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Orphan Drug Designation Series

ORPHAN DRUGS IN THE UNITED STATES

Eligibility, Designation, Incentives

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April 2021

How FDA Defines an Orphan Drug?

In USA, the term "Orphan drug" has two definitions. The first describes drugs or biologics that are used for the prevention, diagnosis, or treatment of diseases or conditions affecting fewer than 200,000 persons in the US. The second definition describes a drug or biologic that is intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year, where the drug will not be profitable within 7 years following FDA approval.

When to Request an Orphan Drug Designation (ODD)?

A sponsor may request for an orphan drug designation (ODD) at any time during the drug's development process and prior submitting a marketing application for the drug for the same rare disease or condition. The sponsor can also request and ODD of an already approved drug for an unapproved use without regard to whether the prior marketing approval was for a rare disease or condition. More than one sponsor may receive (ODD) of the same drug for the same rare disease or condition, but each sponsor seeking orphan-drug designation must file a complete request for designation.

How to Submit an ODD Application to FDA?

The submission of ODD application to the FDA Office of Orphan Products Development (OOPD) is performed online through FDA CDER NextGen Portal for Submission of Orphan Drug Designation Requests: online Portal for submission of new orphan drug designation requests.

This submission process is easy and has many advantages. It provides the applicant an automated confirmation just after submitting the ODD application. It allows the applicant to see all historical records related to its application and check on the status of any submission at any time.

How long it takes FDA to Review an ODD Application?

After receiving the ODD application, the request is assigned a designation request number, logged into OOPD database, and an acknowledgement letter is sent to the sponsor (or sponsor's agent). The assigned OOPD reviewer completes the review of the request, which may require consultation with an FDA Center. Based on the outcome of the review, a designation letter, or a deficiency letter requesting additional information, or a denial letter is prepared and sent to the sponsor. In general , it takes FDA 90 to 120 days to review an application for an ODD.

What is the Content of the ODD Application?

The sponsor shall submit two copies of a completed, dated, and signed request for designation using FDA form (FDA 4035). The Content of the application of ODD is the following:

Section of the application form	Description
1. Date of Request	▪ A statement that the sponsor requests orphan-drug designation for a rare ▪ disease or condition, which shall be identified with specificity.
2. Designation Request Number	▪ It is requested only for amended applications of ODD
3. Sponsor Contact Information/ Sponsor U.S. Resident Agent Information	▪ The name and address of the sponsor, the name of the sponsor's primary contact person and/or resident agent including title, address, telephone number, and email address; the generic and trade name, if any, of the drug, or, if neither is available, the chemical name or a meaningful descriptive name of the drug; and the name and address of the source of the drug if it is not manufactured by the sponsor.
4. Product Information	▪ Product description should include the chemical name, generic name, or trade name, if any, of the drug and a list of the drug product's components or description of the drug product's formulation, and chemical and physical properties.
5. Manufacturer	▪ Name and address of the manufacturer(s) for the drug substance and drug product.
6. Requested Orphan Disease or Condition	▪ Name of the orphan disease or condition ▪ The request of ODD is given to a drug / biologic for the treatment, diagnosis, or prevention of a rare disease or condition, not to proposed drug indication or how a sponsor may wish to study a drug. ▪ The type of use of the drug, treatment or diagnosis of the disease, should be specified.
7. Description of the Disease or Condition, the Proposed Use of the Drug, and the Reasons why such Therapy is Needed	▪ Explanation of the Disease or Condition that directly affects the population estimate. ▪ Designation is given to a drug for a disease or condition, not to an indication. ▪ Designation granted is typically for a broad disease or condition and not a specific indication. ▪ Factors not taken into consideration when determining the disease or condition: – Presence of an unmet need – Sponsor's intent to study the drug only in a certain population. ▪ Factors for determining a disease or condition include: – Mechanism of Action (MOA) of drug – Pathophysiology – Etiology – Treatment options

Section of the application form	Description
8. Scientific Rationale Relevant to the Disease/ Condition	▪ Drug must demonstrate "promise" to treat, diagnose or prevent the disease condition. ▪ The following should be provided: – Drug description and Mechanism of Action (MOA) relevant to disease or condition – Data: in vitro, in vivo, clinical studies relevant to drug and disease/ condition ▪ Clear explanation when the study drug to be administered in relation to the onset of disease or condition. – Treatment: study drug administered after disease/condition developed. – Prevention: study drug administered before disease/condition developed. ▪ The following should not be included in this section: – Safety/toxicology information. – Pharmatox data. – Data from use of the drug in other diseases/conditions – Data from use of a similar product in the disease/condition. ▪ Drug description (brief paragraph): – Active ingredient(s) – Drug class/type – Structure – Physical/chemical properties – Route of administration/formulation ▪ MOA: Brief paragraph describing drug's mechanism of action(s) (MOA) and its relevance to the disease/condition. ▪ Clinical Data A strongest rationale for establishing medically plausible basis for expecting drug to be effective in disease/condition should be provided, it should include details about clinical studies (study design, treated population, inclusion/exclusion criteria, outcome measures, timing of treatment) if available. ▪ In-Vivo Data If no clinical data is available, animal studies conducted in a relevant animal model of disease may be provided. • Animal model need not perfectly recapitulate disease seen in humans. • Provide details about the study (how the disease was created, symptom development time-frame, timing of treatment). ▪ In-Vitro Data Considered with supporting information, if no relevant clinical or animal animal data is available. ▪ "Same Drug" – Must include a plausible hypothesis for clinical superiority

Section of the application form	Description
9. Clinical Superiority	▪ Plausible hypothesis for clinical superiority – Must be provided if the same drug is approved for the same use for which the sponsor is requesting orphan drug designation. – It should be based on greater effectiveness, safety or a major contribution to patient care, or MC-to-PC, over the previously approved same drug. It is important to realize that only a plausible hypothesis of clinical superiority is needed at the orphan drug designation stage if there is a same drug already approved for the same use. However, in order to be eligible for the 7-year marketing exclusivity upon approval, the sponsor needs to demonstrate that their drug is clinically superior to the previously approved same drug or drugs and this may require head-to-head clinical studies. ▪ Superiority: MC-to-PC – What constitutes a major contribution to patient care (MC-to-PC) – Only considered when neither greater safety nor greater effectiveness has been shown • Example: IV to oral dosage form • Example: once daily injectable to once a month injectabl – Each request for a major contribution to patient care stands on its own. – Factors not accepted for a major contribution to patient care: cost of therapy or improved compliance
10. Orphan Subset	▪ Applies to diseases or conditions occurring in 200,000 or more individuals. ▪ Based on a characteristic or feature of the drug (e.g., MOA, toxicity profile, prior clinical experience) which would limit its use to a subset of a non-rare disease/condition ▪ Not based on: – Sponsor's plan to study the drug for a select indication – Cost of the drug – Clinical trial eligibility – Disease grade or stage *Note: Orphan subsets are not commonly granted*
11. Regulatory Status/ Marketing History	The regulatory status should Include: ▪ Pre-IND and IND numbers with respective indication(s) ▪ NDA and BLA numbers with respective indication(s) ▪ EMA designation status and designated use, if applicable ▪ Brief regulatory history for drug both inside and outside of the US – Relevant regulatory determinations for combination products. – Any orphan drug designations held for the drug in other uses. ▪ Self-certification. ▪ Do not include listing of all orphan drug designations for the drug and/ or use held by other sponsors.

Section of the application form	Description
12. Population Estimate	*Prevalence vs Incidence:* ▪ **Prevalence**: number of persons in the US diagnosed as having disease/condition ▪ **Incidence**: the number of new cases of the disease/condition. Generally, only used for acute diseases with a duration of <1 year that are curable and do not recur. ▪ If there is a prevalence or incidence range, generally use the highest estimate to provide the most conservative population estimate. ▪ Data sources and general tips: – Foreign, geographically restricted, or old data. – Registries, databases, literature searches. – Estimate must be current as of the time of application submission. – Include all calculations and references used to derive the population estimate ▪ Methodology – Methodology for calculating size of target population is different for treatment, prevention, and diagnosis. – Treatment: use the highest incidence or prevalence rate and apply it to the most current US population (http://www.census.gov/popclock/) – Alternatively, may multiply incidence by the mean disease duration. – Prevention: include the number of persons to whom the drug will be administered in a given year – Diagnosis (initial diagnosis): see prevention above – Diagnosis (for management of disease/condition): see treatment above.

Can ODD be Transfered to another Company?

A sponsor may transfer ownership of the ODD to a new sponsor. At the time of the transfer, the new and former owners are required to submit the following information to FDA:

1. The former owner shall submit a letter or other document that states that all or some rights to the orphan-drug designation of the drug have been transferred to the new owner or assignee and that a complete copy of the request for orphan-drug designation, including any amendments to the request, supplements to the granted request, and correspondence relevant to the orphan-drug designation, has been provided to the new owner or assignee.
2. The new owner or assignee of rights shall submit a statement accepting orphan-drug designation and a letter or other document containing the following:

    ▪ The date that the change in ownership or assignment of rights is effective;
    ▪ A statement that the new owner has a complete copy of the request for orphan-drug designation including any amendments to the request, supplements to the granted request, and correspondence relevant to the orphan-drug designation; and

- A specific description of the rights that have been assigned and those that have been reserved. This may be satisfied by the submission of either a list of rights assigned and reserved or copies of all relevant agreements between assignors and assignees; and
- The name and address of a new primary contact person or resident agent.

The transfer of ODD ownership should be approved by FDA to be considered effective.

What are the Incentives of Orphan Drugs in USA?

Incentives	Description
Financial incentives	▪ **Tax incentives**: The **Orphan Drug Tax Credit (ODTC)**: sponsors who have an orphan designation can collect tax credits for expenses incurred after the issue of the designation for U.S. clinical trial costs on the orphan indication (50%) ▪ **User fee**: Orphan drugs and products are **exempt** from the usual new drug application or "user" fees charged by the FDA.
Regulatory incentives	▪ **Fast-track review** by FDA of registration dossier. ▪ More FDA regulatory assistance during the overall drug development plan.
Clinical development incentives	▪ **Orphan Product Grant** program provides funding for clinical testing of new therapies to treat and/or diagnose rare diseases that lower the cost of drug development.
Marketing incentives	▪ Product Exclusivity: 7-year period of exclusivity from product approval by FDA.

Frequently Asked Questions About ODD

What Information about the Orphan Drug is Publicly Available?

When a product receives an orphan drug designation, FDA post the following information: sponsor's name, address and contact information, name of drug, orphan designated use and date of designation in the searchable database on the OOPD website. If a designated product is approved for marketing, certain additional information is available on the FDA website (approval date, approved indication, and exclusivity status).

Can a foreign Sponsor submit ODD to US FDA?

A foreign sponsor is required to have a U.S. permanent-resident agent to file a request for an orphan drug designation. FDA requires that all correspondence to and from OOPD related to international sponsors go through the U.S. agent. This includes submitting subsequent annual reports after a product is designated.

Global Regulatory Partners Inc (GRP) can act as U.S. agent for foreign sponsors. GRP can submit the ODD to FDA on their behalf of foreign sponsors and serve as the contact between them and FDA.

Where to find the list of Rare diseases in USA?

The list of rare diseases in USA is available at FDA OOPD website (https://www.fda.gov/industry/developing-products-rare-diseases-conditions) and also at the NIH Genetic and Rare Diseases Information Center (GARD) . However, the purpose of these list is to provide general information about rare diseases and not provide the current prevalence information that would support a request for an orphan drug designation. OOPD will not accept the fact that a disease is listed as a rare disease on a website as evidence of prevalence of <200,000.

What Happens to ODD when the formulation of the drug is changed?

Orphan drug designation is generally conferred to the active moiety rather than the product formulation; therefore, changes to the product formulation doesn't not generally affect the ODD status.

The first sponsor to bring an active moiety to market receives the benefits of exclusivity if that sponsor has orphan designation. If the sponsor makes a change in formulation to the original product, that has ODD status and was approved for marketing, the sponsor will keep the ODD status for the active moiety. However, the sponsor will not receive a new term of exclusivity upon approval of the changed formulation unless the sponsor demonstrates that the changed formulation is clinically superior to the original approved product.

When an ODD is approved in USA / Europe, is it approved in other countries as Well?

No, the ODD approval is based on the prevalence and incidence of the disease in each country. Some diseases can be considered rare in one country and not in others. Sponsors have to submit different applications to different health authorities, and request ODD based on local data on prevalence and incidence of the disease in those countries.

General Tips for ODD Application

- Use the sponsor template form, follow 21 CFR 316.20(b) 1-8 format, or the common application format
- Use page numbers
- Do not reiterate information in multiple sections
- Designation requests for prevention and treatment uses for the same drug for the same disease/condition generally must be submitted as two separate applications, each with its own scientific rationale and population estimate calculation
- Hard copy applications should be bound using a report cover or binder
- References: Include a copy of each cited reference and separate references.
- Suggested page limits:
  - Entire application (excluding references): 20-30 pages
  - Administrative information: 1-2 pages
  - Explaining the disease/condition: 1-3 pages
  - Scientific rationale: 3-5 pages
  - Same drug: 2-3 pages
  - Orphan subset: 2-3 pages
  - Regulatory status: 1 page
  - Population estimate: 2-3 pagess

References

- https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products
- https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs
- https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_USA

About the Author

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Suzan Davis is the Founder, President and CEO of Global Regulatory Partners. Inc, (GRP), which provide regulatory affairs, clinical and quality services to pharmaceutical and medical device companies globally. She led GRP since its inception in January 2010. Suzan has more than 25 years of experience in providing regulatory affairs strategy, registering drugs and biologics, including Orphan Drugs, with FDA and in international markets, managing global products' development programs and conducting quality audits.

Before GRP, Suzan assumed many leadership and executive responsibilities in small and large pharmaceutical and biotech companies, such as GSK, Pfizer, Genzyme, EMD Sereno, Takeda, Merk, in United States and international markets as well. Suzan received a Pharm.D from pharmacy college (Université Paris 1 Panthéon-Sorbonne) in Paris, a Master in Regulatory Affairs (MRA) and an Executive Master in Business Administration (EMBA) from Northeastern University in Boston. She is also certified as a quality auditor, certified in US regulatory affairs, European regulatory affairs and international Regulatory Affairs.

About Global Regulatory Partners, Inc

Global Regulatory Partners Inc, (GRP) provides regulatory affairs, clinical, quality and safety services to medical devices and pharmaceutical companies globally. As a qualified and licensed legal representative with offices in USA, China, Japan, Brazil, Mexico and Argentina, the company can represent life science companies in those countries and help them register their products in compliance with local regulations and in record time.

GRP has a team of certified quality auditors who perfoms on regular basis GMP, ISO, GCP, GCTP audits for different organizations globally.

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