Rare Diseases Task Force

How Many Drugs for How Many Patients?

Recommendations of the Rare Diseases Task Force

July 2007

Introduction

Rare diseases (RD) and orphan drugs (OD) represent an important discussion at the Public Health level. Orphan drug regulations have proven to be effective in boosting the development of therapeutic solutions that are otherwise expensive to produce and, by definition, benefit a small number of patients. Previously, healthcare systems could cover the costs of expensive OD because the treatments were rare enough that the effect on healthcare services and costs was minimal. As the number of drugs for RD grows, increased costs are straining healthcare budgets. The RD community has somewhat become the victim of its own success. Many health professionals have begun to fear that there may be a day when every RD could be treated with an OD and an endless increase of innovative therapies will cause an increased financial strain. The RD community is somewhat a victim of its own success.

In order to provide a sound framework for policy makers to discuss the forecast of OD in Europe, the Rare Disease Task Force (RDTF) organised a workshop on 30 June 2007 with participants from the RDTF, the European Commission, EMEA, Orphanet, and industry professionals of companies who already have a market authorised (MA) OD in Europe.

The specific aim of this workshop was to assess the number of treatable RD and estimate the proportion of patients eligible for treatment to serve as a basis for recommendations in the Communication on Rare Diseases to the European Commission. This workshop also serves as a preparatory meeting to ensure an effective debate during the Session of Epidemiology of Orphan Drugs "How Many Drugs for How Many Patients?" during the 8th European Platform for Patients' Organisations Science and Industry (EPPOSI) Workshop on Partnering for Rare Diseases Therapy Development.

Analysis and Recommendations

Methods

This report has been prepared by an expert group from the Rare Disease Task Force (RDTF). The RDTF was set up in January 2004 by the European Commission's Public Health Directorate. It is led by Ségolène Aymé, a medical geneticist and Director of the Orphanet, a database of rare diseases. The deputy leader of the RDTF is Helen Dolk, Director of the Eurocat Programme on Congenital Disorders. The aims of the RDTF are to advise and assist the European Commission Public Health Directorate in promoting the optimal prevention and case management of rare diseases in Europe, recognizing the unique added value to be gained for rare diseases through European co-ordination.

Three Working Groups (WG) have been established within the RDTF to focus on the following topics: Coding and Classification, Public Health Indicators, and Standards of Care. This last WG has been divided into two sub-working groups, the sub-WG on European Networks if Centres of Reference and the sub-WG on OD, established to contribute to knowledge about expectations in the field in the next 10 years. Members of this expert group included representatives of the RDTF, the European Commission, EMEA, Orphanet, and industry professionals of companies who already have a market authorised (MA) OD in

Europe. RDTF members are current and former project leaders of European funded initiatives related to rare diseases, member state experts and representatives from relevant international organisations, including patient groups.

Results

Prevalence of RD Patients

A bibliographic report published on the Orphanet website assesses the prevalence of rare diseases (http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases.pdf). This information in the Orphanet database can help predict the future of OD and patients eligible for treatment in Europe.

Meeting participants agreed on the following concerns in estimating the prevalence of rare diseases and the proportion of treatable rare disease patients:

- Estimates can be made using information from all European Economic Area (EEA) countries with developed healthcare systems capable of providing useful estimates. Barriers in countries whose healthcare systems do not allow for patient estimates include: no centres of expertise, thus no place for evaluation; distance (due to scare centres of expertise), lack of awareness on government level; lack of awareness on patient and health provider level; and cost.

- The rarer the disease, the greater the deviation of the estimate from true prevalence.

- The phenotype of many of these RD is heterogeneous even if the genotype is simple. In addition, as a result of predominantly being genetic and X-linked many RD are racially or regionally concentrated. As a result, many epidemiological investigations occur at the local level and prevalence appears high. With new born screening a much more accurate prevalence is obtained, which is often times much rarer than what was initially concluded with a local study.

- In many prevalence studies, only the most severely affected patients are documented. Under diagnosis, however, is a problem common to rare and major diseases.

Future of OD

A model to forecast OD Development in Europe using US and EU experiences was proposed by Eurordis and endorsed by the members of the group. This model, describing the kinetics of development from OD designation to market authorisation (MA) in the US, was created using data collected (since the implementation of the 1983 Orphan Drug Act) on three kinetics parameters: designation rate, marketing half-life (the time between designation and marketing authorisation), and the MA rate. Analysis of EU data, since the implementation of the Regulation on Orphan Medicinal Products, shows that the development of OD in Europe follows that same pattern. As such, the proposed model can be applied in Europe where it is estimated that the designation rate is 80 designations/year, the half-time of development of an OD in Europe is 3 years (50% are developed in 3 years and 75% in 7 years), and the rate of MA is 15%. This robust model brings into consideration withdrawn products and variability

of types of OD (i.e. biological, chemical, for oncology) and predicts ~200 new OD in the market in the next ten years.

Meeting participants agreed on the following questions for consideration in using this model to predict the number of market authorised drugs in Europe:

- It was suggested that there be two models, one for early designation OD and one for later designation.
- The model would be even more valuable if compared to a similar model for non-orphan drugs.
- How does the model allow for a cumulative effect of new drugs entering the market and replacing older drugs?
- Is this model sensitive to a change in designation criteria?
- The model could be compared to other similar drug categories in order to compare MA half-life of OD to other drugs.
- How does the difference of OD designation criteria in US affect the use of the model in Europe?

The Orphanet database also serves as a valuable tool in predicting the number of OD on the European market in the next decade. The Orphanet OD database aims to centralise information on current OD and currently, OD in Europe can be searched by disease, laboratory, active substance or brand name, stage of development and designation. All non-orphan drugs with RD indication are also included in the database and searchable with similar criteria. Currently this database includes 449 OD designations with the following breakdown of product types: 58% chemical, 30% biotechnology, 3% cellular therapy, 3% natural, 3% oligonucleotides, 2% gene therapy (Annex 1).

The group agreed on the following predictions:

- Biotechnological products will increase
- Cellular therapy products will only increase a bit. As there are few such products today, the % increase will be large but the number of products will remain small.
- Chemical therapies will decrease
- Gene therapy will increase; vectors will be used and designated as orphan products; the application of these therapies will be different than most drugs as they will most likely be administered in one dose in a hospital setting or a kit and not regularly consumed.
- Oligonucleotide therapy will greatly increase

It was also suggested that including all drugs with rare disease indications in this type of analysis would be persuasive as would the presentation of paediatric and non-paediatric data separately.

Conclusion

The 1983 American Orphan Drug Act has been an unbelievable booster for innovation. Orphan drug regulations in Europe and other parts of the world have since proven to be effective in boosting the development of rare disease therapeutic solutions that were previously considered to expensive to produce for too few beneficiaries. Considering the novelty of this legislation in Europe, it is not obvious what the future of OD holds. Similarly, the true prevalence of rare disease patients is also an area that requires more investigation. The exact prevalence rate of each rare disease is difficult to assess from the available data sources. There is a low level of consistency between studies, a poor documentation of methods used, confusion between incidence and prevalence, and/or confusion between incidence at birth and life-long incidence. In addition, it is likely that there is an overestimation for most diseases as the few published prevalence surveys are usually done in regions of higher prevalence and are usually based on hospital data. As such, it can be concluded that the number of rare disease patients is lower than often reported. Furthermore, although many rare disease patients benefit from off-label drugs, surgeries, and other therapies, of the total of rare disease patients only a fraction is eligible for treatment with OD. Investigation into the true prevalence of rare disease patients and the forecast of OD will allow policy makers to make sound decisions regarding legislation on orphan drugs and for rare diseases patients

Annex 1

Orphan Drug Designations by Medical Designation and Product Type - Orphanet

Orphan Drug Designations (449)

Designation	Number	Percent
solid tumors	106	24
oncohemetology	79	18
neurology	31	7
transplantation	26	6
inflammation	24	5
infectious diseases	23	5
cystic fibrosis	22	5
pneumology	19	4
cardiovascular	18	4
endocrinology	17	4
metabolic	16	4
lysosomal	14	3
hepato-gastro	12	3
ophthalmology	10	2
dermatology	9	2
hematology	9	2
muscular dystrophies	6	1
toxicology	6	1

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