EURORDIS
Rare Diseases Europe

S T A T E M E N T

Orphan drugs: rising to the challenge to ensure a better future for 30 million patients in Europe

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Summary

Nine years after the implementation of orphan drug regulation in Europe, the impact has been evaluated as extremely positive for numerous rare, chronic and serious diseases, which were previously without treatment. As of the beginning of 2009, 577 molecules had received orphan designation and 57 had received marketing authorisation in Europe.
It is now justifiable to ask questions about the future: how many orphan drugs may receive marketing authorisation in the future, for how many patients, and at what cost?
An analysis, summarised below, is being conducted by EURORDIS using data from the US Food and Drug Administration (FDA), and the European Medicines Agency (EMEA). The Orphan Drug Act adopted in the USA in 1983 led to two-thirds of the products authorised in the US being authorised in Europe, without any consequences for European economies prior to the 2000 EU Orphan Drug Regulation. Currently, the regulatory process for orphan drugs in Europe requires a declaration of intent-to-file at the time of request for designation. The development of orphan drugs is thus more transparent and more easily predicted than that of conventional drugs, for which competition pushes manufacturers toward a higher level of confidentiality until marketing authorisation is obtained.
It is now clear that there will not be a "tidal wave" of new orphan drugs. We can anticipate approximately 100 drugs between 2009 and 2019, equating to about ten new products per year. The cost varies depending on the nature and conditions necessary for their manufacture. The cost increases with the rarity of the indication, however not proportionally. As is the case for conventional drugs, orphan drugs are not effective in all patients affected by a given pathology: the frequency of use of the authorised treatment is always less than the known prevalence of the disease (with the notable exception of Gaucher's disease). Furthermore, access to diagnostic facilities and specialised centres remains difficult, preventing access to treatments for many of the patients requiring these treatments. Therefore, the number of patients with real access to treatment is even lower than the prevalence of the disease.
Since the adoption of EU Regulation on orphan drugs, there has been a need to change the widely accepted ideas concerning their cost to society: the current costs to national healthcare systems arise primarily from two product families: i) Glivec® and its numerous therapeutic applications for rare cancers, and ii) enzyme replacement therapies in extremely rare diseases. This represents two drug families with enormous added therapeutic value, which would in any case have been fully reimbursed by National Competent Authorities. It is estimated that the remainder of orphan drugs represent less than 1% of national healthcare costs. In addition, two-thirds of the 230 orphan drugs approved in the United States prior to 1999 were already available in all EU member states or for the majority of the EU population, without having raised any debate. The real questions arising are the cost of innovation (this is also true for common diseases) and the return on investment for innovative treatments, as well as the implementation of a new approach of a common European evaluation of added clinical value (i.e. the relative effectiveness), cost and conditions of reimbursement, and the coordination of post-marketing studies and responsibilities (in particular relative effectiveness studies), primarily in the context of the European registers.

How many orphan drugs: an impenetrable mystery?

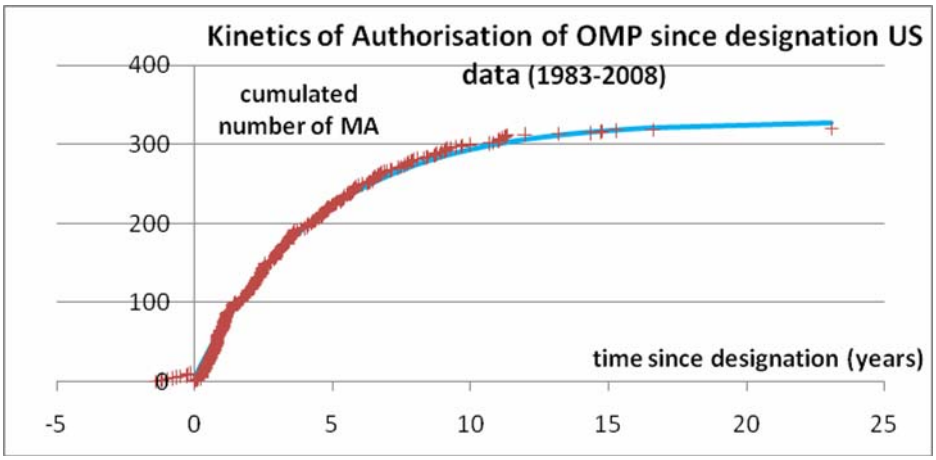
As for all drugs, the development process for orphan drugs is long. However, in contrast to conventional drugs, the target population (i.e. the drug's market) is extremely restricted. It is precisely for this reason that the European regulation adopted in December 1999 attempts to compensate this low commercial appeal for developers by providing various specific incentives. To benefit from these measures, the candidate orphan drug must already be "designated" by the Committee for Orphan Medicinal Products (COMP) of the EMEA. This "designation" is based on the criteria of prevalence of the indication and the medical plausibility of the drug's interest. The request for designation can occur at any stage of development, from early preclinical to advanced clinical stage, at the sponsor's initiative. Therefore, all orphan drugs are clearly identified prior to

their potential future marketing authorisation request. The arrival of new orphan drugs on the market is thus more predictable than that of conventional drugs.

EURORDIS analysed the transition of a drug from "candidate designated drug" to that of "orphan drug with marketing authorisation", using two questions: what percentage of designated drugs receive marketing authorisation? and after how long?

The US Experience

As development of drugs is a dynamic process with variable kinetics and the amount of European data is relatively small and therefore insufficient to develop a model, we chose to analyse US data, as the Orphan Drug Act, having been adopted in 1983, provide a longer perspective.



Over the period November 1983 to December 2008, the FDA issued 1951 designations and 319 marketing authorisations (MA) for orphan medicinal products (OMP).

(The 11 drugs given orphan drug status after marketing authorisation are not taken into account here).

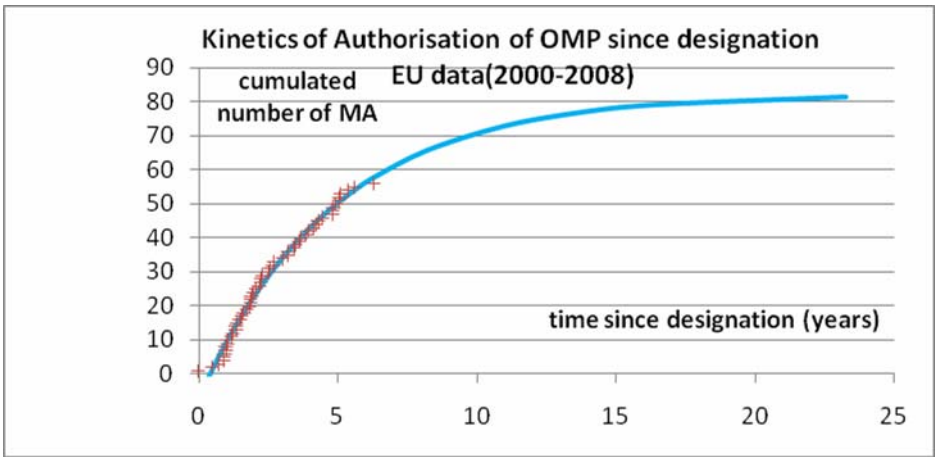
Figure 1: Kinetics of obtaining marketing authorisation of orphan drugs following designation, US data.
Each cross represents cumulative new marketing authorisations issued, as a function of time elapsed since designation. The blue line represents the model describing the cumulative number of marketing authorisations issued at any given time: $MA_{\partial} = 330\ (1\text{-}e^{-((\log 2/3.13)\times(\partial - 0.08))})$; the correlation coefficient r=0.988, "MA_{∂}" represents the cumulative number of marketing authorisations, and "∂" the time between designation and marketing authorisation, expressed in years.

This model (Figure 1) shows that the total number of orphan drugs with marketing authorisations (330) represents 17% of the 1940 drugs that have received orphan designation from the FDA. It also shows that using an average duration poorly describes the time taken to obtain marketing authorisation, which follows an exponential growth curve, with a delay π =3.13 years: after a lag-time of a month (0.08 years), 50% are obtained in 3.13 years, 75% in 6.26 years, 87.5% in 9.39 years, etc.

This suggests that the global kinetics of a designated drug from development to authorisation can be described by a simple model, both in terms of quantity as well as rate of emergence on the market, which is potentially predictable.

The EU Experience

As the data available for Europe cannot yet provide a comparable perspective, we analysed European data using the model pre-determined from the US data.



Since the implementation of the legislation in the EU in December 2008, there have been 577 designations and 57 marketing authorisations (MA) for orphan medicinal products (OMP).

Figure 2: Kinetics of obtaining marketing authorisation of orphan drugs following designation, EU data.
Each cross represents cumulative new marketing authorisations issued, as a function of time elapsed since designation. The blue line represents the model describing the cumulative number of marketing authorisations issued at any given time: $MA_{\partial} = 82\ (1\text{-}e^{-((\log 2/3.36)x(\partial - 0.42))})$; r=0.996, "$MA_{\partial}$" represents the cumulative number of marketing authorisations, and "∂" the time between designation and marketing authorisation, expressed in years.

A good fit with the model is apparent (Figure 2), with parameters similar to the US situation. For an expected total of 82 marketing authorisations of the 577 designations, and a lag-time of about 5 months, 50% are obtained in 3.36 years after designation, 75% after 7.72 years, etc. (i.e. a delay π of 3.36 years v 3.13 years for the US data). The projection of this evolution is extrapolated, taking into account the shorter perspective. This extrapolation concerns almost 30 potential future marketing authorisations, which is not surprising given the similarity of the US and EU kinetics. Note that, almost a quarter of marketing authorisations were issued more than six years after their designation, whereas less than four years of data are available for half of the drugs designated by the EMEA (from 2004 to 2008)!

The lack of EU data leads to an underrepresentation of later events (little data after five years, none after eight years) and probably to a slight underestimation of the total number of expected marketing authorisations. This situation may in part explain the lower percentage of marketing authorisations (p) obtained in Europe (82/577= 14%) compared to the USA (330/1951=17%) by an underestimation of the quantity of late authorisations.

Using this model, we can simulate the number of marketing authorisations that will occur in the coming years, on the basis of designations issued. The figure below proposes a simulation based on the designations made up to December 2008, then beyond that at a rate of 80 designations per year.

The probability of a marketing authorisation used is p=20%, allowing for a possible under-estimation, and an authorisation delay of π = 3 years.

For each designated drug, we presume an individual probability of 20% of obtaining a marketing authorisation, half of which are approved after 3 years, 75% after 6 years, etc., taking as an origin for the actual date of designation (d_i) observed up to 2008, then simulated at a regular rate of 80 designations per year. The total number of marketing authorisations (MA) corresponds to the sum of the individual probabilities:

$$MA_t = \sum_{i=1}^{n} p\left(1 - e^{-\left(\ln 2 / \pi (t - d_i)\right)}\right)$$

where "t" is the current date, "p" is the final probability of obtaining marketing authorisation, taken to be 20%, "π" the time taken to obtain half of the marketing authorisations, taken to be 3 years, and, "d_i" the designation date of a given drug.

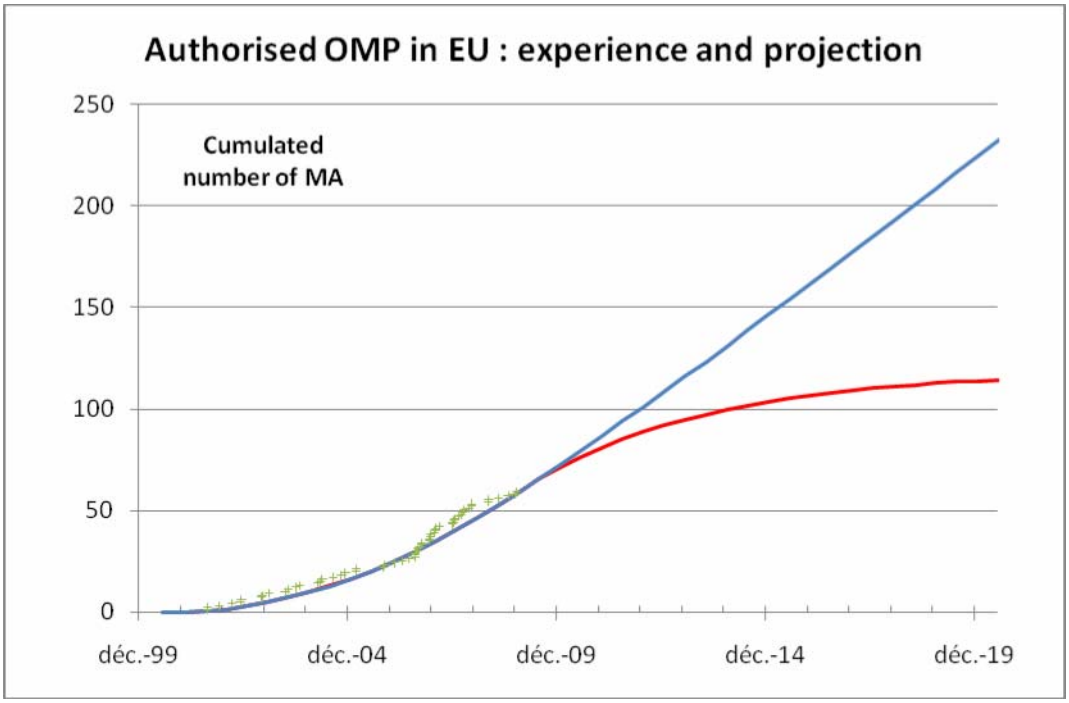


Figure 3: Experience and projections of orphan medicinal products authorised in the EU
Each cross represents actual marketing authorisations, the red line represents potential marketing authorisations for drugs designated up to December 2008, and the blue line represents the total number based on designations occurring at a rate of 80 per year, after December 2008.

According to these deliberately "optimistic" hypotheses, we can envisage the registration of the 100th marketing authorisation in 2012 and the 200th in 2017.

We also consider that this system has quite a lot of "inertia", where even if new designations stopped being registered, it is likely that there will be about a hundred authorised drugs by 2013-2014.

Table 1 shows the number of marketing authorisations for three probabilities (*p*) of obtaining marketing authorisation; average (p = 20%), pessimistic (p = 15%) and optimistic (p = 25%), for 8 years, 13 years and 18 years after implementation of orphan drug regulation. Values observed for the same periods according to US experience, relative to the US Orphan Drug Act, are also shown.

Table 1: Number of marketing authorisations for three different hypotheses

	Data	8-year period	13-year period	18-year period
Europe	**Simulation**	**59** (*44-73*) (December 2008)	**131** (*98-163*) (December 2013)	**209** (*156-261*) (December 2018)
USA	**Observation**	68 (July 1991)	132 (July 1996)	213 (July 2001)

The values in bold are simulated for a probability hypothesis of **20%** of obtaining authorisation. The values in parentheses correspond to the lower and upper hypothesis limits (p =*15%* - p = *25%)*.

It is apparent that according to the "average" hypothesis (p = 20%), the expected values with this model using European data are very similar to those observed for the same time period in the USA.

Overall, it appears that the regulatory pathway for orphan drugs with its requirement of a declaration of intent-to-file when requesting designation, results in developmental kinetics that are more transparent and more easily predicted then those of other drugs for which competitive restraints push manufacturers toward a higher level of confidentiality until marketing authorisation is obtained.

How many users?

By definition, orphan drugs concern a limited number of individuals in the general population. Calculations used for designation (and reviewed for eventual marketing authorisation) concern the prevalence of **the condition.** In the European Union the prevalence must be under the threshold of 5/10 000 EU inhabitants.

The real figure is always less than this: only one-third of the indications for the 57 orphan drugs authorised have a prevalence greater than 1/10 000 and one-third are less than 0.5/10 000. It is even reported that for 15%, the condition has a prevalence less than 0.1/10 000, i.e. 10 per one million inhabitants. For all this, not all people affected by a given condition expect to be prescribed drug treatment. Depending on the stage of the disease, the age of the patient, the presentation of the disease etc., a patient with any given disease may or may not be a potential beneficiary of a drug. As is the case for conventional drugs, there are no miracle orphan drugs that work effectively in all patients. Furthermore, for certain pathologies, several drugs are available that are not simultaneously prescribed, such as Fabrazyme® and Replagal® for Fabry disease, Thalomid® and Revlimid® for multiple myeloma, and Tracleer®, Revatio®, Thelin®, Volibris® and Ventavis® for pulmonary arterial hypertension.

Social cost and social benefit of orphan drugs

Orphan drugs, like many anticancer agents, as well as a large number of general health services, diagnostics or therapeutics, are very costly. In the case of orphan drugs, whose use is by definition very restricted, the fear is that their cost is so exorbitant that they represent a considerable expense to the community.

In 2007, we examined the relationship between the annual cost of a treatment and the prevalence of the relevant disease for 19 drugs for which data were available.

The calculation used was: Individual cost = K /prevalence $^{0.53}$ ($p<0.02$) where K is the geometric mean cost.

This demonstrated that although there is naturally a lot of variability according to the nature and conditions of the drug's production, cost does clearly increase with the rarity of the disease, however not proportionally. The regulation was indeed adopted so that orphan drugs are produced in spite of their limited market. Relative to an average value, the cost of one year of treatment increases with the square root of the rarity of the disease: i.e., it will be ten times more expensive if the disease is 100 times rarer, 100 times more expensive if the disease is 10 000 rarer etc. Therefore logically, the rarer a disease, the lower the cost of its treatment to society.

Furthermore, it is important to note that the absence of an efficient specific treatment (i.e. non-existent or unavailable orphan drugs) does not represent zero cost. Indeed, the overall cost of treating all complications represents considerable cumulative costs. In addition, frequent hospitalisations and the cost to society of the activity limitations and participation in society restrictions due to these serious, chronic and disabling diseases must also be taken into account. In the same way as with the number of orphan marketing authorisations, a factual evidence-based approach would be desirable, i.e. to perform economic studies of public healthcare balancing the costs and social benefits of orphan drugs rather than considering only their cost to society.

Conclusion

It seems that economic criticism formulated against orphan drugs lack any real basis. The circumstances of development of these drugs, destined for the treatment of rare diseases, are not mysterious or unpredictable, and the costs involved are not going to blow out of proportion.
As a result of the designation process, orphan drugs have a more transparent, and hence more predictable, development process than standard drugs.
An approach based on fact, enables us to reproduce what is at stake in terms of health and economics for orphan drugs. At an individual level, treatment of a rare disease is more costly than treating the majority of common illnesses. However, the rarity of the disease and the, unfortunately, limited number of orphan drugs available, compensate the burden of cost at the level of society, relative to the public health challenge that these 6000 to 8000 rare diseases represent. In addition, all individual and social added values of orphan drugs have to be considered in an evidence-based evaluation of the social cost of orphan drugs.
Subjectively, orphan drugs are perceived to be very expensive, when in fact, objectively, the rarer the disease, the lower the cost of the treatment.