DOI:10.1111/j.1365-2125.2006.02579.x

Orphan drug development is progressing too slowly

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Keywords
development, orphan drugs, rare diseases

Received
27 May 2005
Accepted
3 October 2005
Published *OnlineEarly*
20 January 2006

Aims
To assess the methodological quality of OMP dossiers and to discuss possible reasons for the small number of products licensed.

Methods
Information about orphan drug designation and approval was obtained from the website of the European Commission-Enterprise and Industry DG and from the European Public Assessment Reports.

Results
Out of 255 OMP designations, only 18 were approved (7.1%). Their dossiers often showed methodological limitations such as inappropriate clinical design, lack of active comparator where available and use of surrogate end-points.

Conclusions
The paucity of European incentives for manufacturers and the poor documentation underpinning the applications may have limited the number of new OMP. The over 5000 rare diseases awaiting therapy are an important public health issue.

Introduction

The law [1] on orphan medicinal products (OMP) for rare diseases stipulates that the European Medicines Agency (EMEA), through its Committee for Orphan Medicinal Products (COMP), is responsible for reviewing designation applications from 'sponsors' (persons or companies) intending to develop medicines for rare diseases, so-called 'orphans'. The designation is allowed on the basis of epidemiological data (prevalence of the rare disease ≤5/10 000), medical plausibility, and potential benefit.

In the European Union (EU) the recognition of orphan drug status implies no direct licensing but incentives for sponsors/pharmaceutical companies to develop OMP, including 10 years of market exclusivity in the EU once a marketing authorization has been granted, scientific advice to optimize development, guidance on preparing the dossier according to European regulatory requirements, direct access to the EMEA centralized procedure for marketing authorization, fee reductions for all centralized activities including applications for marketing authorization, inspections, variations, and protocol assistance, and eligibility for grants from EU and Member State programmes and initiatives supporting research and development. Other benefits such as grants-in-aid and detaxation of the expenses for orphan drug development, acknowledged elsewhere [2], have never been applied in Europe.

This paper aims to evaluate the methodological quality of orphan drug dossiers by a retrospective analysis of the OMP approved by the EMEA since the new legislation came into force in August 2000 up to Decem-

ber 2004 and to discuss the possible reasons for the small number of products licensed.

Methods

Information about orphan drug designation and approval was obtained from the web site of the European Commission-Enterprise and Industry DG (http://pharmacos.eudra.org/F2/register/index.htm). We critically evaluated the European Public Assessment Reports (EPAR) of the approved OMP, from the EMEA web site (http://www.emea.eu.int/index/indexh1.htm). This report only includes products already marketed in the EU or licensed by the European Commission, and does not take into consideration products that had received a favourable opinion from the EMEA in 2004 but had not yet gained formal marketing authorization from the European Commission.

Results

Out of 255 OMP designations for the period August 2000 to December 2004 only 18 drugs were approved (7.1%); 14 OMP designations (5.5%) were withdrawn or suspended, and the orphan designation was not granted to three active principles (histamine, midazolam, mycobacterial cell wall complex). In the same period, out of the total 193 marketing authorization applications submitted to the EMEA, 153 (79.3%) drugs were licensed. The proportion of withdrawals was higher for OMP (14 out of 32 applications, 43.7%) than for the overall procedures (43 out of 236, including two negative opinions, 18.2%).

Out of 50 OMP designated during the first year (August 2000 to July 2001) 14 had been approved (28.0%) as of December 2004, with an average interval between designation and approval of 24.0 (± 12.1 SD) months (6 months for imatimib, 47 months for anagrelide) (http://pharmacos.eudra.org/F2/register/index.htm). From August 2000 up to December 2004 in the USA, 387 OMP got the designation and 21 (5.4%) drugs were approved (http://www.fda.gov/orphan/designat/list.htm). A comparison with the American situation is limited to the proportion of approved/designated OMP as the applications to the EMEA and FDA are kept secret and the number of orphan applications as a proportion of the total of submissions is not known.

It is noteworthy that between 1995 and August 2000, before the orphan drug law came into force, 12 orphan drugs were approved (alemtuzumab, alitretinoin, deferiprone, factor VIIA, two factors IX, imiglucerase, mercaptmine, phenylbutyrate, protein C, riluzole, temozolomide).

According to the Anatomic Therapeutic Chemical (ATC) system only a few areas were covered by OMP: six products were intended for metabolic diseases (A16), seven for cancer (L01), two for pulmonary hypertension (C02), one for cardiac (C01) and one for endocrine (L02) therapy, one antithrombotic agent (B01) and one somatropin antagonist (H01). Six approved OMP (agalsidase alpha and beta, carglumic acid, ibuprofen, laronidase and miglustat) were intended for diseases typically appearing in childhood/adolescence.

Although preclinical data basically met regulatory requirements (Table 1), we found several methodological limitations. Repeated-dose toxicity studies were not always done in the two recommended animal species [3] or with long enough exposure. Lack of genotoxicity, carcinogenicity and reproduction toxicity studies was only acceptable for agalsidase alpha, agalsidase beta and laronidase, in view of the nature of the drugs (recombinant human enzymes), and an incomplete toxicological dossier was justifiable for drugs already on the market for other more common indications (e.g. busulfan and mitotane).

Table 2 reports the main characteristics of the clinical studies included in the dossier. Out of 18 OMP approved, 10 (55.5%) were authorized 'under exceptional circumstances', which means that the dossier was not complete and the CHMP required additional studies in order to maintain the marketing authorization. Randomized controlled trials were done for nine products (50%). In all the trials but one placebo was the comparator. It was used in place of suitable active comparators in the case of arsenic trioxide (retinoic acid being an adequate control), cladribine (IFN-alpha), imatinib (IFN-alpha), ibuprofen (indomethacin), miglustat (imiglucerase), pegvisomant (somatostatin), anagrelide (hydroxyurea) and zinc acetate (tetrathiomolybdate, penicillamine, or trientine).

In five cases the approval was granted with an uncontrolled phase II study; carglumic acid was approved on the basis of a retrospective study, and for mitotane only a literature analysis was submitted. In seven cases the number of study patients was 50 or less, five drugs were tested in 100–200 patients, three in 200–500, one in 500–1000 and the remaining two drugs were studied in over 1000 patients. While for some very rare diseases the small number is justifiable, in other cases it is not. For Fabry disease the pivotal studies included 41 and 56 patients out of 10 000 potential cases in Europe. Similar figures apply to miglustat, tested on only 28 patients.

Typically the primary end-points are surrogate. Biochemical parameters such as GL-3, GB-3, IGF-1, GAG

Table 1
OMP preclinical data

Drug	Repeated dose toxicology	Exposure	Genotoxicity	Carcinogenicity	Reproduction toxicity
Agalsidase alpha	Rabbits, rats, monkeys	2–26 weeks	NA	NA	Yes (not conclusive)
Agalsidase beta	Rats	27 weeks	NA	NA	NA
Anagrelide	Rats, monkeys, dogs	12–52 weeks	Yes (negative)	NR	Yes (negative)
Arsenic trioxide	Mice, rats, dogs, monkeys	Not specified	Yes (positive)	NR	NR
Bosentan	Rats, dogs, marmosets	1–4 weeks	Yes (negative)	Yes (negative)	Yes (+ in rats, – in rabbits)
Busulfan	Dogs	4 days	NA	NR	Yes (positive)
Carglumic acid	Rats	2–18 weeks	Yes (positive)	Yes (negative)	Yes (not conclusive)
Celecoxib	Rats, dogs	24–52 weeks	Yes (negative)	Yes (not conclusive)	Yes (positive)
Cladribine	Mice	4 weeks	Yes (positive)	NR	Yes (positive)
Ibuprofen	NR	NR	Yes (negative)	Yes (negative)	Yes (negative)
Iloprost	Rats, dogs	24–52 weeks	Yes (negative)	Yes (negative)	Yes (positive)
Imatinib	Monkeys	39 weeks	Yes (+ *in vitro* and – *in vivo*)	Ongoing	Yes (positive)
Laronidase	Dogs, monkeys	8–26 weeks	NA	NA	Yes (not conclusive)
Miglustat	Rats, monkeys	4–52 weeks	Yes (negative)	Yes (negative)	Yes (positive)
Mitotane	NA	NA	NA	NA	NA
Pegvisomant	Rats, monkeys	24 weeks	Yes (negative)	NA	Yes (negative)
Porfimer	Rats, dogs	13 weeks	Yes (positive)	NA	Yes (negative)
Zinc acetate	Rats	53 weeks	Yes (not conclusive)	Yes (not conclusive)	Yes (negative)

NA, not available; NR, not required.

or ammonia are certainly important for Fabry disease, acromegaly, mucopolysaccharidosis, and N-acetyl glutamate deficiency, but there is very little proof that their changes are clinically relevant, justifying long-term treatment. Similarly, the improvement in walking induced by bosentan, though statistically significant, is of questionable clinical importance. The efficacy of anti-cancer drugs was measured through tumour responses rather than survival or quality of life.

In some cases the trial was too short in relation to the natural history of the disease: 20 weeks for agalsidase beta in the treatment of Fabry disease, and 12 weeks for pegvisomant acting on resistant acromegaly seem inadequate.

Discussion

In general the dossiers for OMP approved over the last 4 years show several limitations: frequent lack of dose-finding studies, of controlled studies, of active comparator where available, of multicentre phase III trials with a suitable number of patients (particularly for diseases with a frequency from 5/100 000 to 5/10 000), insufficient exposure to the treatment, use of surrogate endpoints or weak proof of clinical benefit. The requirement for follow-up studies for the 10 drugs approved 'under exceptional circumstances' will not necessarily be met and in any case many years are likely to pass before the results are known. This may reflect a general approach to the development of OMP that might have hampered the approval of other products and could have made the proportion of licensed OMP out of those applied for lower than that of drugs for common clinical indications.

It is certainly difficult to find a balance between the urgent need for drugs for patients with rare diseases while guaranteeing at least their quality, efficacy and safety and, when necessary, making comparisons with existing drugs. Probably the lack of reliable methods for evaluating the effect of drugs on small numbers of patients is partly responsible for the general poor quality of the dossiers. Unquestionably, less stringent criteria are acceptable for orphan drugs, than for drugs for more common diseases, particularly in view of the small or very small numbers of patients. However, even when few patients are available at least a phase II study should be done, comparing the new treatment with the best available care, to establish the clinical benefit of the new therapy. It must be borne in mind that in a small popu-

Table 2
Main information of the OMP clinical dossier

Active principle	Trade name	Indication	Prevalence disease (1/10.000)	Dose finding	Type of trial	Control	End-point	n
**Agalsidase alpha	Replagal	Fabry disease	0.25	Yes	RCT	Placebo	Reduction of pain; reduction of GB3 (NS); Reduction of cardiac mass;improvement of renal function	41
**Agalsidase beta	Fabrazyme	Fabry disease	0.25	Yes	RCT	Placebo	Reduction of GL-3	56
**Anagrelide	Xagrid	Essential thrombocythaemia	2–3	Yes	Open label; nonrandomized; uncontrolled	None	Platelet count <600 × 109/l or reduction >50% from baseline and maintenance of the reduction for at least 4 weeks (= CR)	1446
**Arsenic trioxide	Trisenox	Acute promyelocytic leukaemia	NA	No	Uncontrolled phase II	None	Complete response; overall survival	52
**Bosentan	Tracleer	Pulmonary arterial hypertension	0.005–0.07	No	RCT	Placebo	Exercise (walking)	32
Busulfan	Busilvex	Conditioning haematopoietic progenitor cell transplantation	0.66	No	Uncontrolled phase II	None	Same effect of i.v. as oral busulfan	104
**Carglumic acid	Carbaglu	N-acetyl glutamate synthase deficiency	0.00125	No	Retrospective study	None	Decrease of ammonia concentration	20•
Celecoxib	Onsenal	Familial adenomatous polyposis	0.3–1	No	RCT	Placebo	Decrease of colorectal polyps	970
Cladribine	Litak	Hairy cell leukaemia	NA	No	Uncontrolled phase II (+ literature analysis)	None	Complete + partial responses	120

Ibuprofen	Pedea	Patent ductus arteriosus in preterm newborn infants (<34 weeks of gestational age)	NA	Yes	RCT; controlled (+ metanalysis)	Placebo	Proportion of patients requiring surgical ligation of PDA after prophylactic or curative/or treatment with i.v. ibuprofen	131
**Iloprost	Ventavis	Primary pulmonary hypertension	0.005–0.07	No	RCT	Placebo	Improvement in walking; improvement of 1 NYHA class	203
**Imatinib	Glivec	Chronic myeloid leukaemia GIST (unresectable)	0.18–0.5	Yes	Uncontrolled phase II	None	(CML) Haematological and cyto-genetic response; (GIST) Tumour response	1225; 147
**Laronidase	Aldurazyme	Mucopoly-saccharidosis MPS-1	0.025	No	RCT	Placebo	Reduction of urinary GAG; reduction of hepatosplenomegaly; increase forced vital capacity; exercise-walking (NS)	45
**Miglustat	Zavesca	Gaucher disease type 1	0.33	No	Uncontrolled phase II	None	Reduction of linea and spleen volume	28
Mitotane	Lysodren	Adrenal cortical carcinoma	0.1	No	Literature analysis	None	Survival; remission time; tumour size reduction	500
Pegvisomant	Somavert	Resistant acromegaly	0.5–0.7	No	RCT	Placebo	Decrease in IGF-1	112
Porfimer sodium	Photobarr	Dysplasia in Barrett's oesophagus	2.3	No	RCT	Omeprazole	Complete responses	208
Zinc acetate dihydrate	Wilzin	Wilson's disease	0.6	Yes	Open label; nonrandomized; uncontrolled	None	Effects on copper metabolism 24 h copper excretion and non-coeruloplasmin plasma copper (NCPC); effect on speech and neurological function measured on integer scale; effect on liver function tests, liver enzymes (bilirubin, albumin)	148

*n, number of patients; NA, not available; • retrospective patients; ** approved under exceptional circumstances.*

lation it is difficult to assess the safety of OMP, as adverse drug reactions are often much rarer than events adopted as measures of outcome.

The low rate of OMP licensing and the poor quality of the dossiers accompanying the marketing authorization applications can be explained to some extent by the paucity of European funds for companies willing to develop OMP. There is an urgent need to establish programmes setting aside a special fund and providing tax relief for sponsors producing OMP. The fact that it took 4 years to develop 18 drugs and that there are still several thousand rare diseases [4] awaiting therapy is a public health issue that cannot be neglected.

Source of funding: None. Conflict of interests: None declared for each author.

The authors state that their present paper has not been and will not be published in whole or in part in any other journals.

SG and VB acted, respectively, as member and expert of the CPMP. The views presented in this article/paper are those of the authors and should not be understood or quoted as being made on behalf of the EMEA and/or its scientific committees.

The authors are grateful to Ms Graziella Scalvini of the G.A. Pfeiffer Memorial Library and Ms Judy Baggott for editorial assistance, and to Ms Elena Pozzoli for precious secretarial support.

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