential patients per disease may limit the economic attractiveness of undertaking research and development of medicines to treat orphan diseases.

To promote such research and development, the European Union has adopted the European Regulation on Orphan Medicinal Products in 2000 (Regulation (EC) No 141/2000**).**This Regulation defines an orphan drug as a medicines (a) for a life-threatening or chronically debilitating condition, (b) that affects not more than 5/10,000 persons or for which a low return on investment is expected without additional incentive and (c) for which no satisfactory alternative treatment method exists or for which this new medicine brings significant benefits to patients compared to the existing treatment. This Regulation has brought some efficient incentives for R&D, in particular the provision of a 10-year market-exclusivity which has led to a significant increase of research and development in the field of rare diseases. By February 2008, 541 molecules got an orphan designation. 45 of them have gone through the entire development-process and have effectively led to a new treatment for which a marketing authorisation was granted (see annex). As such, a medicinal therapy has been developed for many diseases which previously could not be treated. For the coming 5 years a steady inflow of about 10 to 12 new orphan medicines per year is expected. By end 2012, it is anticipated that around 100 orphan medicines will be authorised in the EU. The adoption of recent European legislations like the Paediatric Regulation (Regulation (EC) No 1901/2006) or the Regulation on Advanced Therapies (Regulation (EC) No 1394/2007), has provided an additional stimulus for many orphan medicines. Many measures that were taken by individual Member States on the national level have largely contributed to this success.

In spite of this, newly developed orphan medicines are not available for all citizens in the EU in a timely and equitable manner. Effective market access and utilisation vary strongly between and within Member States. Different studies, like e.g. the Alcimed study[2] or the

[1] These figures come from different institutions' official documents, such as the Background Paper on Orphan Diseases for the "WHO Report on Priority Medicines for Europe and the World" - 7 October 2004; the European Commission Consultation "Rare Diseases: Europe's challenges" - November 2007; documents from the National Institutes for Health – Office of Rare Diseases, as well as documents from patients organisations: NORD, the National Organization for Rare Disorders in the USA, and EURORDIS, the European Organisation for Rare Diseases in the EU, in particular the document "Rare Diseases: understanding this Public Health Priority.

[2] Commissioned and published by the Commission on 16/11/2004 on http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/archives_en.htm

Eurordis survey[3] series, confirm this variation in access. European reference networks between centers of expertise are a way to reduce this variation in access.

This paper aims to identify the main bottlenecks orphan medicines meet on their way to all affected EU citizens. These bottlenecks relate no longer just (1) to development, but also (2) to assessment, (3) to pricing and reimbursement practices by companies and by national authorities and (4) to awareness building. Consequently this paper puts some ideas forward that should be seriously explored in order to ensure timely and equitable access for all EU citizens to more orphan medicines.

Specific bottlenecks linked to rarity

In spite of increased incentives and in spite of increased flexibility in marketing authorisation procedures, the **development** of a medicine for an orphan indication remains a risky enterprise. The low number of potential patients, the absence of patient registers and the lack of national centres of expertise complicates research and development while it makes the future return on such R&D investments uncertain. Besides the usual R&D difficulties, researching and developing orphan medicines need to deal with the identification of rare patients, the heterogeneity of the diseases, a limited basic knowledge on the diseases, the application of often novel technologies and specific logistics and infrastructure requirements to run the clinical studies (e.g. flying patients in worldwide to one expert centre). Also manufacturing processes need to be developed at the same high standard-levels of safety, quality and efficacy as for other medicines. The low number of potential patients limits the future sales volume while often high levels of pricing and reimbursement make negotiation processes difficult. Overall, this may make the expected future revenue and return on investment uncertain and unattractive, while it potentially jeopardises the important societal benefits that orphan medicines could offer. The Orphan Medicinal Products Regulation is aiming exactly to address these bottlenecks in development.

Assessing the clinical added value of innovative medicines has proven to be a difficult task. Capacities and knowledge to do so are still under development. Orphan medicines add to this complexity due to the rarity of patients, the severity and the heterogeneity of the diseases addressed and the scarcity of clinical experts. Scientific data that are presented to Marketing Authorisation authorities are often limited as clinical trials can only include a low number of patients. The severity of the disease, combined with the lack of satisfactory alternatives, regularly leads to early Market Authorisations, before running phase III- trials which bring more data on a higher number of patients. Often ongoing clinical data-registration (phase IV) needs to be organised in the post-marketing phase as required by regulatory authorities. Data for value assessments (post marketing authorisation) are therefore limited, in particular for the initial assessments. In addition the know-how to make these value assessments of orphan medicines is strongly fragmented over national procedures within the individual Member States and their regions, in spite of some first efforts to collaborate. The disconnection of these national and regional processes from the knowledge and experience gathered upfront in the centralised processes (like for Orphan Designation, for Marketing Authorisation or for Paediatric Use) add to this fragmentation.

Pricing and reimbursement decision-making is an area of increasing sensitivity within almost all of the European Member States. The uncertainty about the value, the lack of information, the usual high-prices, the high risk for development, the low and uncertain volumes, the occasional extensions of indications and the often life-long need for treatment add to this sensitivity when discussing pricing and reimbursement of orphan medicines.

[3] Available through www.eurordis.org

Decision-making is further complicated by the frequent use of these treatments in hospitals. As explained above, only a limited set of data on clinical added value is available to justify the initial requests for high prices, while data on drug-specific costs for R&D are usually not available, as is the case for most medicines. When prices are negotiated, initial negotiations between companies and authorities should not only include agreements on price and reimbursement levels but also on monitoring utilisation (based on medical best practices), in order to control budgets in spite of high prices. Negotiations can be further complicated in case of further extension of indications. In many Member States, the national budgets for orphan medicines are still relatively limited, but seem to grow fast. These budgets may lead to different levels of affordability depending on the economic situation of a Member State. To manage budgets and make the right choices, an increasing number of Member States complement the price negotiations with practices to monitor and manage utilisation like e.g. prescription limitations, pre-utilisation approvals or exclusive use in designated expert centres.

In contrast to other disease areas, health professionals have limited **awareness and skills** with diagnosing and treating orphan diseases. The low incidence of these diseases allows only a limited number of health professionals, usually in specialized centers, to build expertise with diagnosing and providing medical care to people affected by a rare disease. Nevertheless, an early diagnosis of these diseases, which often have a genetic origin, is one of the best guarantees for an efficient treatment from a therapeutic and cost perspective. In addition, treatments are often not curative but usually offer from limited to extensive symptomatic support. The novelty of the treatment options offered by innovative orphan medicines further limits awareness and skill levels of health professionals. Some Member States therefore organise the monitored utilisation of orphan medicines through dedicated centres of expertise, to which all patients with a specific orphan disease are referred. Alternatively Member States ask these centres of expertise to issue good practice guidelines to advise all potential concerned physicians and experts.

Potential ways forward

In addition to ongoing activities promoting the development and access to medicines in the European Union, the Working Group Pricing believes that some specific activities can be explored to promote further development and access to orphan medicines. These include:

- **Establish early dialogue** between companies and pricing and reimbursement authorities, including clinical value assessment authorities regarding orphan medicines in the pipeline and the future needs for these medicines. This dialogue will allow in an early stage to clarify the need for a new orphan medicine under development and give an idea of the number and profile of patients in need. It would offer an early occasion to discuss what clinical data would be required for later clinical value assessments and pricing and reimbursement decisions. This will give the sponsoring company more certainty on its potential future return and will give authorities more knowledge and trust in the value of medicines it will be requested to assess and fund. Also, this will significantly facilitate long-term planning both for companies, for funding authorities and for society. Such dialogue could even help identify areas where further research and development for orphan medicines are needed, taking account of public health priorities. Early dialogue would also bring an opportunity to get more transparency on costs, including the role of publicly funded studies, and on pricing. Such dialogue might require an upfront coordination between Member States and European authorities, in full respect of different competences, in order to jointly pass common messages to the individual companies. This coordination and dialogue can be continued after regulatory approval and after initial

pricing and reimbursement decisions, where additional studies are requested regarding the utilisation of medicines. Where appropriate this can include the set-up and use of disease registries[4].

- **Exchange of knowledge amongst** Member States and European authorities on the **scientific assessment of the clinical added value** of orphan medicines. Such exchange could improve the flow of knowledge from EU-level authorities (e.g., EMEA committees) to the Member State's pricing and reimbursement authorities, in particular with knowledge gathered during marketing authorisation procedures (quality, safety, efficacy), revision of the orphan designation at the time of marketing authorisation (significant benefit) and potentially the evaluation of paediatric use (paediatric investigation plans). Bundling the fragmented know-how to assess the clinical value of orphan medicines would allow the timely production of well-informed opinions, based on more data, shared information, experiences and in-depth discussion. Such opinions will form a good input and may reduce the information deficit for the national pricing and reimbursement decisions. Clinical/therapeutic aspects, rather than economic and quality-of-life aspects, should be the first focus in common approaches, as variation between Member State practices is lowest in this area. Based on exchange of knowledge, these collaborations could lead to non-binding common clinical added value assessment reports with improved information that facilitate the national pricing and reimbursement decisions, without pre-empting respective roles of the authorities. Of course the applicable rules regarding confidentiality should be considered when exchanging such information.
- **Promotion** of the initial uptake of orphan medicines through **conditional pricing and reimbursement decisions**. Such conditional decisions could allow fast access for patients to medicines, while the related conditions can, case by case, control the utilisation, specify the expected annual budgets, fix the timings for review and clarify the expected results of further studies and future pricing and reimbursement adjustments. To fully profit from conditional agreements, costs, risks and benefits must be clearly aligned and clarified upfront, in order to avoid later legal and ethical conflicts. At extension of indications a review of the conditions should be organised taking account of the additional development costs and the additional number of patients benefitting from the medicine. The related conditions usually ask for monitored utilisation allowing collection of additional data e.g., in the context of a post-marketing trial or a registry. A high quality of monitoring and data-analysis is needed in these trials. The earlier Member States adopt the utilisation of orphan medicines in such controlled settings, the earlier a substantial set of data on the impact of orphan medicines can be developed. This in return will provide a basis for the future review of pricing and reimbursement decisions. To ensure that patients in all EU and EFTA Member States can benefit early on from orphan medicines other ideas should be explored, like simultaneous applications for pricing and reimbursement to all Member States authorities, early start of national pricing and reimbursement procedures, parallel decision making with common information bases and coordinated follow-up of use and outcomes in clinical practice. Some of these ideas are already in place in some Member States, and these experiences should be shared amongst Member States. [5]
- **Building EU-level awareness and expertise on orphan diseases.** Controlled utilisation can very well be linked to the creation of standardised patient registers[6] at international level and networks of centres of expertise. Registers would also allow upfront estimates of

[4] Disease registry is a specially designed database with voluntary, observational clinical data collected from physicians and intended to explore and define the natural course and clinical characteristics of disease, as well as to track and characterize response to treatment.

[5] For more specificities regarding conditional pricing and reimbursement we refer to the paper "Risk-Sharing practices and Conditional Pricing of pharmaceuticals - How to deal with uncertainty", as well as to the "Guiding Principles Paper", adopted by the Working Group Pricing.

[6] Patient register is a database (list) containing baseline information on the existence of patients with (a) certain disease(s), but without any longitudinal follow-up.

numbers and profiles of patients for study and budget purposes. Another key benefit of such registers is the upfront knowledge of where rare disease patients live so that they can be quickly enrolled in trials for new potential medicines, to the benefit of both the patient and the sponsoring company. At the same time, the set-up of disease registries will facilitate the generation of additional data on the benefits of the medicine in real life settings. These data, in their turn, will form the basis for later reviews of pricing and reimbursement decisions. All registers and registries are to be managed in compliance with data protection rules and other relevant national requirements. To fully leverage collected knowledge, the efforts need to be well coordinated within and between Member States. Within Member States, coordination should be a key element in national plans for rare diseases and orphan medicines. Between Member States, national and regional centres of expertise need to be connected in a cross-border European Reference Network for Rare Diseases. The Orphanet initiative could be a helpful reference for cross-border work in this area[7]. This will improve access to orphan medicines, increase quality of care, and allow to compile and compare data of all Member States.

[7] www.orpha.net

List of Orphan Drugs with European Market Authorisation - 16 June 2008

Product Name	MA Holder	Date of MA	Indication
Replagal	Shire	4-may-01	Fabry Disease
Fabrazyme	Genzyme	4-may-01	Fabry Disease
Glivec	Novartis	27-aug-01	Chronic Myeloid Leukaemia
Trisenox	Cephalon	5-march-02	Acute Promyelocytic leukaemia
Tracleer	Actelion	15-may-02	PAH
Somavert	Pfizer	13-nov-02	Acromegaly
Zavesca	Actelion	20-nov-02	Gaucher Disease
Carbaglu	Orphan Europe	24-jan-03	NAGS Deficiency
Aldurazyme	Genzyme	10-june-03	MPS I
Busilvex	Orfagen / Pierre Fabré	9-july-03	Conditioning prior to transplant
Ventavis	Schering	16-sept-03	PAH
Onsenal	Pfizer	17-oct-03	Familial Adenomatous Polyposis
PhotoBarr	Axcan	25-march-04	Dyplasia in Barrett's Esophagus
Litak	Lipomed	14-apr-04	Indolent Non Hodgkins Lymphoma
Lysodren	HRA Pharma	28-apr-04	Adrenal Cortical Carcinoma
Pedea	Orphan Europe	28-july-04	Patent ductus Arteriosus
Wilzin	Orphan Europe	13-oct-04	Wilson's disease
Xagrid	Shire	16-nov-04	Essential Thromobythaemia
Orfadin	Swedish Orphan	21-feb-05	Tyrosinaemia
Prialt	Eisai Ltd.	21-feb-05	Chronic pain
Xyrem	UCB	13-oct-05	Narcolepsy
Revatio	Pfizer	28-oct-05	PAH
Naglazyme	BioMarin Europe	24-jan-06	MPS VI
Myozyme	Genzyme	29-march-06	Pompe Disease
Evoltra	BioEnvision (Genzyme)	29-may-06	Acute Lymphoblastic Leukaemia
Nexavar	Bayer	19-july-06	Advanced Renal Cell Cancer
Sutent	Pfizer	19-july-06	GIST
Savene	TopoTarget	28-july-06	Anthracycline Extravasation
Thelin	Encysive (UK) Ltd.	18-aug-06	PAH
Exjade	Novartis	28-aug-06	Iron overload req chelation
Sprycel	BMS Pharma EEIG	20-nov-06	Chronic Myeloid Leukaemia
Diacomit	Laboratoires Biocodex	4-jan-07	Myoclonic Epilepsy
Elaprase	Shire	8-jan-07	MPS II
Inovelon	Eisai Ltd.	16-jan-07	Lennox Gastaut syndrome
Cystadane	Orphan Europe	15-feb-07	Homocystinuria
Revlimid	Celgene	14-jun-07	Multiple Myeloma
Soliris	Alexion Europe	20-jun-07	Haemolysis in Paroxysmal Nocturnal Haemoglobinuria (PNH)
Siklos	Addmedica SAS	29-jun-07	Vaso-occlusive crisis
Increlex	Tercica Europe	3-aug-07	Growth failure
Atriance	Glaxo	22-aug-07	T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblas

			LBL)
Gliolan	Medac	7-sept-07	Visualisation of malignant tissue during surgery for malignant gliom
Yondelis	Pharma Mar	17-sept-07	Advanced soft tissue sarcoma
Torisel	Wyeth	19-nov-07	1st Line Renal Cell Carcinoma
Tasigna	Novartis	20-nov-07	Philadelphia chromosome positive chronic myelogenous leukaemia
Thalidomide Pharmion	Pharmion Ltd	16-apr-08	Untreated multiple myeloma
Volibris	GlaxoSmithKline	21-apr-08	PAH
Firazyr	Jerini AG	11-july-08	Acute attacks of hereditary angioedema

* estimated cumulative number of patients treated since launch in EU-27 (non-repetitive treatment).
** reimbursed in 15 countries