

## INSIGHT

# EUROPEAN MEDICINES AGENCY SUPPORT MECHANISMS FOSTERING ORPHAN DRUG DEVELOPMENT

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### INTRODUCTION

#### Importance of orphan drug development: understanding the need

Rare diseases are a wide and heterogeneous group of diseases, including metabolic diseases, rare cancers, autoimmune diseases and congenital malformations. A large number of these diseases affect children and newborn babies. To date, 5000–8000 distinct rare diseases have been described in the medical literature and this number is still on the rise. Although rare diseases have a particularly low prevalence by definition (< 5 per 10,000 persons in the E.U.), as a group, they may affect between 27 and 36 million people in the European Union (1).

Under normal market conditions, the pharmaceutical industry has little interest in developing and marketing products intended for only a small number of patients suffering from rare conditions. The cost of bringing a so-called orphan medicinal product to the market would indeed not be covered by its expected sales.

#### Legislative framework

On December 20, 1995, the Council of Ministers adopted a Resolution (2) calling on the European Commission (EC) to investigate the need for a European orphan drug regulation. The EC carried out a wide consultation on the subject and in July 1998, submitted a proposal for a European Parliament and Council Regulation on

orphan medicinal products for adoption by the co-decision procedure laid down in Article 251 of the Treaty establishing the European Community (3).

The Regulation (EC) 141/2000 on orphan medicinal products was adopted on December 16, 1999 (4) and came into force following the adoption of its implementing Regulation (EC) 847/2000 by the EC on April 27, 2000 (5). Thus, in April 2000 a new Committee on Orphan Medicinal Products (COMP) was established at the European Medicines Agency (<http://www.ema.europa.eu>). Composed of one member nominated by each member state, three patient representatives and three members proposed by the agency and appointed by the EC, the COMP meets 11 times per year.

The incentives laid down in orphan legislation aim to assist sponsors in the development of medicinal products for rare diseases, the so-called orphan drugs. These incentives include a mandatory access to the centralized procedure, a 10-year period of market exclusivity once the orphan products are authorized, free protocol assistance in the form of scientific advice from the Agency and the possibility to be granted other types of fee reductions by the agency.

#### UNDERSTANDING THE PROCESS: HOW TO OBTAIN ORPHAN DESIGNATION IN THE E.U.

Individuals or pharmaceutical companies, the so-called sponsors, may apply for orphan designation at any time prior to the application for marketing authorization and many sponsors apply early on in the development. There is no fee payable for an

With more than 690 medicinal products officially designated as orphan by the European Commission, one can state that the orphan initiative has been very successful.

### SUMMARY

A legislative framework introducing European public health measures on orphan medicinal products came into force in the European Union in April 2000. The aim of the orphan legislation is to stimulate research and development of medicinal products for rare diseases by providing incentives to the sponsors. Incentives include, among others, an unreserved access to the centralized procedure with a 10-year period of market exclusivity and fee reductions including free scientific advice for drug development. Nine years after the implementation of the orphan legislation, more than 690 products have been designated and 58 have received marketing authorizations in Europe. The orphan designations granted to date cover a wide variety of diseases for which there are either no authorized treatments or only limited treatment options with a need for improvement. At the dawn of the tenth anniversary of the orphan legislation, the aim of this article is to review how the European Medicines Agency has supported the mechanisms fostering development of orphan medicines in the E.U. since 2000.

application for orphan designation. Within a 90-day period from the receipt of a valid application, the COMP will reach an opinion on whether designation should be granted or not. This will be followed by a decision on

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orphan designation granted by the EC. In case the outcome of the assessment is not successful, sponsors have the possibility to reapply later on, for example when they have more data to support their application.

The following discussion refers mainly to the regulatory process of the orphan designation, while the qualitative aspects of the applications received so far are discussed later on in the article.

### Submission

Before applying, sponsors are asked by the Agency to notify their intent to submit an application for orphan designation as early as possible, and at least 2 months prior to the planned submission date. In the meantime, two coordinators (one COMP member and one Agency staff member from the orphan team) are appointed. Moreover, sponsors may request a meeting with agency staff before submission to help them to submit their proposed application according to the EC's guidelines on the format and content of applications (ENTR/ 6283/00, Rev 3) (6), which are also available on the web sites of the Agency and the EC.

Since November 2007, sponsors may use the European Medicines Agency/FDA common application form to apply to both agencies (7). Currently, the annex containing the scientific support information remains different. So far, the European Medicines Agency has dealt with 104 common application forms and these applications are at various steps of the procedure, from notification of intent to file to decision on designation granted by the EC (Fig. 1).

### Validation

The Agency is responsible for validating the application. If it is incomplete, the sponsor will be asked to provide additional information. A teleconference may be organized to help sponsors clarify the issues raised during the validation.

### Evaluation

Once validation is successfully completed, the evaluation phase starts and the sponsor will receive a 90-day evaluation timetable. The Agency coordinator, in association with the COMP coordinator, is responsible for drafting a summary report. Additional expert(s) may be involved at that stage to comment on the application.

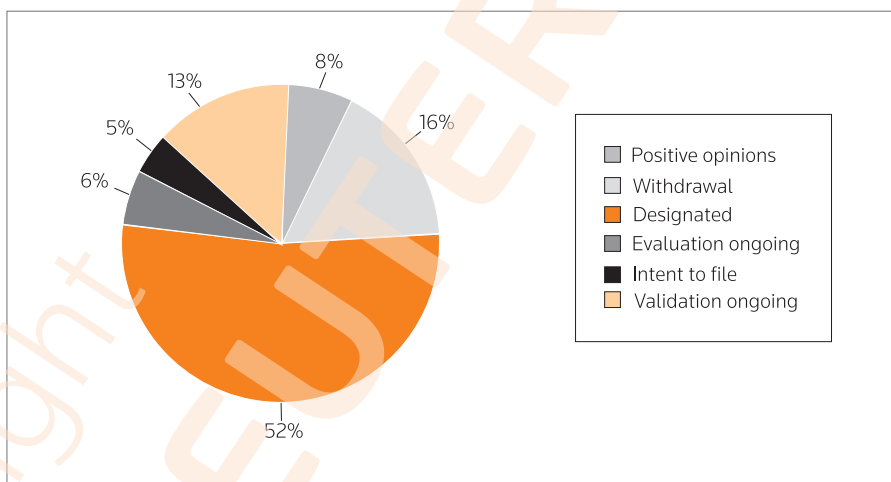


Figure 1. Distribution of common European Medicines Agency/FDA application forms per step of procedure.

A first version of the assessment report is circulated to all the COMP members prior to the plenary session by day 60. The COMP may raise questions on the application, to which the sponsor should provide their responses before day 90; there are no clock stops in the procedure. The sponsor is invited to an oral explanation before the EC and may ask for advice from expert(s). At that stage, the COMP may also appoint expert(s) to comment on the sponsors' responses to the list of questions.

### What is a valid condition for orphan designation?

Distinct recognized medical entities are generally considered as valid conditions, e.g., Fabry's disease, acute myeloid leukemia, pancreatic cancer or cystic fibrosis. Such entities are defined in terms of their specific clinical, pathophysiological or histopathological characteristics.

With reference to the updated Guideline on Format and Content (ENTR/6283/00, Rev 3) (6), the characteristics of a distinct condition should correspond to a group of patients in whom the development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmacodynamic evidence and assumptions for the product.

Distinction should be made between the proposed orphan indication, which is the subject of the application for designation, and the proposed therapeutic indication, which is subject of the application for mar-

keting authorization at a later stage. Applying for the broadest orphan indication may leave more options in terms of therapeutic indications at the time of the application for marketing authorization (MAA). For the latter, the proposed orphan indication is worded in broad terms, generally as diagnosis/prevention/treatment of a medical entity.

A large proportion of the unsuccessful applications received so far for designation are due to sponsors applying for an artificial subset of a condition, which on its own has a prevalence above the threshold. In addition, different degrees of severity or stages of a condition are not generally considered by the COMP as distinct conditions. As a consequence, the subsets of patients within a condition who have failed first- or second-line treatment, or who cannot tolerate standard treatment, are generally not considered as a distinct entity for the purposes of orphan designation. This has been the case for applications for advanced stages of melanoma, for example.

Exceptions are possible if there is a rationale for excluding some patients from the broader population because they might not benefit from the product's activity. In other words, a subset may be considered as a valid condition if patients present with common characteristics related to the medicinal product's action, which are absent in the other patients affected by the same condition. For example, the COMP might accept an anticancer drug targeting a specific protein that is expressed only by a subset of patients within the whole condition. In this

regard, the following were considered valid subsets in the context of orphan designation and with regard to the product's activity: treatment of TERT-positive non-small cell lung cancer in HLA-A2-positive patients, treatment of Ep-CAM-positive squamous cell carcinoma of the head and neck and treatment of MART-1-positive malignant melanoma in HLA-A2-positive patients.

### **What are the criteria for orphan designation?**

The designation is based either on the prevalence of the condition in the EC or the insufficient return generated by the product to justify the investment. In addition, the application has to fulfill two other criteria to obtain orphan designation, as set out in Article 3(1) of Regulation (EC) No 141/2000 (4). Therefore the three criteria for orphan designation are the following:

1) The first criterion is based on the condition's "rarity", i.e., the fact that it affects no more than 5 in 10,000 persons in the E.U. Alternatively, the sponsor can apply for more frequent conditions if it can be shown that the development would not be covered by sufficient financial return, i.e., if without incentives it is unlikely that the marketing of the medicinal product in the EC would generate sufficient return to justify investment by the sponsor. In March 2002, the EC finalized a document entitled "Points to Consider Document on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation" (COMP/436/01) (8), which is available on the Agency's web site. Sponsors are advised to consult this document prior to preparing the prevalence section of an application for orphan medicinal product designation. It is worth pointing out that for conditions of very short duration (< 1 year), yearly incidence rather than prevalence is considered the most appropriate measure in view of the objectives of the orphan drug legislation.

2) The second criterion for designation is based on the condition's life-threatening or debilitating nature. The sponsor is invited to provide any scientific and/or medical references that may support the life-threatening or seriously debilitating nature of the condition.

3) Lastly, sponsors are required to demonstrate that no satisfactory methods of diagnosis, prevention or treatment of the condi-

tion exist, or, if such methods do exist, that the medicinal product will be of significant benefit to those affected by the condition. In that context, "significant benefit" over authorized products has been defined in the legislation as a clinically relevant advantage or a major contribution to patient care. This could be based on an alternative mechanism of action that will result in an improved clinical outcome, more favorable pharmacokinetic properties or potentially better clinical effects. The claims of significant benefit must be justified and supported by a scientific discussion, based on data from the literature or by any preliminary preclinical and/or clinical results. A justification of significant benefit that is based on a safety-related clinical advantage may be difficult to accept, since most often, the product has not been widely used at the time of application for orphan drug designation and therefore, its safety profile remains largely unknown. Significant benefit based on a major contribution to patient care may be related to a new route of administration that improves patient care, such as a significant decrease in the number of intakes/day with the same clinical outcome. Exceptionally, availability/supply is considered as justification for significant benefit, when a clear long-term supply shortage of the existing marketed product has led to its restricted use and consequences for patients. So far, more than 60% of positive opinions adopted on orphan designations were based on significant benefit.

### **Opinion**

Before day 90 of the procedure, the COMP is required to adopt an opinion on the application. It is generally obtained during a COMP meeting and rarely by written procedure. If a consensus cannot be reached, the opinion will be adopted by a majority of at least two-thirds of the COMP members. The opinion with the final summary report is forwarded by the Agency to the EC and to the sponsor. In case of a negative opinion, the sponsor may appeal, provided the latter forwards the grounds for appeal to the agency within 90 days of receiving the negative opinion.

### **Decision and publication in the register**

Decisions on designation are granted by the EC. The legislated time frame for the decision-making phase is 30 days. Upon a favorable decision by the EC, designated orphan

medicinal products are published in the Community Register of orphan medicinal products on the EC's web site (9). Following the adoption of a decision on orphan designation, the agency also publishes a Public Summary of COMP Opinion. This document contains a brief description of the condition, the product and its mechanism of action, the prevalence of the disease and the product's stage of development at designation. The content and readability of summaries of COMP Opinions are commented upon by representatives of patients' organizations and the relevant sponsor prior to publication.

### **ORPHAN INCENTIVES**

Sponsors with an orphan designation for a medicinal product may benefit from incentives such as: financial incentives related to the Agency's procedures (fee reductions and exemptions); protocol assistance (scientific advice on orphan medicines during the product's development); mandatory access to centralized marketing authorization; 10-year market exclusivity once a marketing authorization is granted in all E.U. member states; and additional national incentives detailed in an inventory made available by the EC.

### **Fee reductions**

A further incentive offered by the orphan legislation is the possibility to request fee reductions, for all fees payable under European Community rules pursuant to Council Regulation (EC) No 297/95 (10, 11). In accordance with Article 7.2 of Regulation (EC) No 141/2000, a special contribution is allocated annually to the Agency by the European Community to fund fee reductions for orphan medicinal products. This contribution covers reductions for fees for activities preceding authorization (e.g., protocol assistance) and for products using the centralized procedure, the application for marketing authorization, inspections and activities following authorization, such as variations and annual fees. Fee reductions can only be processed once the decision on orphan medicinal product designation has been granted by the EC. Effective February 1, 2009, the current fee reduction policy for designated orphan medicinal products reinforces support to micro-, small- and medium-sized enterprises (SME) (Table I).

**Table 1.** Revised fee policy (effective February 1, 2009)

• Full (100%) fee reduction for protocol assistance and follow-up
• Full (100%) fee reduction for inspections preceding authorization
• A 50% fee reduction for new applications for marketing authorization to applicants other than small- and medium-sized enterprises
• Full (100%) fee reduction for new applications for marketing authorization only to small- and medium-sized enterprises
• Full (100%) fee reduction for activities following authorization, including annual fees, only to small- and medium-sized enterprises in the first year after granting a marketing authorization

Each year the Agency prepares a budget report on the use of the special contribution (Fig. 2).

**Protocol assistance**

The Agency is required to provide protocol assistance through its scientific committee that is responsible for the evaluation of applications for marketing authorization, i.e., the Committee for Medicinal Products for Human Use (CHMP) and the latter’s Scientific Advice Working Party (SAWP), in which three COMP representatives sit.

Protocol assistance takes the form of scientific advice and may cover different aspects of the application for marketing authorization: chemical–pharmaceutical, preclinical, clinical efficacy and/or safety development. The procedure has a maximum duration of 70 days, with the possibility of finalization on day 40. In half of the cases, it includes a discussion meeting with the sponsor, but this is generally triggered by a major disagreement with the sponsor on the product’s development, or by the need for additional information. The final advice letter is adopted by the CHMP and the COMP when there are questions on significant benefit.

Protocol assistance is considered a priority, as it is a way to both improve and speed up the applications for marketing authorization of orphan medicinal products and therefore increases the chances for patients affected by rare diseases to get effective treatments. One of the most utilized incentives for orphan medicines development, it represents almost half of the use of the special contribution for orphan medicines as shown in Figure 1. The Agency grants full fee reduction for protocol assistance, indicating the high importance given to this procedure by the agency.

**Mandatory access to centralized marketing authorisation and 10-year market exclusivity**

Designated orphan medicinal products have mandatory access to the centralized procedure. The assessment of the benefit–risk balance of the applications for marketing authorization is done by the CHMP and is based on the same standards applied to products intended for nonrare disease. The medicinal products’ quality, safety and efficacy are evaluated by the experts from the member states contributing to the CHMP and coordinated by the Agency. Within 210 days, the CHMP will reach a scientific opinion on whether a marketing authorization should be granted. Upon the grant of the marketing authorization by the EC, orphan medicinal products will benefit from 10 years of market exclusivity for the authorized indication.

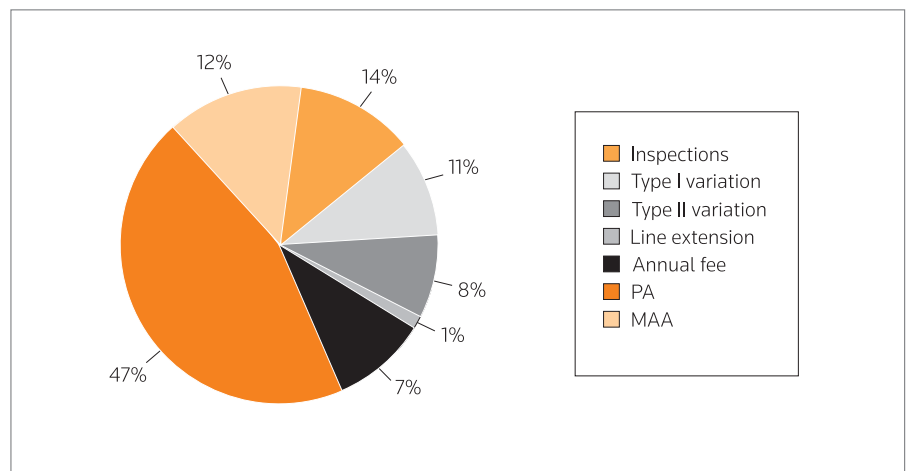
At the time of application for marketing authorization, the COMP reviews the orphan

designation criteria and checks whether the following criteria are fulfilled:

- 1) The proposed therapeutic indication falls within the scope of the designated orphan indication for the medicinal product
- 2) The condition is still being judged life-threatening or chronically debilitating
- 3) The prevalence of the condition is no more than 5 in 10,000 at the time of the review of the designation criteria
- 4) When the designation is based on significant benefit, the assumption that the product might be of benefit to those affected by the orphan condition is established

If the orphan criteria are still fulfilled, the COMP will issue a (positive) opinion recommending “not to remove” the product from the Community Register of orphan medicinal products. If the criteria are no longer fulfilled, the COMP may issue an opinion recommending removal of the medicinal product from the register, and the product is marketed without the right to access the incentives offered by the regulation.

Once a medicinal product is marketed, the marketing authorization holder is responsible for maintaining the quality of the product on the market and for monitoring its safety through pharmacovigilance. In this period, amendments to the marketing authorization may be requested or required and variations to the marketing authorization may be submitted. Additionally, as laid



**Figure 2.** Distribution of fee reductions granted per type of request since 2000. PA, protocol assistance; MAA, marketing authorization application.

down in Regulation (EC) No 1901/2006 on medicinal products for pediatric use (12), orphan medicinal products may be granted a 2-year extension of the market exclusivity if they have agreed and complied with a Pediatric Investigation Plan and the information arising from the latter is incorporated into the Summary of Product Characteristics.

### National incentives detailed in an inventory made available by the EC

An inventory of the European Community's and national incentive measures to aid the research, marketing, development and availability of orphan medicinal products was published in 2002 (13), whereby 14 member states provided information. Of these 14, not all had taken specific measures for the marketing and development of orphan medicinal products. Initiatives at national level include fiscal incentives, national research projects, fee reductions and scientific/administrative advice.

### VALUE OF THE PROGRAM

#### Designated products

As the 10<sup>th</sup> anniversary of the E.U. orphan legislation approaches, one can state that the orphan initiative has been very successful, with more than 690 medicinal products officially designated as orphan by the EC. Around 30% of the orphan designations involve innovative products, e.g., various types of monoclonal antibodies or products using new techniques such as nanotechnology. The most visible application of nanotechnology is certainly its use in drug delivery; orphan designation has been granted to medicinal products using advanced drug delivery systems for cancer therapy, aiming to improve bioavailability and pharmacokinetics and/or to replace invasive routes of administration by noninvasive ones.

Of all orphan designations, 7% are for advanced therapy medicinal products, as is

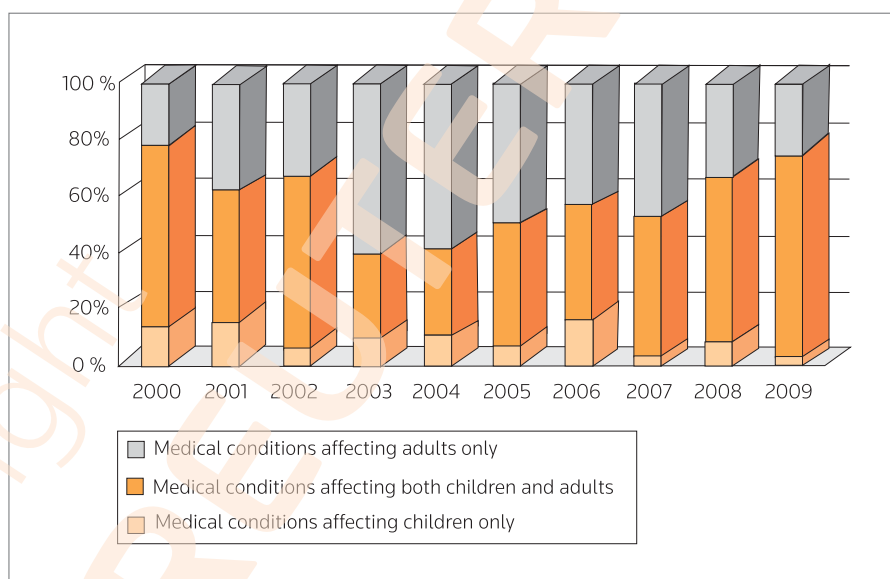


Figure 3. Distribution of the opinions of the Committee on Orphan Medicinal Products by age of target population.

established by Regulation (EC) No 1394/2007 on advanced therapy medicinal products (14). Advanced therapy medicinal products include tissue-engineered, cell-based and gene therapy medicinal products. They offer groundbreaking new treatment opportunities, in particular for genetically inherited diseases ranging from neuromuscular conditions such as Duchenne muscular dystrophy to ophthalmologic conditions such as retinitis pigmentosa. However, due to the complexity in developing these types of products, no orphan advanced therapy medicinal product has yet reached the market.

Considering the age of patients affected by rare diseases, it is obvious that many orphan medicines may be of use for the pediatric population, as is shown in Figure 3.

Table II provides an overview of the status of orphan designation applications since 2000, the first year the orphan legislation

was implemented. It shows that the number of applications is increasing over time and has reached its highest value so far, with 164 applications received in 2009. Several factors may have played a role, such as the economic environment and the closer collaboration between the orphan drug teams at the European Medicines Agency and the FDA. Sponsors are encouraged by both agencies to apply to both regions, using the common European Medicines Agency/FDA application form for orphan designation. Furthermore, 74 designated products have been removed from the register by sponsors' requests, for administrative reasons or when product development was discontinued. The distribution of positive COMP opinions by therapeutic area is provided in Figure 4. More than one-third of the designated products are related to orphan diseases affecting less than 1 in 10,000 patients in the EC (i.e., < 50,000 patients), such as rare metabolic disorders

Table II. Overview of the status of orphan designation applications since 2000

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Total
Applications submitted	72	83	80	87	108	118	104	126	119	164	1061
Positive COMP opinions	26	64	43	54	75	88	81	97	86	113	727
Final negative COMP opinions	0	1	3	1	4	0	2	1	1	2	15
Withdrawals	6	27	30	41	22	30	20	19	31	23	249

COMP, Committee on Orphan Medicinal Products.

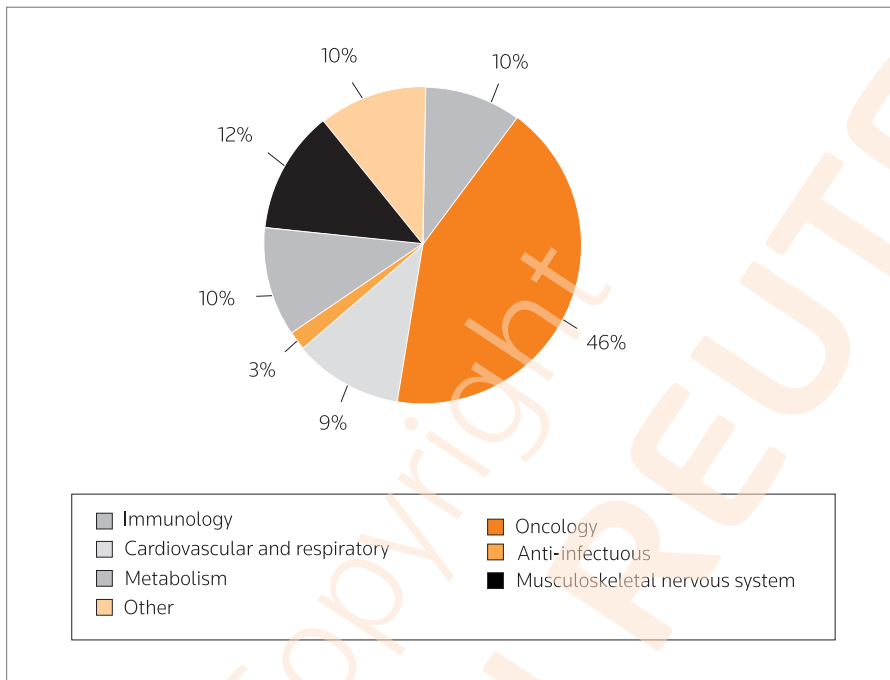


Figure 4. Distribution of positive COMP opinions on designation by therapeutic area.

(e.g., hereditary tyrosinemia type 1) or rare cancers (e.g., neuroblastoma) (Fig. 5).

(38%) were antineoplastic and immunomodulating agents (Fig. 6). Sponsors may face various issues in the development of

**Marketing authorizations for orphan medicines**

To date, 58 designated orphan medicinal products have received marketing approval in the E.U., whereby more than two-thirds

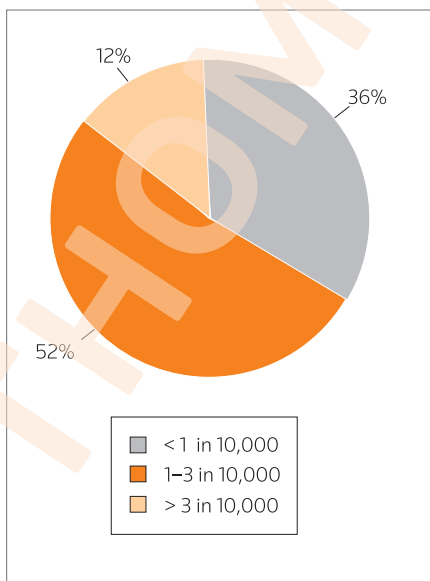


Figure 5. Prevalence of the designated conditions (up to October, 2009).

medicinal products for rare diseases. In many cases, there is a lack of preclinical models to screen the potential activity of new agents. Furthermore, for many rare conditions it is difficult to recruit sufficient numbers of patients to conduct clinical trials adequately powered to show significant effects. As a result of the difficulty to enrol enough patients, the studies may be very lengthy (15-18).

Of the 58 orphan medicinal products authorized, 40% of the marketing authorizations were granted under "exceptional circumstances" and 5% as "conditional approval" (Table III). Exceptional circumstances mean that at the time of the evaluation, it was deemed unreasonable to expect the applicant to provide comprehensive evidence on the compound's safety and efficacy. In case of conditional approval, further studies will be needed to maintain the marketing authorization; this will be reviewed annually by the Agency (18).

It seems that some developments of medicinal products encounter more difficulties than others to reach the stage of marketing authorization. For example, although

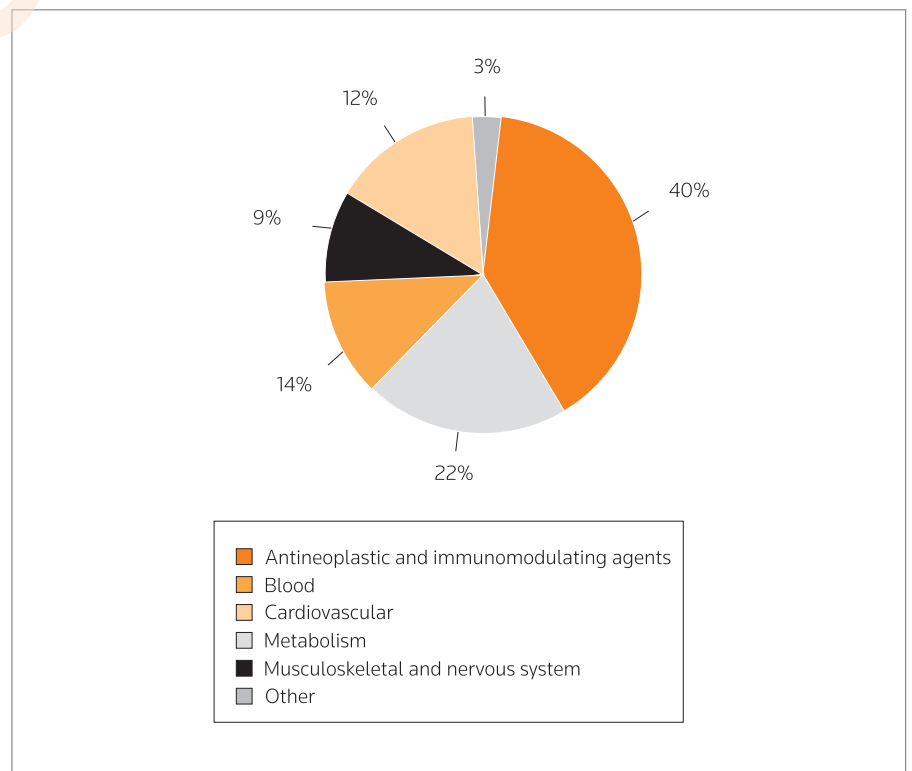


Figure 6. Distribution of orphan marketing authorizations per therapeutic area.

**Table III.** List of the 58 orphan medicinal products approved through the centralized procedure since 2001

Year	Orphan MA	Significant benefit	Type of MA	Prevalence £ 1/10,000	Received PA/SA
2001	<i>Fabrazyme</i> ® for Fabry's disease	No	EC	Yes	Yes
	<i>Replagal</i> ® for Fabry's disease	No	EC	Yes	Yes
	<i>Glivec</i> ® for chronic myeloid leukemia	Yes	EC	No	Yes
2002	<i>Tracleer</i> ® for pulmonary arterial hypertension	Yes	EC	No	Yes
	<i>Trisenox</i> ® for acute promyelocytic leukemia	Yes	EC	No	No
	<i>Somavert</i> ® for acromegaly	Yes	Normal	No	Yes
	<i>Zavesca</i> ® for Gaucher's disease	Yes	EC	Yes	Yes
2003	<i>Carbaglu</i> ® for hyperammonemia	No	EC	Yes	No
	<i>Aldurazyme</i> ® for mucopolysaccharidosis	No	EC	Yes	Yes
	<i>Busilvex</i> ® for hematopoietic progenitor cell transplantation	Yes	Normal	Yes	Yes
	<i>Ventavis</i> ® for pulmonary arterial hypertension	Yes	EC	No	Yes
	<i>Onsenal</i> ® for familial adenomatous polyposis	No	EC	No	No
2004	<i>Litak</i> ® for hairy cell leukemia	Yes	Normal	No	No
	<i>Lysodren</i> ® for adrenal cortical carcinoma	Yes	Normal	No	No
	<i>Pedea</i> ® for patent ductus arteriosus	Yes	Normal	No	No
	<i>Photobarr</i> ® for Barret's oesophagus	No	Normal	No	Yes
	<i>Wilzin</i> ® for Wilson's disease	Yes	Normal	Yes	No
	<i>Xagrid</i> ® for thrombocythemia	Yes	EC	No	Yes
2005	<i>Orfadin</i> ® for hereditary tyrosinemia type 1	No	EC	Yes	No
	<i>Prialt</i> ® for chronic pain requiring intrathecal analgesia	Yes	EC	No	No
	<i>Xyrem</i> ® for cataplexy in patients with narcolepsy	Yes	Normal	No	Yes
	<i>Revatio</i> ® for pulmonary arterial hypertension	Yes	EC	No	No
2006	<i>Naglazyme</i> ® for replacement therapy in patients with mucopolysaccharidosis VI	No	EC	Yes	No
	<i>Myozyme</i> ® for glycogen storage disease type II (Pompe's disease)	No	Normal	Yes	No
	<i>Evoltra</i> ® for acute lymphoblastic leukemia	Yes	EC	Yes	No
	<i>Nexavar</i> ® for advanced renal cell carcinoma	Yes	Normal	No	Yes
	<i>Sutent</i> ® for gastrointestinal stromal tumor and metastatic renal cell carcinoma	Yes	CA	No	Yes
	<i>Savene</i> ® for anthracycline extravasation	No	Normal	Yes	No
	<i>Thelin</i> ® for idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension	Yes	Normal	No	No
	<i>Exjade</i> ® for chronic iron overload due to blood transfusions	Yes	Normal	No	No
	<i>Sprycel</i> ® for acute lymphoblastic leukemia and chronic myeloid leukemia	Yes	Normal	No	Yes
	<i>Diacomit</i> ® for severe myoclonic epilepsy in infancy	Yes	CA	Yes	No
	<i>Elaprase</i> ® for mucopolysaccharidosis type II (Hunter's syndrome)	No	EC	Yes	Yes
	<i>Inovelon</i> ® for Lennox-Gastaut syndrome	Yes	Normal	No	No
	<i>Cystadane</i> ® for homocystinuria	Yes	Normal	Yes	No

Continued

**Table III.** Cont. List of the 58 orphan medicinal products approved through the centralized procedure since 2001

Year	Orphan MA	Significant benefit	Type of MA	Prevalence £ 1/10,000	Received PA/SA
2007	Revlimid® for multiple myeloma	Yes	Normal	No	Yes
	Soliris® for paroxysmal nocturnal hemoglobinuria	No	Normal	Yes	Yes
	Siklos® for sickle cell syndrome	No	Normal	Yes	Yes
	Atriance® for acute lymphoblastic leukemia	Yes	EC	No	No
	Increlex® for primary insulin-like growth factor 1 deficiency due to molecular or genetic defects	No	EC	No	No
	Gliolan® for intraoperative photodynamic diagnosis of residual glioma	Yes	Normal	Yes	Yes
	Yondelis® for soft tissue sarcoma	Yes	EC	Yes	No
	Tasigna® for chronic myeloid leukemia	Yes	Normal	No	Yes
	Torisel® for renal cell carcinoma	Yes	Normal	No	Yes
2008	Thalidomide Celgene® for multiple myeloma	Yes	Normal	No	Yes
	Volibris® for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Yes	Normal	No	Yes
	Firazyr® for angioedema	Yes	Normal	No	Yes
	Ceplene® for acute myeloid leukemia	Yes	EC	No	No
	Kuvan® for hyperphenylalaninemia	Yes	Normal	No	No
	Mepact® for osteosarcoma	Yes	Normal	Yes	Yes
	Vidaza® for acute myeloid leukemia and myelodysplastic syndromes	Yes	Normal	No	No
2009	Nymusa® for primary apnea in premature newborns	Yes	Normal	No	No
	Afinitor® for renal cell carcinoma	Yes	Normal	No	No
	Mozobil® for mobilize progenitor cells prior to stem cell transplantation	Yes	Normal	Yes	No
	Cayston® for Gram-negative bacterial lung infection in cystic fibrosis	Yes	CA	No	Yes
	Arcalyst® for cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome	No	EC	Yes	No
	Ilaris® for cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome	No	EC	Yes	No
	Nplate® for idiopathic thrombocytopenic purpura	Yes	Normal	No	Yes
Total	58	73%	Normal: 55% EC: 40% CA: 5%	40%	48%

MA, marketing authorization; PA, protocol assistance; SA, scientific advice; EC, exceptional circumstances; CA, conditional approval.

glioma is one of the most frequently designated conditions (26 times), no product has been authorized so far. Of the 58 orphan medicinal products that have received marketing authorization, 48 received protocol assistance or scientific advice prior to the submission of the application for marketing authorization.

**Protocol assistance**

Protocol assistance is an excellent opportunity for sponsors to agree with the Agency on the best way to generate data and develop

their product in view of a future submission for marketing authorization. The protocol assistance can be followed by follow-up procedure(s) to address further questions regarding the compound’s development. Follow-up procedures can also address changes in the plans introduced by the sponsor, and when medical or scientific developments lead to changes that might affect the advice given. The number of procedures for protocol assistance has followed an increasing trend since its start in 2002, with currently more than 50 procedures per year (Fig. 7).

Protocol assistance can address questions relating to quality, efficacy and safety of the product and queries regarding the demonstration of significant benefit can also be made. In most cases, protocol assistance is sought for questions in different areas of development within a single procedure. In practice, 90% of the questions put to the SAWP include clinical issues, followed by preclinical (44%) and quality issues (27%). For the clinical development, the trials most frequently discussed are phase III studies (> 60%) followed by phase II (20%) and

phase I (13%) trials. This distribution is in line with what can be observed for scientific advice for non-orphan products (Fig. 8).

Recently, new questions emerged on novel topics such as adaptive designs, conditional approval with regards to the demonstration of positive benefit-risk with preliminary evidence, issues about the interim analyses such as blinding, stopping rules and type I error control and finally queries regarding similarity issues.

A recent analysis has been made by the Agency's scientific advice team to identify

factors associated with success of MMAs (19). Between January 1, 2004 and December 31, 2007, out of 188 marketing authorizations with an outcome, positive opinions were obtained on authorization for 137 applications (72.9%), whereas 51 (27.1%) produced a negative CHMP opinion (n = 10) or were withdrawn by the sponsor (n = 1).

A total of 69 (37%) of these 188 MAAs with an outcome had received scientific advice. Of the 61 MAAs for biologics, including recombinant therapeutic proteins, vaccines, blood and blood components, somatic cells,

gene therapy, tissues and allergenics, 29 (48%) received scientific advice. Finally, scientific advice was received for 16% (7/43) and 39% (33/84) of the MAAs for new chemical entities or known chemical substances, respectively.

Out of the 188 MAAs with an outcome, 50 (27%) concerned orphan medicinal products. Of these 50 orphan medicines, 21 (41%) came for protocol assistance and 29 (58%) had a positive outcome versus a success rate of 78% (108/138) for non-orphan drug products. However, if company size was independently analyzed, the designation did not seem to play a role (success rate similar by company size strata). The analysis of the association between positive outcome of marketing authorization and company size revealed an odds ratio of 2.85 (95% confidence interval [CI] 1.81–4.49) for company size. Overall big, medium and small pharma success rates were 89% (74/83), 73% (37/51) and 48% (26/54), respectively. Compliance with scientific advice was found to be associated with positive outcome of marketing authorization, with an odds ratio of 1.65 (95% CI 0.56–4.9). The highest compliance levels were detected in big pharmaceutical companies (respective compliance of 25%, 60% and 84% for small, medium and large companies).

In conclusion, company size seems to be associated with outcome, with larger size associated with positive outcome. The failure of smaller companies could be due to limited resources in relation to the marketing authorization preparation and handling, and/or lack of regulatory experience. Finally, compliance with protocol assistance seems to be associated with positive outcome.

**Other European Medicines Agency/COMP activities in the field of rare diseases**

Besides its core activities related to designation, the European Medicines Agency and its COMP are involved in other activities related to rare diseases, such as collaboration with stakeholders and medicines development promotion.

For example, the COMP has supported DG Research's proposal that from 2009, the Seventh Framework Programme (<http://cordis.europa.eu/fp7>) should offer the possibility to fund clinical as well as preclinical development of medicines for rare diseases.

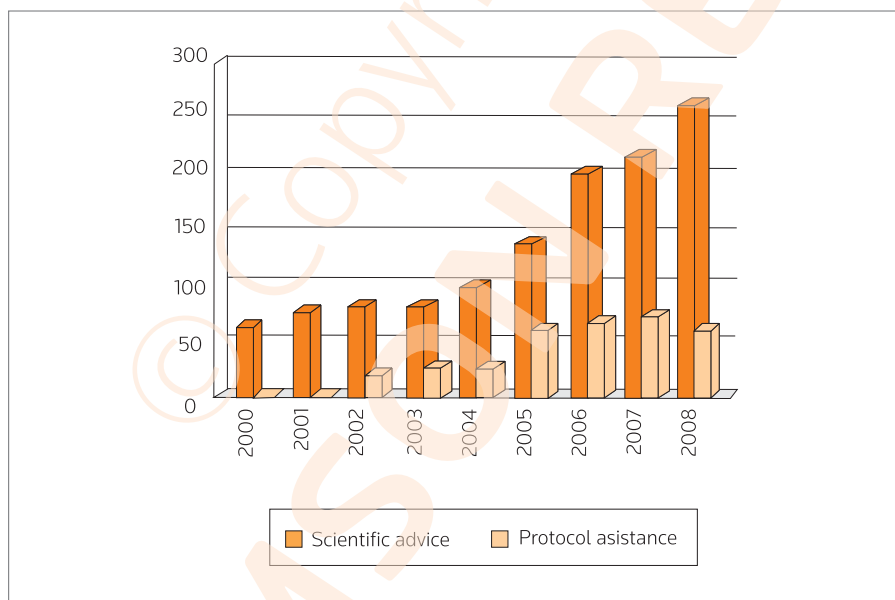


Figure 7. Number of procedures for scientific advice and protocol assistance since 2000.

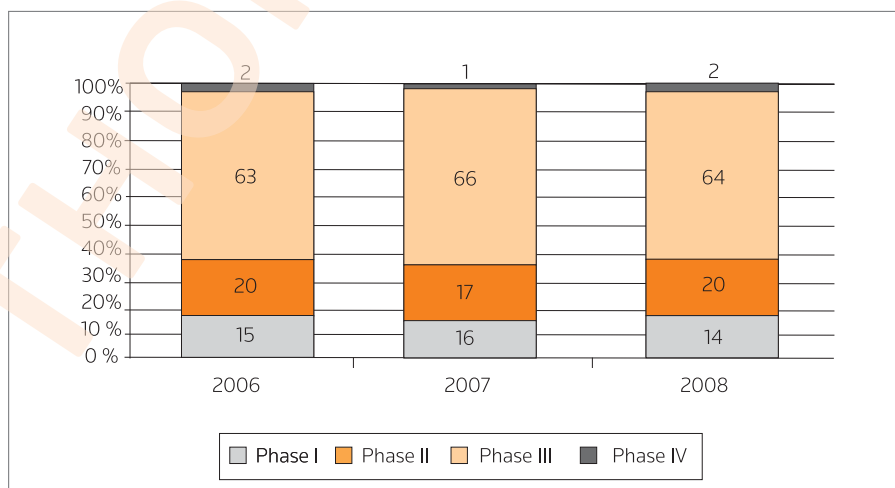


Figure 8. Clinical trial phases of scientific advice requests (2006–2008).

In its first phase, the E.U.'s Seventh Framework Programme for Research and Technological Development (FP7, 2007–2013) contributed to boosting research on rare diseases and focused on innovative and multidisciplinary projects investigating the natural course and pathophysiology of non-infectious, nonmalignant rare diseases on an E.U.-wide scale.

One of the working groups of the Rare Diseases Task Force has taken the initiative to propose the inclusion of rare diseases in the next revision of the International Classification of Diseases (ICD) classification. The COMP has also been involved in the World Health Organization ICD-11 revision process for rare diseases and is collaborating with DG Sanco in the Rare Diseases Task Force.

## CONCLUSION

Success is evident 10 years after the inception of the orphan regulation in Europe, with 58 medicines having reached the market and available for the treatment of rare diseases, which affect up to 2.6 million patients in Europe. Furthermore, with 690 products for orphan conditions designated in Europe and several ongoing marketing authorization applications, more orphan medicinal products are expected to be authorized in the following years. More than one-third of the designated products are intended for patients affected by very rare diseases, and until 2000, the pharmaceutical industry was unlikely to develop medicines for these conditions.

Orphan designation provides access to the European Medicines Agency's support mechanisms fostering orphan medicines development and the incentives such as free protocol assistance, fee reductions and market exclusivity. In particular, sponsors are encouraged to seek protocol assistance in order to increase the chances of favorable outcome at the time of marketing authorization. As a further example of success, these incentives are now widely used by sponsors.

The European Medicines Agency has regularly invited various stakeholders, patient organizations, the pharmaceutical industry or organizations such as Orphanet (<http://www.orpha.net>) to attend the plenary sessions of the COMP representatives of the EC (its Directorates General for Research for

Health and Consumers and Enterprise, [http://ec.europa.eu/health/ph\\_threats/non\\_com/rare\\_diseases\\_en.htm](http://ec.europa.eu/health/ph_threats/non_com/rare_diseases_en.htm)) and to present and discuss topics of common interest.

Through the COMP, the European Medicines Agency is involved in supporting orphan drug development, which goes beyond its "core" orphan designation activities and consists of advising and promoting networks and participating in projects aimed at improving research and policies in that domain. In particular, with the COMP, the agency has supported collaboration and medicine development promotion, e.g., in the context of the Seventh Framework Programme, collaboration with DG Sanco through the Rare Diseases Task Force, and the World Health Organization classification review.

The field of rare diseases is one where the collaboration between member states and different regulatory authorities is of particular importance due to the spread and limited number of patients, and the scarcity of relevant knowledge and expertise in the E.U. Collaborations have very high added value not only at the European, but also at the global level. The close collaboration of the European Medicines Agency and the FDA on orphan drugs and the ongoing collaboration with other countries or regions must be stressed as other examples of successful initiatives. More work is needed to facilitate administrative steps for sponsors and to develop and extend the collaborations. Eventually, this will serve all patients affected by rare diseases throughout the world.

## DISCLOSURE

The views presented in this article are those of the authors and should not be understood or quoted as being made on behalf of the European Medicines Agency and/or its scientific committees.

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