

Healthcare funding: Rare diseases, a priority? AIM's proposals

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About 5000 to 7000 rare diseases are recognised¹. These life-threatening or chronically debilitating diseases are complex and have low prevalence – defined as² not more than 5 people affected per 10000 – so general knowledge and expertise about them can be limited. The limited number of patients affected by rare diseases also makes research difficult and potentially unattractive for the pharmaceutical industry. People affected by rare diseases can have difficulties in getting local diagnoses, in referral to suitably specialised health professionals who may be abroad, and in getting good information about their disease in their own language. In some countries or health systems the socio-medical coverage may not be well-adapted. These are some of the reasons why a 'European' approach – which includes cooperation and coordination – is needed, wanted and supported by all concerned parties and actors in the health sector. Affordability and financial access to specific treatments represent a major challenge for national health systems as well as affected patients and their families. Due to legislation in several continents to encourage the development of drugs for rare diseases, the number of registered so-called 'orphan drugs' is increasing and recent statistics show that the costs of such orphan drugs are increasing exponentially. Improving the financial affordability of tremendously high cost individual treatments remains a real challenge and AIM sees here a new opportunity for action at EU level.

AIM welcomes the commitment of the European Commission, dating from the late '90s, to helping tackle the problems of 'rare diseases'. This accords with Article 152 of the Treaty, highlighting the role of the EU in encouraging cooperation between the Member States regarding health and if necessary supporting their action.

¹More information on Orphanet: http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN.

²According to the EU Regulation on Orphan Medicinal products the definition of rare diseases consists of two elements: prevalence (5:10,000) and they have to be life-threatening or chronically debilitating. Regulation (EC) N° 141/2000 published in OJ L18/1-5 on 22 January 2000.

In AIM's view, the engagement, efforts and activities of the European Commission have already produced positive results: greater awareness led more and more Member States to engage in specific reflection about how to tackle rare diseases. Among the Member States, France has been a pioneer and has played a leading role since the early '90s. France originated the creation in 1996 of the multi-lingual database ORPHANET. Now France has been joined by the Netherlands, Germany, Sweden, Bulgaria, Italy, Portugal, Romania and Spain who have each put in place a specific health policy on rare diseases and/or who support R&D of orphan drugs. Still further countries have started to set up informal working groups on these topics.

AIM has expressed its support for a 'European' approach, in its response to the public consultation prior to the European Commission's communication on "*Rare Diseases: Europe's challenges*" (as adopted in November 2008). AIM fully supports the three main areas on which the Community strategy is intended to be built:

- Improving Recognition and Visibility of Rare Diseases
- Supporting Member States' activities
- Developing European cooperation and coordination

1. Information and visibility

As 'knowledge is the key' for any activity in this field, a harmonised classification system must be the basis on which collaboration, cooperation and coordination is built. This needs to be done in close collaboration with the WHO, to ensure a coherent and efficient approach at international level. The importance and utility of the ORPHANET database is commonly recognised; it provides information and knowledge about rare diseases for health professionals and also for patients, their families and carers. The financing of ORPHANET deserves therefore to be assured on a permanent basis, to ensure its sustainability over time and ideally to secure the future of an integrated information system.

2. Supporting Member States' activities

To improve the efficiency of national activities and projects, with the ultimate aim of improving patients' access to care and information, a coherent and common approach in the activities of Member States is desirable. Codification and an inventory of rare diseases will allow sharing of knowledge and expertise on which good practice guidelines can be built. Fostering collaboration in research is absolutely necessary to maximise the output of inevitably-limited financial resources. During the last five years of debate on 'services of general interest', AIM has been calling for the European Commission to promote a comprehensive approach in integrating health and social care.

3. Identification of expertise in particular through reference centres

Given the differences in size and wealth of European countries, Member States cannot all have the same experience on rare diseases. AIM believes that gathering national expertise and identifying 'reference centres' for research, diagnosis and treatment of rare diseases are key to improving quality of care. AIM and its member organisations' opinion on the proposed Directive on *patients' rights in cross-border healthcare* therefore supported the proposal for a European network of reference centres in the field of rare diseases. These should help to promote transfer of knowledge, as well as the necessary mobility of patients with rare diseases: patients' 'health pathways' could be greatly improved by referral to European Reference Centres with skills which cannot be sustained in their own country (or, by using telemedicine if appropriate). Questions about the principles of authorisation and reimbursement of the costs of cross-border care can however be resolved by the application of European Regulation 883/2004 to statutory health schemes, or by structured crossborder or bilateral agreements between countries. Two reservations are however important: where financial resources from the European Union are used to construct or equip medical centres of reference, in principle this should not result in subsidised competition with existing facilities. And financial implications should be carefully considered when organising improved treatment for patients using new means for exchange of knowledge and experience.

Examples of collaboration on rare diseases between reference centres are already available or in preparation:

- The Netherlands has a policy to encourage the accessibility of expensive orphan drugs, which have recognised 'added value', in the eight university hospitals. This policy also concentrated knowledge of specific, ultra-rare, disorders in these expert centres by introducing a specific rule for European-registered orphan drugs in 2006³.
- In Israel, the clinical centres manage affected patients and coordinate with the health funds that cover the treatment. Due to the yearly process of health technology assessment, the treatments for rare diseases are in the public basket

³This policy rule provides provisional funding of 100% for three years and requires the collection of more evidence on the clinical- and cost-effectiveness of the orphan drugs during this period. A special research programme has been dedicated to funding research on effectiveness of expensive orphan drugs and on expensive (innovative) drugs that are listed in the policy rule for orphan drugs or in the policy rule for expensive (innovative) drugs – with 80% reimbursement. After a maximum of three years, the evidence that has been developed as a result of the additional studies will be appraised and the decision will be made on whether the product is to be reimbursed definitively. At the end of 2008 eight orphan drugs are provisionally listed on the policy rule of orphan drugs: six are biotechnical products (recombinant enzymes) for ultra rare metabolic disorders, one is a biotechnological product (monoclonal antibody) for an ultra rare blood disorder and one is a chemical oncology product for children with a specific rare cancer for which other treatments have failed. (*Information transmitted by Sonja van Weely, scientific officer of the Dutch Steering Committee WGM, weely@zonwm.nl and www.orphandrugs.nl*)

of services. There is also close coordination with a patient's family physician, who continues to provide the care for all other medical problems not directly related to the rare disease. The health funds have special committees to monitor the care of rare disease patients and to give necessary approval for their special medication and treatment.

- Germany is planning to introduce an obligation for the hospital sector to obtain a second opinion from a qualified specialised medical doctor confirming the use of new very costly therapies. For the time being, this initiative concerns 4 pharmaceuticals to treat different forms of pulmonary arterial hypertension which affect about 3000 patients in Germany. In October 2008, the Medical Review Board of the Federal umbrella organisation of the German sickness funds (MDS) welcomed the 'second opinion' process as a step in the right direction. The aim is to strengthen coordinated, systematic and solid assessment of the therapeutic value of new processes and methods in the hospital sector⁴.

4. Access to treatments and orphan drugs: How ensure sustainable affordability?

By definition, limited numbers of patients suffer from each rare disease, so the complexity and limited knowledge involved can frequently make research difficult and potentially unattractive for the pharmaceutical industry. This was among the reasons why the EU adopted in 2000 a Regulation on orphan drugs, establishing several incentives at European and national level to encourage and facilitate research on orphan drugs. Since then about fifty orphan drugs have been authorised and about five hundred products remain under development. In the coming years it is expected that every year 10 to 12 new orphan drugs will come onto the market, leading to around 100 authorised orphan drugs by 2012 in the EU⁵.

AIM considers that the major hurdle to equal access to orphan drugs is the problem of affordability: these drugs typically may have very high prices, set ostensibly to recover high research costs on small volumes of sales. The cost of an annual treatment with orphan drugs differs greatly according to the indication and also between Member States⁶. For example:

- In The Netherlands, in 2006, the price of an orphan drug per patient per year

⁴MDS – Medizinischer Dienst des Spitzenverbandes Bund der Krankenkassen e.V. <http://www.mdsev.de/print/3084.htm>.

⁵Document of the Pharmaceutical Forum, pp. 93–99. http://ec.europa.eu/pharmaforum/docs/ev_20081002_frep_en.pdf.

⁶Alcimed study of 2004. http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/pricestudy/final_final_report_part_1_web.pdf.

has varied between 1,075 € (Wilzin; zinc acetate dihydrate) and 293,389 € (Al-durazyme; laronidase)⁷.

- In Belgium in 2008, the prices of some of the new products⁸ exceeded 100,000 € per patient per year, 3 products cost 300,000 € per patient per year and another reached 600,000 €. Even with a limited number of patients, these expenses represent a high burden for health systems. About 900 patients received reimbursement for dedicated orphan drugs: the annual average cost for an orphan drug per patient was about 45,000 € and the total cost for these 900 patients amounted to 4% of the total hospital budget for pharmaceuticals.
- In France, Eculizumab, a new medicine for paroxysmal nocturnal hemoglobinuria, became available in 2008. In a full year, this new treatment will cost 350,000 €/patient. Before it qualified for reimbursement, this medicine had already been prescribed to 76 patients. About 300 patients are expected to be treated per year in coming years. 'Orphan diseases' affect 3 to 4 million people in France.

European solidarity-based health systems are in general committed to cover these expenses provided the price is seen to be fair. With such tremendously high price levels, it is normal that public authorities and health insurance organisations request full transparency on the underlying costs of these products. As real costs of R&D are typically a 'black box', not always costed and often incurred abroad anyway, several major AIM members request companies to disclose key elements of the cost components, in order to have a rational basis for price negotiations. Such 'transparency' of the components underlying the final price is of utmost importance for economic optimisation between supplier, payer and patient across Europe.

Furthermore, experience shows that the number of clinical indications for utilisation of a new product tend to be enlarged over time, so the number of patients taking the medicine will be correspondingly enlarged. If so, it would be normal to divide the price accordingly, but this never seems to happen. The acceptance of high prices should therefore be linked to cost-volume contracts which would lead to proportional decrease of prices linked to the increase of sales volume. For example in England the statutory health service sets volume-related national budgets as a key instrument for funding very expensive drugs, whether or not for rare diseases.

AIM has also called for the organisation of a systematic review at the end of the fifth year of sale of 'orphan medicinal products' as laid down in the Regulation on orphan drugs adopted in 2000⁹. The orphan drug product sponsor should have the obligation to compile a review file (based on the five years of experience and providing data

⁷<http://www.gipdatabank.nl> (extramural data) and CVZ/CFH reports (2006) www.cvz.nl (intramural data).

⁸Mutualité chrétienne (Belgium), June 2008, http://www.enmarche.be/Actualite/Editos/Editos_2008/innovation_a_tout_prix.htm.

⁹Article 8 B2 of Regulation (EC) N°. 141/2000.

on the original designation criteria: prevalence – return on investment – significant benefit). This review file should be submitted to the EMEA and in particular to the COMP committee. The information should also be made available to the Member States, to payer organisations and to the general public. If the original criteria are found no longer to be fulfilled, then ‘market exclusivity’ should be accordingly reduced, as proposed in the Regulation¹⁰. AIM has also called for those obtaining marketing authorisation for an orphan drug to be obliged to make that product available in *all* Member States, if the request is made by competent authorities, at a reasonable and fair price.

AIM believes that improvements in financial access to orphan drugs have to find solutions at European level too. Europe has already taken measures to improve the availability of dedicated treatments for rare diseases (funding of research projects, orphan drug regulation, etc.). In addition to these, and now on the basis of the Union’s objective to strengthen social cohesion and the protection of citizens’ health and rights, the EU has a unique opportunity to show that European solidarity in the interest of citizens can be possible.

AIM also believes that in addition to the orphan drug regulation which mainly involves the pharmaceutical industry, academic research in preclinical development should be supported by the public sector, the EU and charities. AIM recommends that independent academic clinical trials should be supported at European and national level (on the model of what has been done so far in Italy, France and Spain) and these efforts should be coordinated in a way that ensures sufficient patient participation for efficiency in each trial. The European Commission should also review whether the implementation of the Clinical Trials Directive has succeeded in facilitating efficient and safe EU product development¹¹.

AIM supports public-private partnerships, for instance between industry and universities, in R&D on new medicines in the field of rare diseases. But for social health insurance schemes represented in AIM it could not be acceptable to have R&D financed by public money while private for-profit companies on the other hand take all the profit on resulting pharmaceuticals. Therefore any such partnership should be well designed and regulated to avoid such situations. The Drugs for Neglected Diseases Initiative¹² is a good example of a new way of developing drugs, where the partnership model is effective and where at the end the price of the drugs can also be affordable for patients and for society.

Awareness campaigns, calling for more private funding e.g. from large foundation funds, could also contribute to the financing of specific activities.

¹⁰According to an analyse in 2007 of the evolution of volume of sales of orphan drugs between 2001 and 2006 in Germany, the maintain of the specific market exclusivity agreed for orphan drugs is not justified any more for 2 products, Glivec and Tracleer due to their commercial success. Source: GAmSI-Daten, BKK InfoNet, Stand 4.10.2007.

¹¹Directive 2001/20/EC of 4 April 2001.

¹²DNID, www.dndi.org.

5. Continuous evaluation through networking

It is of utmost importance that all data arising from evaluation of orphan drugs are made available for each intended indication. There is a notable lack of comparative studies versus alternative treatments, lack of long-term data, lack of end-point data and lack of 'real life' data. Networking for Health Technology Assessment as well as for pharmacovigilance should therefore be improved. Due to the rarity, dispersion, complexity and severity of many rare diseases orphan drugs need continuous evaluation after the marketing authorisation, in particular of the benefit-risk relationship. Such post-marketing studies under 'real life' circumstances should be made compulsory for all orphan drugs. The marketing authorisation holder should also keep the national authorities informed about sales volume.

6. The way forward – key elements for European collaboration

To conclude, AIM encourages the European Commission to continue to help the Member States in giving European citizens access to reliable, efficient, innovative and affordable medical treatments in the area of rare diseases.

The Commission should present every two years a report to the Council and the Parliament identifying remaining *bottlenecks in access* to orphan drugs across Europe (e.g. delays, prices, reimbursement).

The report should also note progress in the field of R&D, *new indications for orphan drugs, the existence and coordination of national plans, use of referral procedures to centres of expertise and the impact of orphan drugs on the health expenses for each country*.

AIM invites the Commission to make proposals on the necessary legislative modifications in order to guarantee *equal access to orphan drugs* throughout the EU.

Brussels, 16 January 2009

A German version of this article is available from the AIM Secretariat.