Chapter 8

Principles of Orphan Drugs

OBJECTIVES

- ❑ Examine the characteristics of orphan diseases, in particular their rarity
- ❑ Obtain a basic understanding of the principles for orphan drug designation and authorization
- ❑ Understand the differences between current orphan laws
- ❑ Understand the incentives introduced to stimulate development of drugs for orphan diseases

REGULATIONS AND GUIDELINES COVERED IN THIS CHAPTER

US

- ❑ *Orphan Drug Act* of 1983, Public Law 97-414, with amendments in 1985 and 1988

EU

- ❑ Regulation (EC) 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
- ❑ Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Australia

- ❑ *Australian regulatory guidelines* for prescription medicines, June 2004

Introduction

Orphan drugs (or orphan medicinal products) are intended for the treatment of orphan diseases, which are typically understood to be rare diseases. In most legislation, the orphan principle is limited to drugs only. However, there are exceptions. For instance, in the US, the definition of orphan products was extended to products other than drugs, such as medical devices and medical foods (e.g., parenteral nutrition).

Orphan legislation originated in the US in the early 1980s. At that time, US Representative Henry Waxman was contacted by the mother of a boy suffering from Tourette syndrome—a neuropsychiatric disorder characterized by vocal and motor tics. Waxman, chairman of the House Energy and Commerce Committee's Subcommittee on Health and the Environment, held a hearing to assess the extent of the rare disease problem. Jack Klugman, the star of the weekly television medical drama, "Quincy," heard about this problem and decided to create an episode of the show on the orphan disease problem using the example of Tourette syndrome. The show triggered thousands of letters asking how one could help. On this basis, Waxman introduced an orphan drug bill. Another hearing was held, and Jack Klugman testified before the committee. The support of the popular actor turned out to be important for the introduction of the bill, which was put on hold on several occasions during the legislative process. Additional "Quincy" episodes on this topic, as well as intense press coverage, such as full-page advertisements in major newspapers by rare-disease activists, were finally successful: the *Orphan Drug Act* (*ODA*) became law in 1983.

Subsequently, orphan drug legislation was introduced in Japan and Australia (1993 and 1997, respectively) and in the EU in 2001. There are other countries or regions where particular orphan drug principles were introduced—e.g., Switzerland and Singapore. This chapter presents the most important principles of orphan drug legislation.

Regulatory Procedure

Essentially all existing legislation provides a stepwise approach for authorization of orphan drugs. First, orphan designation has to be obtained for a product under development for a specified orphan disease. As soon as the development has been completed, the product is granted marketing authorization.

It is evident from this procedure that orphan designation cannot be obtained after the product has been authorized for the respective orphan indication. In 1988, the US act was amended to require sponsors to apply for orphan designation before submitting a marketing application. Similarly, the EU legislation explicitly states that the request for designation has to be submitted before the application for marketing authorization is made. In Australia, authorization prior to 1 January 1998, the date when Orphan Drug Policy became effective, is the relevant cut-off date.

The request for designation in the US should comprise a description of the rare disease as well as a demonstration that its prevalence is below the defined threshold, a description of the product, the scientific rationale for the drug's use for this condition and, if applicable, a demonstration of the medical plausibility, as well as some formal information. Essentially the same information is required for designation in the EU. The seriousness of the disease must be demonstrated, information on alternative treatment should be provided and the potential benefit for the patients must be justified. Furthermore, an overview of the development is requested.

Interestingly, Switzerland plans to allow a sponsor to refer to orphan designations elsewhere if the sponsor demonstrates the product intended for the Swiss market is identical to the reference product. For purposes of designation as an orphan drug in Australia, the product must not have been rejected on safety grounds by the Australian Therapeutic Good Administration (TGA), the US Food and Drug Administration (FDA), the UK's Medicines and Healthcare products Regulatory Agency (MHRA), Sweden's Medicinal Product Agency (MPA), the Netherlands' Medicines Evaluation Board (MEB) or the European Medicines Agency.

In Japan, the applicant should have a clear product development plan and scientific rationale to support the need for the drug of interest.

After designation is obtained, the product can be authorized as an orphan drug (or orphan medicinal product in the EU nomenclature). It should be noted that authorization of orphan drugs generally follows the same regulatory procedures and principles as non-orphan drugs. Safety and efficacy must be demonstrated adequately, and quality must be appropriate. However, some requirements of the approval process are eased. For instance, in certain cases, it is acceptable for studies to be statistically underpowered due to the fact that few patients are available. Still, statistical significance should be demonstrated.

Depending upon the country or region, orphan drugs automatically qualify for particular authorization processes, such as accelerated or priority review. This is discussed in more detail in the section on incentives for orphan drugs on page 83.

Australia's TGA will usually accept the same data submitted to FDA if the product has been registered as an orphan drug in the US, as long as additional, country-specific information on manufacturing and labeling is provided. In cases where the authorization was rejected by FDA due to safety concerns, TGA will accept the application if it includes additional data that address the objectives raised by FDA. This means implicitly that in the absence of such information, such authorization requests may not be submitted to TGA.

Orphan Diseases

Orphan drugs (or orphan medicinal products) are intended for the treatment, diagnosis or prevention of orphan diseases. The word orphan is derived from the Greek word "orphanos"—a child who has lost one or both parents or a parent who has lost a child.[1] One general understanding of an orphan disease is that it describes diseases neglected by doctors—orphan of the medical community. In a stricter sense, it designates diseases that affect only a small number of individuals. In fact, the latter principle is a cornerstone in the definition of an orphan disease in Australia, Japan, the US and the EU, as will be outlined in the following section.

Still, there are other reasons for a disease's being neglected by the pharmaceutical industry or medical community. One is that a drug might be intended for the treatment of the disease but no return on the investment to develop the drug can be expected. Such principles are explicitly included in the legislation in the US and the EU, but in real life, the return on investment is only of minor relevance and therefore not discussed here in detail (in fact, no examples for drugs based on this justification exist in the EU, and there is only one in the US).

A particular case for such a disease could be if it is endemic to countries with little economic power or lacking a substantial pharmaceutical industry. This is typically the case for many tropical diseases. For instance, hundreds of millions of people in Africa are infected with the malaria parasite *Plasmodium falciparum* annually. Since

resistance of the parasite to currently existing drugs is increasing, there is an urgent medical need for new drugs. However, the efforts of most pharmaceutical companies are limited because the threat of malaria tropica in major pharmaceutical markets is primarily infected travelers. Currently, it appears there is a trend for pharmaceutical companies to concentrate more on tropical diseases than in recent decades. In addition, FDA issues priority review vouchers to sponsors of certain tropical disease product applications that sponsors may use themselves or transfer to another manufacturer.

No general definition of the criteria for orphan diseases exists in countries with particular orphan legislation except the disease's rarity. Some legislation requests that the medical need be demonstrated. The EU *Orphan Regulation* states that the applicant shall demonstrate that the condition is life-threatening, seriously debilitating and/or serious and chronic. In addition, there should be no satisfactory method of diagnosis, treatment or prevention authorized in the EU or—in case such methods exist—the product in question must offer significant benefit to the patients (significant benefit might be greater efficacy, an improved safety profile, improved pharmacokinetic properties, compliance-promoting features or evidence of fewer interactions with food or medicinal products). The latter principle of lack of treatment alternatives or superiority to other treatments for the orphan disease is also included in the Japanese orphan legislation, but not in the Australian. This principle was not included in the original US legislation; however, a 1992 amendment to the act added a requirement to demonstrate clinical superiority to any authorized orphan drug for the same disease (it should be noted that non-orphan drugs might also be available for the treatment of orphan diseases, e.g., for historical reasons).

The scope of an orphan disease might also be viewed differently in different countries or regions. For instance, there is an important distinction in the definition of orphan diseases or conditions in the US and the EU. In the EU, the use of subgroups or degrees of severity is strongly discouraged. This avoids having a sponsor define a subgroup of a disease that fulfills the orphan criteria simply to take advantage of the incentives, despite the fact that the product is expected to be active in the broader population. In such a circumstance, the sponsor normally should apply for the broader condition. It should be noted that there are examples where subgroups received orphan designation in the EU, but the number is limited, and the designation process is typically more cumbersome. The US legislation also states that the plausibility of a subset has to be demonstrated, but the European interpretation is stricter. For example, "treatment of stage III and IV melanoma" has been recognized as an orphan disease in the US. In the EU, the applicant would have to demonstrate why the drug is not expected to be active in the treatment of stage I and II melanoma. If this is not possible, the application would have to be extended to "treatment of melanoma" (which does not fulfill the EU prevalence criteria).

Prevalence of Orphan Diseases

The common characteristic for an orphan disease is rarity, i.e., the prevalence must fall below a certain threshold. However, there is no generally accepted definition of such an epidemiological threshold.

The epidemiological threshold for orphan diseases is no more than 200,000 cases in the US, not more than 2,000 cases in Australia and a maximum of 50,000 cases in Japan. Interestingly, these figures refer to absolute patient numbers. In consequence, the fraction of patients suffering from the orphan condition in relation to the total population varies with changes in the total population number. For instance, when the orphan legislation was introduced, the US population comprised approximately 250 million people. This meant the prevalence (i.e., total number of cases of the disease in the population at a given time, or the total number of cases in the population, divided by the number of individuals in the population) for an orphan disease was not more than 8.0 per 10,000 people. Today, while the population has increased to more than 300 million, the prevalence has decreased to 6.7 per 10,000 people. Thus, the relative rarity of an orphan disease is apparently increasing with an increasing population.

In contrast, the EU threshold is defined on the basis of the prevalence, rather than total patient number. Orphan diseases from a European perspective affect not more than five people per 10,000 in the general population (this threshold also applies in Switzerland). This is a reasonable approach given the ongoing expansion of the EU and consequent continuing population increase. When the orphan legislation was introduced in 2001, the total EU population was approximately 400 million, corresponding to a maximum of 200,000 patients suffering from a particular orphan disease. Today, approximately 500 million people live in EU Member States (MSs), resulting in a maximum number of approximately 250,000 patients per orphan disease. If the threshold were defined on the basis of total patient numbers, the possibility exists that drugs would lose their orphan status if the total population increased, despite the fact that the prevalence of the disease is unchanged.

Table 8-1 presents an overview and comparison of the different prevalence criteria. These data show that the strictest criteria are in Australia (1.0 per 10,000) while the World Health Organization's (WHO) definition is the most liberal (up to 10 per 10,000).

Table 8-1. Epidemiologic Thresholds of Orphan Diseases in Various Countries/Regions

Country/ Region	Number of Cases	Prevalence
US	200,000	6.5 per 10,000*
Japan	50,000	1.5 per 10,000*
Australia	2,000	1.0 per 10,000*
EU	250,000#	5.0 per 10,000
WHO definition	4.3 – 6.6 mil#	up to 10 per 10,000

** calculated on the basis of number of cases and current population*
 # calculated on the basis of prevalence and current population

Incentives

Each country with established orphan medicinal product legislation offers incentives to companies that develop drugs to treat orphan disorders. These measures are intended to motivate companies to invest in these diseases by negating the impact of expected low product sales due to the rarity of the disease. Several measures explicitly address this economic issue:

- market exclusivity
- fee reductions
- tax incentives
- support of research and development activities

One of the most important incentives is market exclusivity granted to the sponsor for the orphan drug's use in the treatment, prevention or diagnosis of the orphan disease after the product is authorized. The exclusivity period is 10 years in the EU and seven years in the US. In the EU, the exclusivity includes not just the product itself, but also similar products, to protect the sponsor from "me-too" approaches. Note that this protection does not apply to cases in which a similar product offers significant benefit for patients. In Japan, the applicant will be granted a 10-year period of marketing exclusivity during which no generic versions of the drug may be placed on the market. However, 10 years is the maximum period of marketing exclusivity; it is possible that the Ministry of Health, Labour and Welfare (MHLW) could reduce this period, depending upon circumstances. In contrast, no particular exclusivity is included in the Australian legislation.

For obvious reasons, such exclusivity is of particular importance for products not covered by any patent, since it protects the sponsor against potential imitators.

Japan offers sponsors unique financial support allowing them to receive financial aid from the government for collecting supporting data, such as clinical trials, bridging studies, etc.

Tax incentives are another inducement to develop orphan products. In the US, sponsors may claim 50% of clinical trial costs as a credit against taxes owed. In Japan, the applicant may receive tax exemptions of up to 6% of research costs and 10% of corporate tax. No uniform tax regulation exists in the EU. Instead, this is dealt with at the national level in the different MSs. For instance, in France, sponsors of orphan medicinal products are exempted from taxes on direct sales or distribution of medicines. Similarly, special reimbursement procedures for orphan medicinal products are defined on a national level (e.g., in Italy, reimbursement is granted for all orphan drugs authorized under the Centralised Procedure (CP)). Tax incentives are not included in the Australian orphan legislation.

Several measures have been introduced to simplify the development and authorization processes for orphan drugs. These include Scientific Advice from the regulatory bodies or eligibility for particular authorization procedures.

Scientific Advice or protocol assistance is offered to sponsors of orphan drugs by FDA, MHLW and the European Medicines Agency but not by TGA. Orphan drug sponsors can obtain written recommendations from FDA concerning clinical and preclinical studies in order to register the new drug. In the EU, free Scientific Advice is also offered by the European Medicines Agency for the development of orphan medicinal products. This is called "protocol assistance." In addition, several EU MSs offer free Scientific Advice for orphan medicinal products independent of the Community-wide European Medicines Agency advice. Similarly, MHLW has a free consultation service specifically for orphan drug designation applicants. In contrast, no such procedures are offered by Australian authorities.

FDA offers a fast-track procedure to evaluate registration files. This procedure involves close sponsor interaction with FDA, resulting in an improved understanding of the information needed for registration and a chance to obtain marketing authorization faster and, potentially, with a less-comprehensive development program (accelerated approval).

Orphan products automatically qualify for the CP in the EU, which covers all EU MSs (plus Liechtenstein, Iceland and Norway). In fact, this procedure is mandatory for orphan medicinal products. The idea is that a product intended to treat a rare disease should be available to all patients. In Australia, orphan products are eligible for priority review. This means that marketing authorization applications are handled as quickly as possible, but there are no abbreviated time lines such as those in the US legislation for priority review or in the EU for accelerated assessment. In Switzerland, products for the treatment of rare diseases are eligible for a simplified authorization procedure. The application will be placed on a fast-track approvals process in Japan, which generally proceeds much

Table 8-2. Overview of Different Orphan Drug Legislation

	US	Japan	Australia	EU
Legal basis	*Orphan Drug Act* (1983)	*Orphan Drug Regulation* (1993)	Orphan Drug Policy (1998)	Regulation 141/2000/ EC (2000)
Competent Authority	Food and Drug Administration (FDA) Office of Orphan Products and Development (OOPD)	Ministry of Health, Labour and Welfare (MHLW) Orphan Drug Division	Therapeutic Good Administration (TGA)	European Medicines Agency Committee for Orphan Medicinal Products (COMP)
Prevalence threshold	200,000 patients	50,000 patients	2,000 patients	5 patients per 10,000 in the general population (corresponding to approximately 250,000 cases in total)
Prevalence per 10,000	6.5	4	1.0	5
Absence of adequate treatment alternatives	No	Yes	No	Yes
Market exclusivity	7 years	10 years	No particular exclusivity period	10 years
Tax incentives	50% for clinical studies	Exemptions of up to 6% of research costs and 10% of corporate tax	No	National measures of the different MSs
Fee reduction	No		100% waiver of evaluation fee	100% waiver of fees for Scientific Advice Fee reduction for pre- and postauthorization activities (including marketing authorization fees)
Research grants	Yes	Financial support of development	No	European framework programs and national funding
Authorization peculiarities	Fast-track procedure	Fast-track approval process	Priority review	Centralised Procedure

more smoothly than that of regular drugs. In theory, the fast-track approval process takes 10 months while the approval for regular drugs takes 12 to 24 months.

Research grants are another means to support the development of drugs for the treatment of orphan diseases. For instance, in the US, FDA's Office of Orphan Products and Development (OOPD) funds development through clinical study grants. Academic institutions and other responsible organizations are eligible for such grants, and small companies are also encouraged to apply. In the EU, an orphan drug sponsor can apply for European framework programs and national grants. No such support is available for the development of orphan drugs in Australia.

Summary

Orphan drug legislation always consists of the combination of the product and the intended therapeutic indication (the particular orphan disease). Such legislation has been introduced in the US, Japan, Australia and the EU. Each piece of legislation defines the orphan disease

by its rarity (although the thresholds vary significantly). Other characteristics, such as the severity of the disease, are included in the definition of an orphan disease in some countries.

In general, the Australian orphan legislation is similar to that in the US, while the principles in effect in the EU share many characteristics with the Japanese regulation. Prevalence thresholds are different in all four countries/regions.

It appears that there is only moderate benefit resulting from the orphan legislation in Australia. This is due to the fact that no market exclusivity or tax incentive is granted, while they have the most stringent prevalence threshold for the orphan condition. It is difficult to say where the orphan incentives are most pronounced: market exclusivity extends the longest in Japan and the EU. On the other hand, these areas have a more challenging definition of an orphan condition than the US.

A comparison of different features of orphan drugs and orphan diseases in different countries/regions is presented in **Table 8-2**.

Overall, it appears that orphan legislation has stimulated product development in these neglected therapeutic fields. Today there are more than 300 orphan drugs authorized in the US. In the eight years since orphan legislation was introduced in the EU, 50 orphan drugs have been authorized. Of course, it is difficult to say whether this development would have taken place without orphan legislation. But, the large number of development projects under an orphan designation clearly indicates that these principles are appreciated by the pharmaceutical and biotech industries.

References

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