Łódź, 05.01.2022

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Orphan drugs registration. Designing a clinical trial for an orphan drug

Praca poglądowa w ramach specjalizacji z farmacji klinicznej

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Introduction

Currently there are more than 6 000 rare diseases known for their chronic and debilitating effects, affecting up to 8 % of the population. In total, these conditions end up being quite common — they affect an estimated 25 million people in the U.S. and 30 million in Europe. Most of the diseases affect less than 1 in 100,000 people. Genetic origin has been identified for 80 % of rare diseases, affecting 3 – 4 % of births. Other rare diseases occur due to degenerative and proliferative causes. Medical and scientific knowledge about rare diseases is insufficient. Despite numerous scientific publications about rare diseases, less than 1 000 diseases benefit from at least minimal amounts of scientific knowledge.

Rare disease does not have one definition worldwide. Prevalence threshold differs from 5 to 76 per 100,000 people depending on jurisdiction.

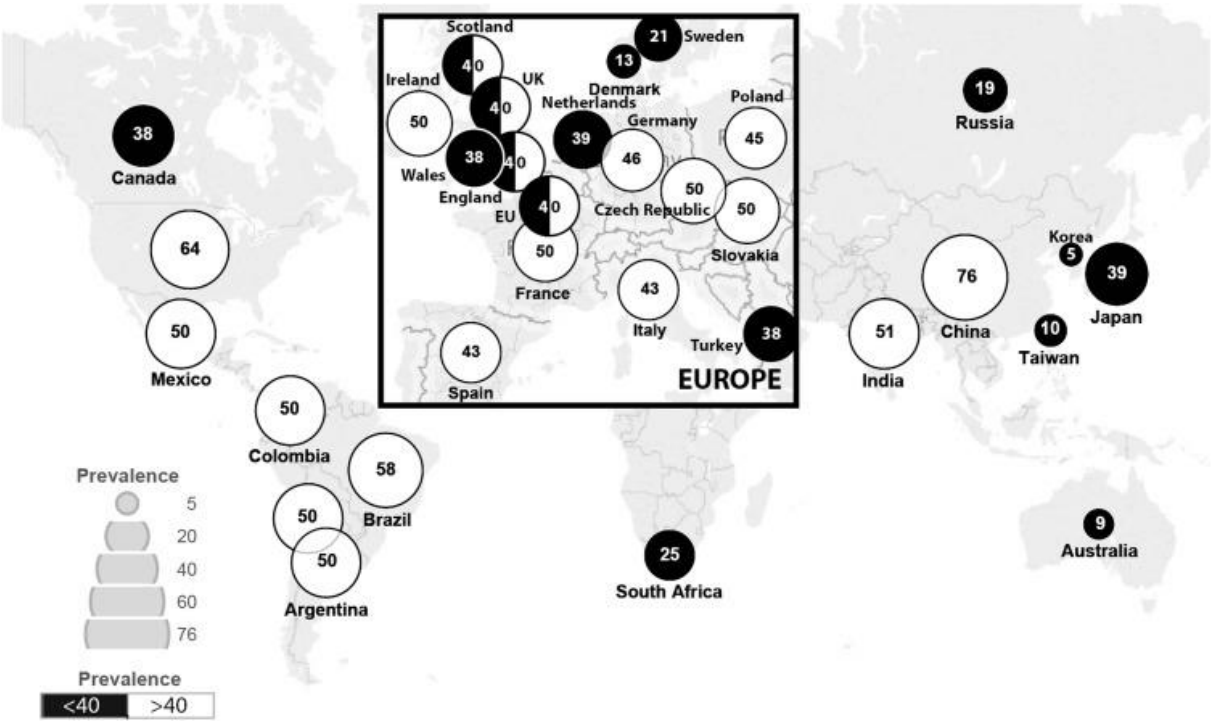

Fig. 1. Regional distribution of prevalence thresholds for jurisdictions across the world. The size of the circles corresponds to the average prevalence threshold (number of cases per 100,000 people) for all organizations within a jurisdiction. Black and white circles correspond to jurisdictions in which the average prevalence in definitions of rare disease is lower or higher, respectively, than the average of 40 cases/100,000 people.[1]

The definitions of rare diseases by the major Organizations are listed in the table below:

Jurisdiction	Organization	Definition of rare disease
United States	Food and Drug Administration	The term "rare disease or condition" means any disease or condition that (A) affects <200,000 persons in the United States, or (B) affects >200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.
European Union (EU)	European Medicines Agency	Rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU.
Japan*	Ministry of Health, Labour and Welfare (MHLW)	The number of patients who may use the drug or medical device should be <50,000 in Japan. *less than 3.9 per 10,000 individuals

Fig 2: Differences in definition of rare disease, depending on jurisdiction (Source: EMA's website)

Orphan drug is defined as a medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare or where the medicine is unlikely to generate sufficient profit to justify research and development costs.

Across Europe, the uptake of available orphan drugs varies considerably. The lowest demand is generally observed in countries with lower gross domestic product (GDP) per capita or severe budgetary restrictions on public health expenditure. Many factors can contribute to the limited use, including low levels of physician awareness, the inaccessibility of diagnostic tests, the lack of certainty about innovative treatment options and/or relatively limited experience. Moreover, the price of orphan drugs is often considered a factor contributing to delayed or limited access to these drugs. Orphan drugs are expensive, and some treatments can cost more than € 500,000 per patient per year. However, as the number of patients treated is usually very low, the total expenditure on orphan drugs now accounts for only a fraction of the total drug budgets. On average across Europe, orphan drugs accounted for around 5.1% of total drug expenditure in 2019, of which biological drugs accounted for around 32% of total orphan drug expenditure in 2019 (compared to 21% in 2014) [2, 3].

The market of orphan drugs may be an interesting area for companies producing biosimilars. In 2020, a total of 1762 orphan designations were granted, and 148 orphan drugs were registered in Europe. From 2020 to 2029 biological orphans will lose their exclusivity. What is more, the five orphan biological medicines, which will expire in 2024, generate around € 500 million per year across Europe [4].

Legislation Background

The problem of Orphan drugs was addressed in USA first, when the Orphan Drug Act was published in 1983. In Europe, first Directive about the orphan drugs was published in 2000. From the publication of original Acts, many additional regulations were established over years, creating clear rules of orphan drugs development and registration.

Europe

The following regulations addressed the issues related to rare diseases and orphan drugs development:

Regulation (EC) No 141/2000 (the Orphan Regulation)

- Procedure for designation of orphan medicines and removal from the register
- Incentives for the development of the designated orphan medicines and placing them onto the market
- Establishment of the **Committee for Orphan Medicinal Products (COMP)**

Regulation (EC) No 847/2000

- Definitions essential for the Orphan Regulation
- Detailed Designation Criteria

Regulation (EC) No 726/2004

- Procedures for the authorization and supervision of medicinal products for human and veterinary use - the legal framework for the centralized authorization and supervision
- Establishment of **European Medicines Agency (EMA)**
- Definition of similar medicinal product, similar active substance and clinical superiority.
    - **Similar medicinal product** – a medicinal product containing a similar active substance or substances as a currently authorized orphan medicinal product, and which is designed for the same therapeutic indication
    - **Similar active substance** – an active substance which is identical or has the same main features of the molecular structure (not necessarily all the same molecular features) and which acts through the same mechanism

Regulation (EC) No 507/2006

- The legal framework for the granting of a conditional marketing authorization to medicines that fall within the scope of Regulation (EC) No 726/2004.
- A conditional marketing authorization possible for orphan medicines

Regulation (EC) No 2049/2005

- Determines the fees to and assistance from the EMA by micro, small and medium-sized enterprises (SMEs)
- Scientific advice and scientific services for designated orphan medicines provided by the EMA to SMEs free of charge

Regulation (EC) No 1901/2006

- Establishment of Pediatric Committee within the European Medicines Agency
- The extension of usual period of market exclusivity for orphan medicines to 12 years if study results are submitted in compliance with an agreed pediatric investigation plan at the time of marketing authorization

Commission notice 2016/C 424/03

- Intended to facilitate the application of Articles of Regulation (EC) No 141/2000
    - Article 3 (criteria for designation)
    - Article 5 (procedure for designation and removal from the register)
    - Article 7 (Union marketing authorization)[5, 6]

USA

Orphan Drug Act

- 4 January 1983

The 1984 amendment

- Defined the concepts of low incidence
- Established the definition of rare disease or circumstance:
    - Affects less than 200 000 individuals in the USA
    - Affects more than 200 000 individuals in the USA, but it is impossible to cover the cost of development and distribution by sales on national territory
    - Limit of prevalence for a rare condition: 7,5/10 000

The 1985 and 1990 amendments

- The definition of orphan product extended to products other than drugs and in particular: biologics, medical devices and medical foods, mainly parenteral nutrition, and nutraceuticals.

The 1988 amendment

- The conditions under which an application for orphan drug status can be submitted
- Orphan drug status: for a disease or a condition

The 1992 amendment

- If the drug is possibly similar to an orphan drug already authorized for the same rare disease, the applicant must prove the clinical superiority of this drug. Then, the new drug is considered in the same way as a new active ingredient.
- The efficacy of the drug must be established regarding prevention, diagnosis, or treatment of this disease.
- More than one sponsor can receive designation for the same drug for the same use
- The seven-year marketing exclusivity is given to the first sponsor to file a complete NDA. Other sponsors are not prevented from developing the drug available for different uses during the seven-year period of exclusivity[7, 8]

Comparison of the various policies on orphan drugs worldwide is presented in the table below:

	USA	**UE**
Legal Framework	Orphan Drug Act (1983)	Regulation (EC) No 141/2000
Administrative authorities involved	FDA/OOPD	EMA/COMP
Prevalence of the disease (per 10 000 individuals), justifying the orphan status	7,5	5
Estimation of the affected population, prevalence rate (per 10 000 individuals)	20 million (7,3)	25-30 million (6,6-8)
Marketing exclusivity	7 years	10 years
Tax credit	yes (50% for clinical studies)	Managed by member states
Grants for research	programs of NHI and others	„FP6” + national measures
Reconsideration of applications for orphan designation	No	Yes (every 6 years)
Technical assistance for elaboration of the application file	Yes	Yes
Accelerated marketing procedure	Yes	Yes (via the centralized procedure)

	Australia	Japan
Legal Framework	Orphan Drug Policy (1998)	Orphan Drug Regulation (1993)
Administrative authorities involved	TGA	MHLW/OPSR
Prevalence of the disease (per 10 000 individuals), justifying the orphan status	1,1	4
Estimation of the affected population, prevalence rate (per 10 000 individuals)	No information	No information
Marketing exclusivity	5 years	10 years
Tax credit	No information	yes (6% for any type of study + limited to 10% of the company's corporation tax)
Grants for research	No information	governmental funds
Reconsideration of applications for orphan designation	yes (every 12 months)	yes
Technical assistance for elaboration of the application file	No information	yes
Accelerated marketing procedure	yes	yes

FDA	Food and Drug Administration
OOPD	Office of Orphan Products and Development
MHLW	Ministry of Health, Labour and Welfare
TGA	Therapeutic Good Administration
EMA	European Medicines Agency
COMP	Committee for Orphan Medicinal Products
NIH	National Health Institute

Submission process

Europe

Orphan designation

The procedure relating to orphan medicinal products consists of two separate phases:

1. **Designation**, which:
    a. can take place at any stage of development prior to the submission of a marketing authorization application, if the sponsor can establish that the designation criteria are met
    b. has no effect on parallel developments by different sponsors
    c. is a tool to identify candidate products in a transparent way and to make them eligible for financial incentives
    d. is confirmed by a separate Commission decision for each candidate product (the designated product is entered in the Community Register for Orphan Medicinal Products
2. **Marketing authorization[5]**

Orphan designation does not itself allow the use of a medicine; it just signals that the medicine looks promising. There might be little or no proof that it works in patients. Only marketing authorization ensures that the medicine has EMA's confidence of efficacy and acceptable safety. Generally, the application for orphan designation comes quite early in the medicine's development – the medicine is considered for marketing authorization only when solid evidence of its effects is reported. Giving orphan designation helps ensure that medicines for rare diseases are developed at all, but not necessarily to speed up such development [9].

Exceptionally, a physician might consider using the medicine before it has its marketing authorization, for example through a compassionate use program (so-called "off-label use"). When considering use of a

medicine without marketing authorization, the patient and the doctor need to be fully convinced that there is no other suitable treatment option, including leaving the condition untreated [10].

To qualify for orphan designation, a medicine must meet several **criteria**:

- It must be intended for the treatment, prevention, or diagnosis of a life-threatening or chronically debilitating disease
- The prevalence of the condition in the EU must not be more than 5 in 10 000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development
- There is no satisfactory method of diagnosis, prevention or treatment of the condition concerned, or, if such a method exists, the medicine must bring significant benefit compared with existing methods [6, 11].

All designated orphan medicines may be assessed for marketing authorization in the European Union in the centralized procedure, through a single application to the EMA, resulting in a single opinion and a single decision from the European Commission, valid in all EU Member States. Sponsor's may also have access via orphan designation to conditional approval, which is also conducted under the centralized procedure[5].

Applications for orphan designation are assessed by the EMA's **Committee for Orphan Medicinal Products (COMP)**. The evaluation process takes a maximum of 90 days.

Obtaining an orphan designation by a pharmaceutical company is associated with number of **incentives** from the EU, such as reduction of fees and protection from competition once the medicine is placed on the market. Sponsors must use EMA's secure online **IRIS platform** for submitting applications for orphan designation and managing all pre- and post-designation activities.

Applications for orphan designation are free of charge. The sponsor may submit an application for orphan designation to the EMA at any stage of development of the medicinal product before the submission of the application for marketing authorization. It is possible to make a request for orphan medicinal product designation for an already authorized medicinal product only if the designation request concerns a new orphan indication (not currently authorized)[6, 11].

Sponsors should follow one of the two options below to submit an application for orphan designation:

1. Directly submit an application to EMA, through the IRIS system
2. Request a pre-submission meeting/teleconference[6]

EMA strongly encourages sponsors to request a pre-submission meeting with the Agency prior to filing an application. Pre-submission meetings usually take place via teleconference. A sponsor can request a pre-submission meeting/teleconference at least 2 months prior to their planned submission date via the IRIS portal. Two coordinators are assigned to each application: one member of the COMP and one scientific administrator from the EMA secretariat. EMA validates the application and sends the sponsor a validation issues letter explaining if the application is considered incomplete or invalid. Once the validation is complete, the Agency will send a timetable for the evaluation procedure to the sponsor. EMA advises sponsors developing advanced therapies to apply separately to the Committee for Advanced Therapies (CAT) to have their medicine classified as an advanced-therapy medicine[6].

Evaluation of applications

The assigned coordinators prepare a summary report on the application, which is distributed to all COMP members and discussed at the COMP's next plenary meeting, and the COMP will either adopt a positive opinion or prepare a list of questions. The sponsor is invited to an oral explanation at the next COMP plenary meeting. The COMP’s opinion should be adopted by day 90 of the procedure. Then it is forwarded to the

European Commission for adoption of a decision. If the outcome for an application is negative, the COMP adopts a negative opinion, unless the sponsor decided to withdraw the application. Information on the orphan designation is published by EMA, and the orphan designation is entered into the Community register of designated orphan medicinal products by European Commission. Sponsor may make a request for orphan designation for a new indication for an already authorized medicinal product. However, at the stage of applying for the marketing authorization, an application for a separate marketing authorization for the orphan indication is required. The extension of the existing marketing authorization to cover the new orphan indication is not possible - orphan and 'non-orphan' indications may not be covered by the same marketing authorization [6, 11, 12].

Orphan designation in the product lifecycle

<table>
<tr><th>Research and development</th><th>Marketing authorisation</th><th>Post-authorisation</th></tr>
<tr><td colspan="3">Orphan incentives</td></tr>
<tr><td>Applying for orphan designation</td><td colspan="2"></td></tr>
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<tr><td rowspan="2"></td><td colspan="2">Applying for marketing authorisation</td></tr>
<tr><td></td><td>Market exclusivity</td></tr>
</table>

Source: EMA's website

Sponsor must submit an annual report to the European Medicines Agency (EMA) via IRIS system every year after receiving an orphan designation, until the submission of an application for marketing authorization. It is not necessary to submit any documents, only the requested fields in IRIS system must be completed. If appropriate, additional documents can be uploaded (e.g.: review of ongoing clinical studies, investigation plan for the next year, current difficulties in the process)[6].

Orphan incentives

The range of incentives is offered in the European Union (EU) for medicines that have been granted an orphan designation by the European Commission.

Scientific advice

The EMA provides scientific advice on the most appropriate way to generate robust evidence on medicine's benefits and risks, to support development of high-quality, effective, and safe medicines. At any stage of a medicine's development, a developer can ask guidance and direction from EMA on the best methods and study designs to generate robust information on efficacy and safety, regardless of whether the medicine is eligible for the centralized authorization procedure or not.

The scientific advice is given by responding to specific questions posed by the developer on the development of a particular medicine. The developer presents plans for development of the medicine and proposes the questions and possible solutions. Then, EMA gives advice on the developer's proposals. Scientific advice from EMA is not legally binding with regard to any future marketing authorization applications for the medicine concerned.

Protocol assistance

A form of scientific advice that EMA provides specifically for orphan medicine. Sponsors can get answers to their questions on the types of studies required to demonstrate the quality, risks, and information on the significant benefit of the medicine or clinical superiority over other medicines. Protocol assistance is available at a reduced charge. The number of times a sponsor can request protocol assistance is unlimited.

For human medicines, both scientific advice and protocol assistance are provided by the Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP).

Parallel scientific advice (PSA) with the United States

The EMA provides scientific advice and protocol assistance in parallel with the FDA. The goal is to provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics). General principles of the procedure are defined in document EMA/309801/2017

Tailored scientific advice on biosimilars

The tailored scientific advice pilot project was implemented to support the development of new biosimilars, by advising developers on the research they should carry out, based on a quality review, and available analytical and functional data.

Fees and fee reductions

Fees charged by EMA may be reduced for certain types of medicines and applicants, including a 75% fee reduction for orphan medicines and even 90-100% fee reduction in case of SMEs.

Examples of current basic fees are shown in the table below:

Fee type	Human medicines	Veterinary medicines
Marketing-authorisation application (single strength, one pharmaceutical form, one presentation)	From €296,500	From €148,400
Extension of marketing authorisation (level I)	€89,000	€37,100
Type-II variation (major variation)	€89,000	€44,400
Scientific advice	From €44,400 to €89,000	From €14,600 to 44,400
Annual fee (level I)	€106,300	€35,600
Establishment of MRLs	-	€73,800

Source: EMA's website

Free rapid scientific advice for COVID-19 treatments or vaccines

EMA has established a rapid scientific advice procedure for potential COVID-19 treatments and vaccines, which is free of charge. Review time is reduced from 40 – 70 days to a maximum of 20 days, with no submission deadlines.

EMA and the COVID-19 EMA pandemic Task Force provide early guidance to sponsors whose development plan is not yet suitable for formal rapid scientific advice.

Market exclusivity

Once they receive a marketing authorization, orphan medicines are covered by ten-year protection from market competition for the particular indication. This protection may be extended by two years, for the medicines with a valid and completed pediatric investigation plan (PIP) at the moment of review of the orphan medicine designation. The PIP is a development plan to ensure that the necessary data are obtained through studies in children to justify a drug's approval for pediatric use. All applications for marketing authorization for new medicines must contain the study's results described in the agreed PIP, unless the drug is excluded because of a postponement or a waiver. This requirement also applies when the holder of marketing authorization wants to add a new indication, pharmaceutical form, or administration route for an already authorized and covered by intellectual property rights medicinal product.

For drugs with multiple orphan designations, each designation is covered by separate market exclusivity period. To benefit from market exclusivity, a medicine must maintain its orphan designation at the time of marketing authorization. The orphan designation for an indication expires when the period of market exclusivity for this indication ends. Then, the European Commission removes it from the Community register of orphan medicinal products.

Additional incentives for micro, small and medium-sized enterprises (SMEs)

Further incentives are available for companies developing medicines with orphan designation, which are classified as SMEs, including fee reductions and administrative and procedural assistance from the Agency's SME office, for example:

- Direct assistance (phone, email, teleconference or briefing meetings) on regulatory aspects of the pharmaceutical legislation
- Assistance with translations of product information into all official European Union (EU) languages in the process of initial marketing authorization
- Inclusion in an online SME register - an important source of information on EU/European Economic Area-based SMEs, also promoting partnering and networking between SMEs
- Guidance on clinical data publication and a free redaction tool license[5, 6, 13, 14]

Grants

Funding of research grants for orphan medicines is available from the European Commission and other sources:

- Horizon 2020, the EU Framework Programme for Research and Innovation (the theme „Personalising Health and Care" which covers New therapies for rare diseases)
- E-Rare, a transnational project for research programmes on rare diseases

Activities after orphan designation

Sponsors are obliged to submit to the Agency an annual report on development, summarizing the status of development of the medicine. What is more, it is necessary to submit an application for maintenance of the orphan designation at the moment of marketing authorization, to be qualified for the ten-year market

exclusivity. There is a possibility to transfer an orphan designation from one sponsor to another. Transfers are free of charge. Removal of an orphan designation can also be requested. All post-designation activities, including annual reports, are conducted via EMA's IRIS system [5, 9, 15].

Orphan similarity

Before submitting an application for a marketing authorization, whether or not the medicinal product is designated as an orphan, the applicant should check the Community Register of Orphan Medicinal Products for information on medicinal products with an orphan designation, which are under market exclusivity protection. If any of the designated orphan medicinal products have obtained a marketing authorization in the EU and the market exclusivity period is in force, the sponsor should enclose to the marketing authorization application a similarity report on the possible similarity between the new medicinal products and the orphan medicinal product (or products) with a marketing authorization.

A marketing authorization may be given for the same therapeutic indication for a similar medicinal product in three cases:

- There is a consent of the holder of the marketing authorization for the original orphan medicinal product
  - A signed letter from the holder of authorized orphan medicinal product confirming the consent for the second applicant must be included to application for marketing authorization
- The holder of the marketing authorization for the original orphan medicinal product is not able to supply sufficient quantities of the medicine
  - The report describing the reason why the supply of an authorized orphan medicinal product is insufficient should include details of the supply problem and an explanation of why the supply is not sufficient to meet the needs of patients in the orphan indication
  - All claims should be justified by qualitative and quantitative references
- The applicant is able to show in the application that the other medicinal product, although similar to an orphan medicinal product that has already been authorized, is safer, more effective, or otherwise clinically superior

Based on definitions mentioned in Regulation (EC) No 847/2000, the similarity assessment between two medicinal products is based on the following criteria:

- Principal molecular structural features
- Mechanism of action
- Therapeutic indication

The two products will not be considered as similar, if any significant difference occurs between them within one or more of these criteria.

If the sponsor of an orphan medicinal product submits an application for marketing authorization or an extension to an existing marketing authorization, it is also obliged to submit a **report on maintenance of the orphan designation** via the IRIS system. The report should be submitted after receiving the confirmation that the validation of the marketing authorization application has been completed. The sponsor's report must include data on:

- The current prevalence of the condition to be diagnosed, prevented or treated by the particular medicinal product, or the potential return on investment
- The current knowledge of the nature of the condition (life-threatening or debilitating)
- The current existence of other methods for the diagnosis, prevention or treatment of the condition
- A justification of the significant benefit (if applicable)

Based on the submitted report, COMP determines whether the medicine maintains the status of orphan medicinal product and continue to benefit from market exclusivity. If the opinion is positive, COMP issues an **orphan maintenance assessment report.** If an orphan designation application is still pending at the time of submitting the application for marketing authorization, an orphan designation may be allowed, provided that the orphan designation is approved by the COMP and confirmed by the European Commission (EC) prior to granting of marketing authorization. However, some incentives eligible for orphan medicinal products, such as centralized procedure and fee reduction will not be applicable [6, 11].

USA

Orphan-drug designation

The Orphan Drug Act (ODA) enables granting special status to a drug or biological product to treat a rare disease or condition. This status is called orphan-drug designation (or sometimes "orphan status"). For a drug to qualify for orphan designation the disease/condition must meet certain criteria:

- Affecting less than 200 000 individuals in the USA
- Affecting more than 200 000 individuals in the USA without it being possible to cover the cost of development and distribution by sales on national territory
- The prevalence for a rare condition must be lower than 7,5 / 10 000

A sponsor may request orphan-drug designation of:

- A previously unapproved drug
- A new use for an already marketed drug

What is more, a sponsor of a medicinal product that is otherwise the same as an already approved drug may apply for another orphan-drug designation for the same rare disease or condition if it can put a plausible hypothesis supporting the clinical superiority of its drug. More than one sponsor can receive an orphan-drug designation for the same medicinal product for the same rare disease/condition, but any sponsor applying for an orphan-drug designation must submit a full application for designation.

A sponsor of a drug for a specified rare disease or condition shall submit a request for designation that contains:

- A declaration of application for orphan-drug designation for a rare disease or condition, which should be precisely identified
- The name and address of the sponsor; sponsor's contact data; the name of the drug; the name and address of the source of the drug (if it is not manufactured by the sponsor)
- A description of the rare disease/condition of interest, the proposed use of the drug and the reasons why proposed therapy is needed
- Description of the drug, its physical and chemical properties, if they can be determined, the scientific rationale for establishing a medically plausible basis for a drug use for a rare disease or condition, including all relevant data from in vitro studies, preclinical efficacy studies conducted in an animal model for the disease and clinical experience with the drug in a rare disease or condition accessible to the sponsor, whether positive, negative, or inconclusive. Copies of relevant unpublished and published articles are also required.
- If the sponsor seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug is necessary.
- If the sponsor requests orphan-drug designation for a drug for only a subset of persons with a particular disease or condition that generally affects 200,000 or more people ("orphan subset"), a demonstration that the remaining persons with such disease or condition would not be appropriate candidates for use of the drug, due to its properties

- Summary of the legal status and marketing history of the drug in the US and abroad, e.g.: IND and the status of the application for marketing authorization, indications for which the drug is authorized in other countries, what adverse regulatory actions have been taken against the drug in any country
- Documentation with authoritative references attached to demonstrate:
    - The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year, or
    - For diseases with higher prevalence, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States

To enable the FDA assessment whether a drug is eligible for orphan-drug designation, the sponsor should include in its request for orphan-drug designation documentation confirming that the disease or condition for which the drug is to be developed meets the criteria for a rare disease, or that there is no reasonable expectation that costs of research and development of the drug for the disease or condition can be recovered by sales of the drug in the USA.

Since June 2020, the requests may be submitted online via the **CDER NextGen Portal**.

Every foreign sponsor that seeks orphan-drug designation shall name a permanent resident of the USA as the sponsor's agent upon whom service of all processes, notices, orders, decisions, requirements, and other communications may be made on behalf of the sponsor. The permanent-resident agent may be an individual, firm, or domestic corporation and may represent multiple sponsors. The name of the permanent-resident agent, and all its contact data shall be provided to the Office of Orphan Products Development of FDA. Notifications of changes in such agents or changes of agents' contact data should preferably be provided not later than 60 days after the effective date of those changes[8, 12, 16, 17].

Timing of requests for orphan-drug designation

A sponsor may request orphan-drug designation at any time in its drug development process prior to the time of submitting a marketing application for the drug for the same rare disease/condition. A sponsor may also request orphan-drug designation of an already approved drug for an unapproved use without regard to whether the prior marketing approval was for a rare disease or condition [18].

Deficiency letters and granting orphan-drug designation

If the request for orphan-drug designation lacks required information or contains information which is inaccurate or incomplete, FDA will send a deficiency letter to the sponsor. The sponsor must respond to the deficiency letter within 1 year of issuance, otherwise FDA may consider a designation request voluntarily withdrawn, with no notification in writing. When a request for orphan-drug designation is granted, FDA notifies the sponsor in writing and publishes the orphan-drug designation [18, 19].

Amendment to orphan-drug designation

In case of any unexpected findings in research on the drug, information arising from FDA recommendations, or unforeseen developments in treatment or diagnosis of the disease/condition the sponsor may apply for an amendment to the designated use at any time prior to approval of a marketing application for a designated orphan drug [18].

Refusal to grant orphan-drug designation

FDA refuses to grant an orphan-drug designation for any of the reasons listed below:

- There is no sufficient evidence that the drug is intended for treatment of a disease/condition meeting the criteria of rare disease or the sponsor is unable to demonstrate that development and production costs will not be recovered from sales of the drug for such disease/condition in the US
- There is insufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition
- The information about the drug or the disease/condition is insufficient to determine a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition
- The sponsor has not established a medically plausible hypothesis for the clinical superiority of the drug, if it is bioequivalent or biosimilar to an already approved drug for the same rare disease or condition [18]

Publication of orphan-drug designations

Each month FDA updates a publicly available cumulative posting of all drugs designated as orphan drugs, containing the following information:

- The name and address of the sponsor
- The generic name and trade name, the chemical name, or a meaningful descriptive name of the drug
- The date of the granting of orphan-drug designation
- The designated use in the rare disease or condition [20]

Annual reports of holder of orphan-drug designation

Within 14 months after granting an orphan-drug designation and then annually until marketing approval, the sponsor of a designated drug shall submit a brief progress report to the FDA Office of Orphan Products Development on the drug that includes:

- An information about the progress of drug development including a review of preclinical and clinical studies (initiated, ongoing, and completed) and a short summary of the status or results
- A description of the investigational plan for the next year, including any anticipated difficulties in development, testing, and marketing
- A brief discussion of any changes that may affect the orphan-drug status of the product [20]

Incentives to orphan drugs providers in terms of R&D, intellectual property, and marketing

An orphan-drug status may enable the sponsor to benefit from the following advantages:

- 50% **tax credit** on the cost of clinical trials undertaken in the USA
- Seven-year period of **marketing exclusivity** following the marketing approval
- Some **written recommendations** provided by the FDA about clinical and preclinical studies needed to be completed in order to register the new drug
- **a fast-track procedure** for the FDA to evaluate registration documents

The availability of orphan drugs to patients before being granted a marketing approval is possible. In some cases of compassionate use, a Treatment Investigational New Drug (t-IND) may be obtained if the following conditions are met:

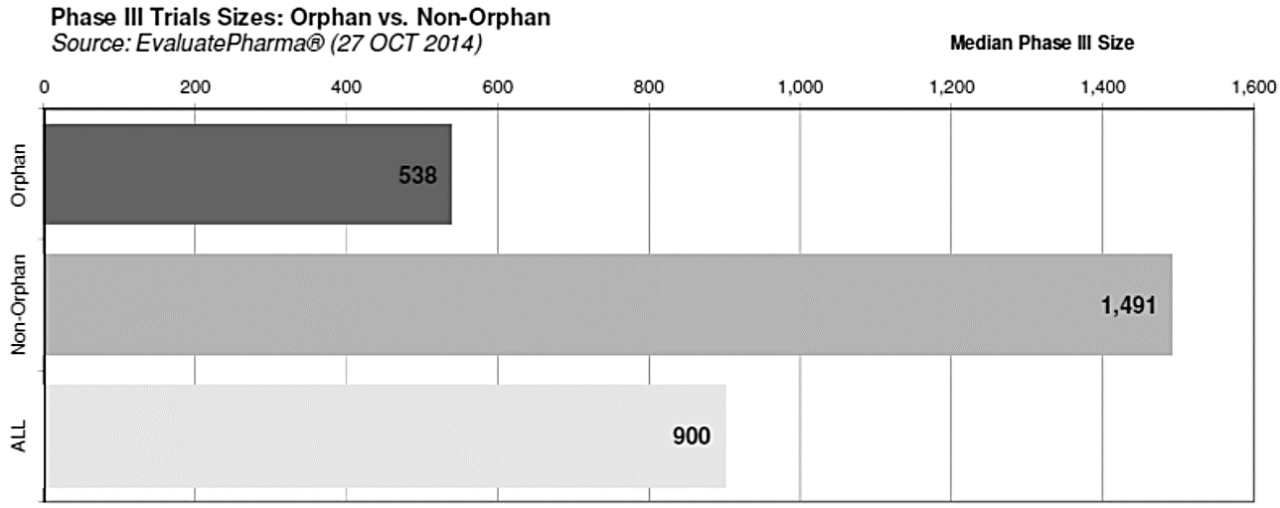
- The drug is intended for the treatment of a serious or life-threatening disease
- No alternative drug or treatment is available
- The product is in the process of clinical trials and in an active phase of marketing approval [12]

Study design for orphan drugs

The USA Orphan Drug Act and EMA Regulation (EC) No 141/2000 (Orphan Regulation) created incentives for pharmaceutical companies to research and create new drug therapies for rare diseases. As a result, the clinical costs associated with the development of an orphan drug are significantly lower in comparison to those associated with non-orphan drugs. From the multitude of new drugs in development with an orphan designation, only a small fraction has reached the market [21].

Despite the research incentives, there are also **unique challenges** associated with running rare disease clinical trials:

Patient Recruitment – Around 30% of Phase III clinical trials fail due to inability to meet enrollment goals. These statistics are particularly prominent in clinical trials of rare diseases where the patient population is not only limited but also scattered around the world. In addition, approximately 50% of rare diseases affect pediatric patients, which is associated with more restrictive ethical and legal requirements for patient recruitment and registration in clinical trials, slowing down recruitment process. Moreover, given the small patient population, it is more difficult to conduct rare disease replication studies [21, 22].



Clinical Trial Design – As the study population is small and often heterogeneous in age, sex, and/or severity of the disease, common methods of designing clinical trials do not show statistical significance and are therefore not suitable for use in rare disease trials. As a result, orphan clinical trials are often nonrandomized, not blinded, and do not use placebo controls. Instead, research into rare diseases uses cross-over, N-of-1 research, and adaptive design. Adaptive designs are the most commonly used, which rely on the analysis of provisional study data to decide how to modify or continue a clinical trial without compromising the integrity of the study [23, 24].

Site Suitability – As patients with rare diseases are scattered around the world, it is necessary to create more research centers adapted to the location of patients. With more research sites, more clinical personnel need to be recruited and trained in order to properly run the study and track patient progress. What is more, the sponsor must ensure that each of the multiple study sites is equipped enough to meet the protocol requirements (freezers, refrigerators, infusion pumps, laminar chambers).

This highlights the necessity to rethink the methodology for designing clinical trials for rare diseases, considering the limitations of sample size impossible to avoid. Randomized controlled trials (RCTs) with one control arm and at least one new treatment arm are the gold standard to prove the treatment efficacy, safety, and benefit-to-risk ratio. The existing statistical methodology is mostly adjusted to large population

surveys. In case of rare diseases, increasing the number of patients for research is not possible and is additionally hampered by the geographical distribution of patients. In addition, the small number of patients limits the investigational options for the same disease. As we may overlook treatment effects in small group when we are using classical statistical methodology, it is necessary to adapt innovative methodologies to clinical trials of rare diseases.

Defining the number of patients required to have a significant effect is an important issue in planning of clinical trials for rare diseases. In all clinical trials, sample size should be planned rationally. The calculation of the sample size requires the collaboration of biostatisticians and researchers with experts in a given field of medicine. Although the sample size depends on external factors such as the duration of recruitment, the prevalence of the disease or the financial issues, the evaluation of the results of the study should be planned on a statistical basis. The attainable power of the test should be calculated during planning (the lower the power of the test, the less chance of proving the hypothesis). According to ClinicalTrials.gov, studies in rare diseases involve an average of several times less patients than in studies in other diseases, and there is active recruitment to a much smaller percentage of studies. In clinical trials in rare diseases, the sample size must accommodate data loss due to discontinuation or drop-out of patients. A pilot study should be always considered to estimate the relevant population requirements. Planning of sample sizes based on already available data must take into consideration the precision of previous results to avoid overestimating the effects that could result in too small sample size [23, 24].

Methods for reducing sample size also include:

- Extending the duration of the study to get more events with fewer patients,
- Focusing on high-risk patients,
- Additional genetic testing and testing multiple treatment arms in a factorial design.

High hopes are currently placed in using large data collections to replace careful research into the efficacy and safety of treatments in certain indications or sub-indications. In this context the use of historical data from registries or previous RCTs to replace a concurrent randomized control arm is discussed. This approach essentially leads to the conduct of single-arm trials for which new methodology has been proposed to incorporate the historical information.

It must not be forgotten that it is only possible to evaluate the outcome of a single-arm trial if the natural history of disease is fully understood and constant over time. Only then it can be certain that the different results between the experimental treatment and the historical control may only be due to differences between the treatment test and the prior treatment.

In other words, each time a single-arm trial is performed, the investigators assume that the outcome in the control group (placebo or standard of care) is fully known and is not subjected to patient selection or timing effects. Consequently, relying on the counterfactual (expected / hypothetical response in the control group) obtained from registries or historical controls raises two issues:

- The estimated difference between treatment and counterfactual may be biased and the potential disadvantages of using historical controls or records are widely discussed
- When it is assumed that the alternative option is sufficiently well known and a one-arm study is performed, the basic assumption about consistency of past findings and drop-out control is impossible to verify with the study data.

The problem is even more pronounced in the case of rare diseases, where often less information from registries or previous studies is available. Even if the information is available, it will be less accurate than for common diseases and therefore the alternative option is less reliable [21, 23].

The EMA's CHMP guideline marks that "no methods exist that are relevant to small studies that are not also applicable to large studies". However, the guideline also states that less common methodological models may be acceptable in small populations if they can improve the interpretation of the study results. The EMA emphasizes that the trade-off between a small amount of high-quality evidence (from small randomized trials) and a large amount of lower-quality evidence (from larger uncontrolled case series) must be assessed on a case-by-case basis. Applications for marketing authorization for orphan products are assessed according to the same standards as for other products but in respect for the limitations of low patient enrollment. If conducting the randomized controlled trials is not possible, regulators are open to discuss the alternative methodologies and sources of evidence to expand the overall database [6].

The FDA also declares the awareness of the challenges of small population clinical trials on rare diseases. In 2010, a draft of the "Industry Guidelines - Adaptive Clinical Trials or Drugs and Biology" was published, providing guidelines for sponsors to develop adaptive clinical trials. While being aware of the risks of adaptive clinical trials, the document provides guidance on possible modifications in a prospective protocol, including inclusion criteria, procedure of randomization, total sample size and endpoints. However, generalization and application of the results of adaptive clinical trials should be carried out with caution. The FDA encourages early communication to assist with drug evaluation and with scientific and medical issues that may arise during a clinical trial [18].

The International Rare Diseases Research Consortium (IRDiRC), aimed at promoting international collaboration and advance rare diseases research worldwide, has established a Small Population Clinical Trials (SPCT) Task Force to better understand the clinical trials process for rare diseases[25-27].

General recommendations issued by SPCT:

- **Use longitudinal data whenever possible:**
    - Methods for repeated measurements lead to a reduction of sample size by 30% compared to change score analysis
    - Such designs allow to model the development of the treatment effect, not just assessment of its existence (or not) at a specified point of observation
    - The question answered by such analysis differs from a simple analysis at a fixed time point, so the question is "how does the treatment effect develop" and not "what is the effect at a given moment in time ".
- **Continuous endpoints should not be dichotomized** in the primary analysis (although this can be done for sensitivity analyses and assessment of clinical relevance). Many measurements in physiology are continuous measurements (e.g.: blood pressure), but there is often a tendency to divide patients, for example into "responsive" or "unresponsive" individuals. It is discussed that differences in response rates may be more clinically significant than differences of means, but dichotomization will almost always require more patients to demonstrate treatment effects.
- **Trials should be long enough** to ensure full observation and patients should remain in trials for as long as possible to ensure adequate assessment of long-term outcomes:
    - In survival trials this can significantly reduce censorship, and in longitudinal data studies it increases the amount of available information.
    - Additional costs may be associated with longer clinical trials, but those costs need to be balanced against the greater amount of information derived from longer follow up.
- **Use analysis of covariance (ANCOVA)** rather than simple "change from baseline" analyses to reduce bias and increase performance
    - ANCOVA is always more effective than the similar "change from baseline" analysis. It captures imbalance at baseline more correctly than "change from baseline" analyses and

takes into consideration the correlation between baseline and endpoint measurements in a more appropriate way than the analysis of "change from baseline".
    - ANCOVA does not need to be limited to situations where the same variable is measured at study start as at study endpoint
- **Use multiple endpoints,** that target multiple study objectives, but with careful attention for multiplicity problems
    - Hard endpoints, such as mortality and quality of life, considerably reduce the number of patients required to provide sufficient evidence on the benefits and risks of investigational medicinal product
    - Historical and surrogate endpoints may not provide sufficiently strong evidence to demonstrate treatment efficacy
- **Use composite endpoints** by combining several results into a single measure, thus increasing the number of events and thereby the statistical power (if the treatment is likely to affect all single composite scores in the same direction). The composite endpoints have some limitations, and it is crucial to ensure that all the individual components of the composite have similar clinical relevance.
- **Use different formulations, doses, and endpoints** as appropriate **in different subpopulations** and consider combining analyses of these distinct groups.
    - E.g.: when the treatment with a broad age range is used, where treatment may have a similar effect in each age group, but required endpoint scales may be different.
    - Methods for combining significance levels are well established, although estimating the size of treatment effects is not yet exactly defined.
- There is a continuing need for **rigorously collected natural history data and patient registries** for rare diseases for clinical trial design
    - Natural history and patient registry data are crucial for better understanding how diseases progress and develop over time, but also help to determine endpoints where a clinically significant difference can be identified
    - Six research grants have been recently awarded in order to establish the methods to use natural history or patient registry data as an external control arm in clinical trials, rather than relying on randomized controls[25, 26, 28].

Summary:

Rare disease clinical trials and research face many obstacles: very or extremely low disease incidence, small and heterogeneous patient populations, difficulties in patient recruitment, very limited knowledge of the natural history of many rare diseases. Industry incentives have been implemented both in the European Union and the United States to accelerate the development of orphan drugs. Thanks to these incentives, since 2013, almost 70 orphan drugs have reached the market in Europe and almost 370 in the United States for treatment of nearly 300 diseases. However, these results are far from meeting the needs of rare disease patients. Half of the marketing authorizations are granted at a stage where the evidence is not yet well established, requiring enhanced post-authorization patient monitoring. Moreover, a significant proportion of rare diseases is found in the pediatric population, and nearly half of the current research focuses on innovative products, adding to the complexity of research design and approval of regulatory authorities.

In situations where randomized controlled trial is not possible, regulators are open to discuss the adoption of complementary methodologies and evidence sources to enhance the overall evidence base. Approval mechanisms exist to recognize uncertainties that are inherent to trials with small sample sizes in the EMA's decision making. As the use of alternative approaches to conduct clinical trials in small patient populations implies increased uncertainty concerning the reliability of results and product effectiveness, safety and risk-benefit ratio, follow-up data is essential. The EMA highlights that the trade-off between small quantities of

high-quality evidence (from small randomized trials) and large quantities of lower quality evidence (from larger uncontrolled case series) must be considered and judged on a case-by-case basis.

Marketing authorization applications for orphan products tested in small populations are assessed according to the same standards as those for other products, but take into account limitations due to low patient recruitment. In rare diseases, the combined evaluation of single case studies might be the only way to provide evidence. In such cases, treatment conditions and data collection must therefore be standardized, and data must comply with good clinical practice (GCP) standards. Such studies must be prospectively planned and described in study protocols. Systematic reviews of all data and combined analysis of individual case reports and observational studies should be considered to contribute to the evidence.

The gold standard of clinical trials is Randomized Clinical Trial with clear endpoints, meaningful for patients. However, it is not always possible to carry out research on rare diseases with sufficient statistical power. Rare disease trials are more likely to be single arm and non-randomized in comparison with clinical trials designed for other diseases. Study designers should consider various design options taking into account both performance and risk of bias. The applicability of each depends on many factors: the type of condition being examined (stable or highly variable), endpoints (short- or long-term), etc. Moreover, the risks and possibilities of alternative research designs should be assessed. In the context of orphan drug development, especially in small studies, it is important to discuss the use of randomization as a design option.

To assist in selecting an appropriate study design, the following aspects should be considered:

- Whenever feasible, the gold standard should be used (**randomized clinical trial**, with a clinically relevant endpoint and long follow-up)
- Explore study design options that allow you to use subjects more than once (for example, multiple n-of-1 studies, crossover study designs, or randomized withdrawal designs).
  - For stable diseases with a relatively short duration of treatment and defined washout period of the drug, **cross-over regimens** should be considered as they can potentially allow a large reduction in sample size. They allow each subject to receive both interventions in different order depending on the assigned group. They will not be applicable under highly variable conditions or in trials, where very long observation is needed.
  - **Group-sequential designs**: The possibility of early stop is associated with potential reduction in sample size but may also increase the size of the study in some circumstances. Such projects involve interim analyses (which usually requires the use of a Data Monitoring Committee) and while they have the advantage of potential identification of early signs of efficacy, they may be also burdened with limited efficacy data in important subgroups and limited safety data
  - Inferentially seamless **adaptive designs**: These designs combine data from the exploratory "phase II" of a study (selection of appropriate doses) with data from a confirmatory "phase III" of the same study. Such projects present many challenges, both in terms of the time needed to design them and appropriate analyses to account for possible deviations in treatment effect estimates and proper control of Type I error (rejecting the null hypothesis that is not actually false).
- Investigators should always consider various design options, quantify what can be obtained from each study plan, and perform a comprehensive risk assessment before selecting a specific study design. The risks and benefits of each option must be carefully assessed in order to make an evidence-based design selection. However, it should be always kept in mind that simplicity is often an advantage and unnecessary complexity in study designs should be discouraged.

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