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SURVEY Drugs for rare diseases: mixed assessment in Europe

● **Worldwide, there are an estimated 6000 to 7000 rare diseases. Patients face special difficulties in obtaining an accurate diagnosis, adequate information about the disease, and access to qualified specialists.**

● **Drug companies do not spontaneously conduct research on drugs for rare diseases, mainly because of the limited market for each indication. Only a few dozen of these drugs were available in France before 2000.**

● **In 2000 the European Union adopted a Regulation, based on experience in the United States, aimed at promoting the development of drugs for patients suffering from rare diseases, i.e. 'orphan drugs'.**

● **In Europe, orphan drug status can be granted when the prevalence of the disease does not exceed 5 cases per 10 000 inhabitants (or when it is more frequent but profitability is likely to be inadequate).**

● **Companies that market an orphan drug receive a variety of financial assistance as well as a 10-year marketing monopoly.**

● **Between April 2000 and April 2005, 268 medicinal products received European orphan drug status and 22 were granted European marketing authorisation.**

● **Access to these drugs varies greatly from one European Union Member State to another, mainly because of the high annual treatment costs (up to 300 000 euros per patient). Worldwide sales of the orphan drug imatinib reached**

more than two thousand million dollars in 2005.

- **Our systematic analyses (see the New Products column of our French edition *la revue Prescrire*) show that only 5 drugs which received European orphan drug status before May 2005 were for diseases for which there had previously been no treatment.**

- **Clinical evaluation of orphan drugs is hindered by the small number of patients available for clinical trials. Some orphan drugs are adequately tested before being brought to market. Others are not compared to existing treatments. In many cases, surrogate criteria are used instead of clinical endpoints. These methodological flaws are in no way limited to orphan drugs.**

- **Not all orphan drugs represent therapeutic advances. Clinical research and evaluation should continue after marketing authorisation has been granted.**

- **More drugs, with better-documented efficacy and safety, are now available for patients who previously had no effective treatment options. Yet there is too much duplication and too little evaluation, and too many drugs are extremely expensive, meaning that patients in many European countries cannot benefit. And many rare diseases are still neglected.**

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More than 20 years of orphan drug legislation in the United States

Since 4 January 1983 (the date the Orphan Drug Act was passed by the US Congress) the American authorities have had at their disposal a system of incentives for the development and marketing of drugs for patients with rare diseases (1). Various amendments have extended its application to medical devices, biological products and dietary products (2).

A disease is considered "rare" in the United States if it affects fewer than 200 000 people, i.e. if it has a prevalence of less than 8 cases per 10 000 inhabitants (**a**), or, alternatively, if it affects more that 200 000 people but the development and distribution costs are not likely to be recouped through national sales (1).

Official orphan product status is granted by the FDA Office of Orphan Products Development (OOPD) (1,2). Application for approval follows at a later date (**b**). According to the FDA website, as of 31 July 2006, about 1600 pharmaceutical and biological products have been granted orphan status. In total, 286 drugs designed for the treatment of patients with rare diseases have received marketing approval (fewer than 10 in the 1970s, 108 between 1984 and 1994, and more than 160 between 1995 and 2005) (3).

The American system gives manufacturers of orphan drugs a 7-year market exclusivity (starting on the date of approval), and a tax break that can cover up to 50% of the costs of clinical trials conducted in the United States for the relevant indication (**c**)(2). Since 1992, a new drug similar to a drug already marketed for an orphan indication can also be granted orphan drug status if it is shown to be clinically superior (2).

a- In Japan a disease is considered "rare" if its prevalence is no more than 4 per 10 000. In Australia the prevalence is 1.1 per 10 000 Australian inhabitants (ref 4).

b- A drug can be made available before marketing authorisation is granted, through a compassionate use programme (Investigational New Drug Treatment (t-IND)) (ref 2).

c- The National Institutes of Health (NIH) have a 5-yearly budget of 71 million dollars for clinical trials in rare diseases (ref 5).

1- U.S. Food and Drug Administration "The Orphan Drug Act (as amended)" Website http://www.fda.gov accessed 6 July 2006: 6 pages.
2- Orphanet "Les médicaments orphelins aux États-Unis d'Amérique" Website http://www.orpha.net accessed 6 July 2006: 3 pages.
3- "Orphan disease research may require new incentives" *Scrip* 2006; (3152): 19.
4- Orphanet "Comparaison des différentes politiques du médicament orphelin à travers le monde" Website http://www.orpha.net accessed 6 July 2006: 1 page.
5- U.S. Department of Health and Human Services - National Institutes of Health "NIH launches clinical studies nationwide to investigate rare diseases" Website http://www.nih.gov accessed 10 July 2006: 3 pages.

Six years after European Union Regulation EC 141/2000 went into effect, on 22 January 2000, the European Medicines Agency (EMEA) and the European Commission examined its impact in the development and marketing of drugs for patients with rare diseases ('orphan drugs'), between April 2000 and April 2005 (1-3). We take this opportunity to examine this policy (4,5), particularly with respect to the number of orphan drugs now marketed in Europe, how they were assessed, their risk-benefit balances, their availability in European Union Member States, and their cost.

Rare diseases: difficulties for the patients concerned

Regulation EC 141/2000 defines rare diseases as those with a prevalence of no more than 5 per 10 000. Assuming that the 25 EU Member States include a total of about 450 million inhabitants, this corresponds to fewer than 225 000 patients (about 30 000 in France) (1,6).

An estimated 6000 to 7000 rare diseases have so far been identified worldwide, and most are genetic in origin (6). There are under 500 published cases for about 200 of these diseases in Europe (7). In France about 50 rare diseases affect several thousand people each (cystic fibrosis and Duchenne's myopathy, for example), while another 500 affect a few hundred people each (leukodystrophy for example). Other diseases affect only a dozen or so people in the entire world; one example is progeria, a form of premature aging (8).

An obstacle course for patients. People with rare diseases, and their families, have difficulties obtaining the correct diagnosis, adequate information concerning their disease, and referral to a specialist (6,9). Their medical and social management is sometimes inappropriate, with individual families often having to shoulder a large part of the financial burden.

A questionnaire-based survey of rare diseases conducted in 2002, involving 6000 patients/families residing in 17 EU Member States, showed that 25% of patients waited between 5 and 30 years after the onset of symptoms before obtaining a correct diagnosis. 40% of patients initially received an incorrect diagnosis, resulting in unnecessary surgery in 16% of cases, inappropriate drug therapy in 33%, and inappropriate psychological management in 10% (**a**)(10). In ►►

a- The eight diseases were Crohn's disease, cystic fibrosis, Duchenne's myopathy, Ehlers Danlos syndrome, fragile X syndrome, Marfan's syndrome, the Prader-Willi syndrome, and tuberous sclerosis (ref 10). This survey was conducted by the European Organization for Rare Diseases (Eurordis), an umbrella group of associations of patients with rare diseases. Eurordis was created in 1997 by the Association Française contre la Myopathie (AFM), the Ligue française contre le cancer (Fnclcc) and the Fédération française contre le HIV (Aides), along a similar model to the North American National Organization for Rare Disorders (NORD) (ref 65).

Orphan: an ambiguous term

Orphan drug. The term 'orphan drug' was first used in the United States, before being adopted in European Regulations. This term is ambiguous, however.

All orphan drugs have at least one indication in a rare disease (imatinib, for example, has several indications in rare diseases), and some have indications in both rare and frequent diseases (for example, sildenafil is indicated in both pulmonary hypertension and erectile disorders).

We propose replacing the term 'orphan drug' with 'drug for a rare disease', which is more accurate.

Rare disease. The term 'rare disease' refers to a disease that only affects a small minority of the general population. The term 'rare disease' implies that the disease in question can be diagnosed, and that its incidence and prevalence in a given population can be estimated with a reasonable degree of accuracy.

The threshold incidence or prevalence below which a disease can be considered rare is arbitrary. It is different in the United States and the European Union, for example.

A rare disease is not necessarily a neglected disease. For example, several drugs are marketed for pulmonary hypertension, which is considered a rare disease.

Neglected diseases. Neglected diseases are diseases for which there are few or no treatment options, and for which no meaningful research is underway.

A neglected disease is not necessarily a rare disease. Many parasitic infections affect large numbers of people in poor countries but are neglected because of the lack of research into treatments. This is the case for sleeping sickness, Kala-azar, Chagas disease, etc.

order to obtain the correct diagnosis, 25% of patients had to go to another region and 2% to another country. Many patients/families said the diagnosis was provided in a tactless or uninformative manner (10).

These difficulties lead to waste in terms of unnecessary delays and inappropriate use of healthcare resources. There is a movement to create European multidisciplinary reference centres for rare diseases (or groups of rare diseases), based on existing infrastructure in Belgium, Denmark, France, Italy, the United Kingdom and Sweden (11).

Uneven access to drugs. With the exception of drugs that have been granted orphan status (as defined by Regulation EC 141/2000) and off-licence uses of drugs developed for other diseases, the obstacles faced by patients seeking drug therapy for rare diseases vary among EU Member States. Options that were available before the enactment of the EU Regulation included compassionate-use programmes, temporary approval (on a cohort or named-patient basis), drug compounding by a hospital pharmacy, participation in clinical trials, and European or national marketing authorisation (12,13).

Situation prior to the EU Regulation. In France a dozen drugs for rare diseases had been approved before Regulation EC 141/2000 came into force. They included alglucerase (subsequently replaced by imiglucerase) and a C1 esterase inhibitor. About 60 products were available through temporary licences in 2005, or through clinical trial participation, or in the form of hospital pharmacy compounding (for example, D-mannose for a form of abnormal protein glycosylation) (13,14).

Six 'orphan-like' drugs received European marketing authorisation between 1996 and 2000, before Regulation EC 141/2000 was enacted: cysteamine, imiglucerase, tasonermine, sodium phenylbutyrate, clotting factor IX, and samarium lexidronam (15). These drugs are considered "orphan-like" because the companies concerned benefited from the advantages provided by Regulation EC 141/2000.

A European incentive policy

Companies are reluctant to develop and market drugs for patients with rare diseases, mainly because these products cannot be patented (well-known chemicals or natural extracts), and/or because the limited number of patients would not make production profitable (16).

Under pressure from patient groups, the United States was the first country to create incentives for manufacturers to develop and market drugs for rare diseases, in 1983 (see inset page 37), followed by Japan in 1993, and by Australia and Singapore in 1998 (4).

Nearly 20 years after the United States' initiative, and largely based on experience in that country, Regulation EC 141/2000 provided a series of incentives for drug companies to develop and market orphan drugs in the European Union (1). The Committee for Orphan Medicinal Products (COMP), composed of specialists and representatives of patient or family groups, is now responsible for examining applications submitted by companies seeking to qualify for the economic advantages of orphan drug status.

Orphan drug status. According to the Regulation, orphan drugs are products designed for the diagnosis, prevention or treatment of a rare disease, and defined by 2 criteria: either epidemiological criteria (a disease affecting "*not more than 5 in 10 thousand persons in the European Community when the application is made*"; or economic criteria (a disease that "*without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment*" (1).

To obtain orphan drug status, a company has to submit an application to EMEA for orphan drug designation of a given substance in a given indication, which is placed on a Community register of orphan drugs (**b**) (1). Designation as an orphan drug does not mean that the product will automatically receive marketing approval.

The manufacturer must provide: information on the prevalence of the disease and its severity; the lack of satisfactory means to diagnose, prevent or treat the condition; a better risk-benefit balance than existing treatments; and the likely return on investment (including the costs of development, production and marketing, and sales figures expected during the first ten years) (1,17).

At this stage, there may be no available clinical data, only the results of animal experiments or in vitro studies showing the "medical plausibility" of using the substance in question in its intended indication (2,18).

European marketing authorisation. After receiving orphan drug status for a product, the company submits a marketing application to EMEA. The centralised procedure has been required since 20 November 2005 (2).

The application must include pharmaceutical and chemical sections guaranteeing the same level of pharmaceutical quality as for other drugs, and also toxicological, pharmacological and clinical sections. These last three parts are often less substantial for orphan drugs than for other drugs: large trials are often impossible to conduct, given the obvious problem of patient recruitment.

Economic advantages. Orphan drug status provides a number of advantages for the companies that market these products.

These include: free technical assistance from EMEA in preparing the application; a 50% reduction in EMEA fees (paid for out of a Community fund) (**c**); and a 10-year pan-European market exclusivity starting on the date that marketing authorisation is granted (1,3).

Individual Member States can also take additional measures (especially tax incentives) to support manufacturers based in their countries (**d**)(1,3,4).

These incentives come with several conditions, however. In particular, the market exclusivity can be reduced to 6 years if, after 5 years, it emerges that the orphan-drug criteria are no longer met: for example, if the epidemiological situation changes and the disease is no longer rare or if profits prove to be adequate (1).

In addition, a "similar" drug can be approved for the same indication as an orphan drug, despite the initial product's market exclusivity, if one of the following conditions is met: the holder of the marketing authorisation for the initial orphan drug does not produce it in adequate amounts, or the second drug has a better risk-benefit balance than the first (1,17,19).

22 European marketing authorisations in 5 years

Between April 2000 and April 2005, 268 medicinal products (out of 458 applications) were designated as orphan drugs for the treatment of about 200 diseases: cancer (36% of cases), metabolic disorders (11%), immunological disorders (11%), cardiorespiratory conditions (10%), musculoskeletal and nervous system disorders (8%), infections (4%), and miscellaneous conditions (20%) (2,3).

Eleven percent of these orphan drugs were developed only for children, 46% only for adults, and 43% for both populations (2,3).

When the applications for orphan drug status were submitted to EMEA, the prevalence of the diseases was less than 1 in 10 000 in 43% of cases, between 1 and 3 per 10 000 in 47% of cases, and between 3 and 5 per 10 000 in 10% of cases (2,3).

By April 2005, 19% of the manufacturers that had obtained orphan drug status had submitted marketing applications: 44 through the centralised procedure and 5 through a national procedure (3). Twenty products received European marketing authorisation through the centralised procedure, and two by mutual recognition of national approval (levodopa-carbidopa duodenal gel, and oral miltefosine) (**e**).

Major differences in access from one country to another. Access to orphan drugs varies greatly between EU Member States, and has been the subject of two studies. The first, conducted between October 2002 and January 2003, focused on five orphan drugs available in 15 EU Member States, while the second (study period not specified) concerned 10 orphan drugs in 25 EU Member States (12,20). According to this second, more extensive study, about half the 25 orphan drugs were effectively marketed in 15 of the 25 EU Member States (12). Patients living in countries where these drugs are reimbursed (Germany, Spain, France, The Netherlands, and Sweden) have better access (12). The annual average cost of treating a patient with an orphan drug is high, ranging from 2000 euros to 300 000 euros (12). Some orphan drugs, such as imatinib (see inset opposite), have even become blockbusters with global sales reaching several thousand million dollars. The cost of using a given orphan drug differs by up to 70% between the 25 EU Member States (12). Differences in taxes, distribution circuits and dispensing practices are factors that influence the price.

Unequal assessment of orphan drugs

The *Prescrire* editorial team had examined the evidence on 22 drugs granted European orphan drug status up to May 2005. The resulting review articles have either been published in the Journal or are in press (21-61). The analysis also includes imiglucerase, which had already been approved before the period covered by the European Medicines Agency report (April 2000-May 2005), but which, during this same period, was granted a licence extension to cover type 3 Gaucher's disease (30). These 23 drugs are approved for 21 different indications (see table page 40).

A rare disease is not always an orphan disease. Although most rare diseases are genetic in origin, only 8 of these 21 indications involve hereditary diseases, and only 4 of the 8 corresponding drugs represent replacement therapy (Fabry's disease, type I mucopolysaccharidosis, and type 1 and type 3 Gaucher's disease). ▶▶

b- This registry is available on the website of the European Commission's Enterprise Directorate at http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

c- The total tax breaks covered by the Community fund grew from 28 000 euros in 2000 to 3 988 700 euros in 2004 (ref 2). In 2005 the Community fund amounted to 3 700 000 euros, but estimated needs reached 6 000 000 euros because of the increase in requests to COMP for technical assistance and post-marketing follow-up (ref 2).

d- In France, for example, drug companies are exempted from taxes and health insurance contributions; an agreement between manufacturers and the State was settled by the health products economic committee; some orphan drugs are registered on the list of costly and innovative medicinal products (refs 8,66). See reference 67 for information on measures taken by other European Union Member States.

e- In late 2005, 342 products had been designated as orphan drugs and 24 had received marketing authorisation (ref 67).

Imatinib: an example not to be repeated

Although economic data are incomplete, orphan drugs seem to account for between 0.7% and 1% of all drug costs in rich countries, but this could reach 6% to 9% by 2010 (1). What used to be considered a "niche" has become a full-fledged market.

Take imatinib for example. Worldwide sales reached about 2.17 thousand million dollars in 2005 (1.63 in 2004; 1.13 in 2003; 0.62 in 2002; 0.17 in 2001), representing about 10% of total income for the manufacturer, Novartis (2). In France, imitanib cost the health insurance system more than 100 million euros in 2005 (for about 3000 patients), ranking tenth in treatment expenditure (3).

European marketing authorisation and orphan drug status were first granted for imatinib in 2001 for the treatment of a form of myeloid leukaemia. There were few patients with this condition, which partly justified the high price.

The indications were then extended to include other forms of myeloid leukaemia and then gastrointestinal stromal tumours. Five new indications are currently being examined by the European Medicines Agency (Darier-Ferrand dermatofibrosarcoma, acute lymphoblastic leukaemia, myelodysplasia and related disorders, mastocytosis, chronic eosinophilic leukaemia, and the hypereosinophilia syndrome) (4).

Thus, 5 years after imatinib was first marketed, the notion of "rarity" needs to be revisited. It is unacceptable that the price remains at the current high level.

1- European Social Health Insurance Forum "Consultation on a general report on the experience acquired as a result of the application of Regulation (EC) n°141/2000 on orphan medicinal products and account of the public health benefits obtained. Comments of the Medicine Evaluation Committee (MEDEV)" March 2006: 4 pages.
2- Novartis "Full year results" Website http://www.novartis.com accessed 10 July 2006: 6 pages.
3- French Assurance maladie "Médicaments remboursables: analyse des principales évolutions de l'année 2005" Website http://www.ameli.fr accessed 10 July 2006: 9 pages.
4- European Commission "Register of designated orphan medicinal products". Website http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm accessed 14 September 2006: 2 pages.

Drugs granted EU marketing authorisation and orphan drug status between April 2000 and April 2005

INN	Indications	Epidemiology (a)	Comparative trials			Non comparative trials		Prescrire score	ASMR (b)	Ref.
			Number	Patients	Endpoints	Patients (total)	Endpoints			
agalsidase alfa	Fabry's disease (G)	P = 0.085 to 0.175	2	26, 15	clinical	—	—	Judgement reserved	II	(7,21,22,46)
agalsidase beta	Fabry's disease (G)	P = 0.085 to 0.175	1	58	surrogate	—	—	Judgement reserved	II	(7,21,22,46)
anagrelide	Essential thrombocytemia	P = 2.75	1	809	clinical	254,242,34	surrogate	Judgement reserved	IV	(40)
arsenic trioxide	Acute promyelocytic leukaemia	P = 0.8	0	—	—	52	clinical	Possibly helpful	Not scored	(7,23)
bosentan	Pulmonary hypertension	P = 0.15	3	32, 213, 33	clinical	—	—	Offers an advantage	I	(7,24)
busulfan	Stem cell grafting	NA	3	42, 62, 24	clinical	—	—	(**c**)	—	(42)
carglumic acid	N-acetyl-glutamate - synthetase deficiency (G)	P = 37 cases managed worldwide	0	—	—	16	clinical	A real advance	I	(31)
celecoxib	Familial adenomatous polyposis (G)	P = 1	1	77	surrogate	—	—	Not acceptable	Not available on 14 Sept. 06	(7,34,55)
cladribine SC	Hairy cell leukaemia	I = 100 cases in France	0	—	—	63	surrogate	Possibly helpful	IV	(36,57)
ibuprofen 10 mg injectable	Patent ductus arteriosus	P = 2	1 (**b**)	33 (**d**)	surrogate	—	—	Offers an advantage	I	(7,38,58)
iloprost for inhalation	Pulmonary hypertension	P = 0.15	1	203	clinical	—	—	Nothing new	II	(7,33)
imatinib	Chronic myeloid leukaemia (last resort)	P = 0.6	0	—	—	1 027	surrogate	Possibly helpful	I	(7,25)
imatinib	Chronic myeloid leukaemia (first-line)	P = 0.6	1	1 106	clinical	—	—	Interesting	I	(7,26)
imatinib	Stromal GI tract tumours	I = 0.1-0.2	3	147, 746, 753	clinical	—	—	Offers an advantage	I	(27,48)
imiglucerase	Gaucher's disease type 3 (G)	5 cases managed in France	0	—	—	60	clinical	Possibly helpful	I	(30,52)
laronidase	Mucopolysaccharidosis type 1 (G)	P = 0.1	1	45	clinical	10	surrogate	Offers an advantage	II	(7,32)
levodopa + ***carbidopa*** duodenal gel	Advanced Parkinson's disease	NA	1	24	clinical	—	—	Possibly helpful	IV	(45)
miglustat	Gaucher's disease type 1 (G)	P = 0.5 (53 cases managed in France)	2	18, 36	surrogate	28	surrogate	Possibly helpful	Not scored	(29,52)
oral miltefosine	Visceral leishmaniasis	—	—	—	—	—	—	(**c**)	—	(44)
mitotane	Adrenal cancer	I = 0.005	0	—	—	312	clinical	Possibly helpful	II	(37)
nitisinone	Hereditary tyrosinaemia type 1	P = 0.005	0	—	—	207	clinical	Bravo	Not available on 14 Sept 06	(7,43)
pegvisomant	Acromegaly	P = 0.5	1	112	clinical	7	surrogate	Possibly helpful	III	(7,28)
porfimer	Barrett's high-grade oesophageal dysplasia	P = 2.2 to 4.6	1	208	clinical	—	—	Judgement reserved	II	(35,56)
ziconotide	Refractory pain	NA	3	220, 112, 257	clinical	—	—	(**c**)	Not available on 14 Sept. 06	(41)
zinc acetate	Wilson's disease (G)	P = 0.58	1	67	clinical	170	clinical	Offers an advantage	IV	(7,39)

a- The incidence rates (I) and prevalence rates (P) are given per 10 000 inhabitants, unless otherwise stated.
b- ASMR: Assessment by the French Transparency Committee (see ref. 63).
c- On 5 October 2006, we had not published our analysis of the clinical data.
d- Other trials are available, but with ibuprofen formulations different from the marketed product.

G: Hereditary disease
NA: Not available – we found no reliable estimate of the prevalence or incidence.

► Only 5 indications were not previously treated by a drug with at least partial efficacy (Fabry's disease, gastrointestinal stromal tumours, type 3 Gaucher's disease, type I mucopolysaccharidosis, and type 1 tyrosinemia) (21,27,30,32,43).

More than one drug was approved for 2 separate indications: Fabry's disease (21,22), and pulmonary hypertension (**f**)(24,33).

Some drugs were properly assessed. Clinical evaluation of drugs for rare diseases mainly faces two specific obstacles.

The limited number of patients can make it difficult to conduct dose-finding studies and comparative trials. On the other hand, most patients with a given rare disease are managed by a small number of specialised teams, and it is often relatively easy to identify them. Secondly, these are chronic diseases, and it is not always easy to find clinical endpoints or satisfactory surrogate endpoints for relatively short-term clinical trials. Dose-finding studies are available for only 7 of the 21 indications (21,27-29), but the evaluation of many drugs marketed for common conditions suffers from the same shortcomings.

Most orphan drugs were tested in randomised controlled trials before licensing. In other cases, comparative trials could not be conducted because of the rarity of the disease such as type 3 Gaucher's disease and N-acetyl glutamate synthetase deficiency (30,31). The *Prescrire* editorial team considered that a simple historical comparison was acceptable in one setting, in which nitisinone was compared with dietary measures and proved to be largely beneficial in terms of survival (43). In 3 cases the absence of comparative trials was more questionable: second-line imatinib for chronic myeloid leukaemia (1027 patients enrolled in non comparative trials), mitotane for adrenal cancer (312 patients enrolled in non comparative trials), and busulfan conditioning prior to stem cell grafting (25,37,42).

Some drugs were tested in trials with only surrogate endpoints even though the use of clinical endpoints was feasible: in Fabry's disease agalsidase alfa was assessed on the basis of clinical endpoints, and agalsidase beta only on surrogate endpoints; and the assessment of second-line imatinib for myeloid leukaemia was not based on clinical criteria such as mortality (21,22,25).

Controversial comparisons. Some diseases are simply too rare to conduct comparative studies; for example, cladribine and interferon alfa cannot be compared in hairy-cell leukaemia, a disease only affecting 100 patients in France (23,36). The lack of randomisation was also justified in the comparative study of zinc acetate and penicillamine in Wilson's disease, as the two drugs are used in different contexts (39).

In other cases the lack of comparative studies is more difficult to justify: imatinib was not compared with interferon alfa in chronic myeloid leukaemia, even though more than 1000 patients participated in trials of second-line treatments for this disease; pegvisomant was compared with placebo in acromegaly, when a trial versus lanreotide or octreotide would have been more appropriate; ibuprofen for injection was compared with placebo in patent ductus arteriosus, despite the existence of a standard treatment, indometacin (26,28,38).

Three authors with no conflicts of interest, two of whom had served with the EMEA, conducted a review of 18 orphan drugs (62). Their conclusions were similar to ours; they also criticised the lack of proper trials (dose-finding studies alone in 6 indications), the lack of comparative trials versus existing standard treatments, and the excessive use of surrogate endpoints. In addition, they examined animal studies and found that genotoxicity studies were lacking for 5 drugs, carcinogenicity studies for 6 drugs, and reproductive toxicology studies for 2 drugs. Overall, they found the evaluations to be of rather poor quality.

Need for transparency. All drug assessment data should be made public, and this is especially important for rare diseases for which there are fewer data.

Take agalsidase alfa and agalsidase beta for example. In the absence of anything better, our initial review of the evidence was essentially based on the EMEA assessment report (21). Some of the data contained in this report were incorrect, however, leading us to initially conclude that agalsidase alfa 'offered an advantage' and that agalsidase beta represented 'nothing new' (21). The FDA released their assessment reports on these two drugs after our article had been published. Although they were based on the same two trials as those examined by the European agency, the FDA analysis was more precise and provided new information that led us to revise our initial ratings for the two drugs. They became 'judgement reserved' for both products (22).

Inadequate post-marketing surveillance. The initial evaluation of drugs for rare diseases often leaves many unanswered questions, which is to be expected considering the small number of patients enrolled in clinical trials and the relatively short-term follow-up. This makes post-marketing surveillance studies all the more crucial.

Patients are usually identified by drug companies and/or managed by a few specialised teams, making it relatively simple to compile patient registries. But this is not enough. These registries must contain pertinent information, be appropriately analysed at regular intervals, and be made available to patients and caregivers. There is currently no such system in the European Union.

Questionable therapeutic advance. As our regular readers know, we use an at-a-glance scoring system (see page 14) to estimate the therapeutic advance represented by new drugs, including orphan drugs. The French Transparency Committee rates drugs on the basis of what it calls the 'improvement in medical service rendered'. The two scores often diverge (63).

These divergences are particularly noteworthy when it comes to orphan drugs (see table page 40), mainly because the Transparency Committee gives a score of I or II (i.e. major or significant advance) despite the lack of comparative trials, even when such trials were feasible: this was the case for second-line imatinib in chronic myeloid leukaemia, iloprost in pulmonary hypertension, mitotane in adrenal cancer, and ibuprofen in patent ductus arteriosus (**g**)(25,26,33,37,38).

Room for improvement

During a 5-year period, European marketing authorisation was granted for 22 'orphan drugs' for patients with rare diseases.

Although insufficient, this is an encouraging start. Indeed, a large number of drugs were already available for rare diseases before the Regulation came into effect, usually approved through national procedures. Moreover, European orphan drug status is not a panacea, especially in terms of access and reimbursement, which vary widely from one EU Member State to another. Rapid and accurate diagnosis of rare diseases is also crucial for appropriate patient management, and this has led some Member States (including France) to create specific reference centres.

Five years after the first marketing authorisation was granted for an 'orphan drug', the initial evaluation data vary in quality, but no more so than for other drugs. Questions remain concerning the quality of post-marketing surveillance, especially the necessary periodic reassessments of risk-benefit balances and the transparency of the results.

Regulation EC 141/2000 is intended to encourage the development and marketing of drugs designed for patients with rare diseases, in exchange for tax incentives for the manufacturers concerned. Some drug companies have been granted very high prices for their products, to the point that some ►►

f- Sildenafil is also indicated for pulmonary hypertension (ref 68). It is not included in this analysis, because it was approved after the end of the study period (April 2000 to April 2005).

g- In the case of ibuprofen, our conclusion that it 'offers an advantage' was mainly based on the fact that this is the only drug approved for this use, which guarantees its pharmaceutical quality and facilitates access to treatment. In the absence of direct comparisons, it is not certain that its risk-benefit balance is better than that of indometacin.

► orphan drugs have become blockbusters in only 5 years. Regulation EC 141/2000 includes a provision that market exclusivity can be reduced from 10 years to 6 years. But will this provision be applied, and how will adequate profitability after 5 years be determined? Should only the 'orphan' indication be taken into account, or all possible indications of a given drug, for example imatinib, sildenafil (also used in erectile disorders) or celecoxib? Also, in which geographic region should profitability be evaluated: in a Member State, in the entire European Community, or worldwide? How should sales volume be measured? And, will these economic data be made public?

Public research investment in the EU has lagged far behind that of the United States (64). The main research incentive for drug companies is profit. In many cases, treatments with more or less efficacy already existed before orphan drug status was granted for a new product. As a result, even research on orphan drugs fails to be adequately targeted to unmet patient health needs. Regulations governing drugs for rare diseases should be refocused on diseases that are both rare and neglected. There is still no treatment for several thousand rare diseases.

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