Recommended Tips for Creating an Orphan Drug Designation Application

A Webinar by the Office of Orphan Products Development (OOPD) 2018
Objectives

• How to create a concise and thorough orphan drug designation application
• What needs to be included in the designation application
• Common issues encountered during the review of the designation application
• General tips to consider prior to submitting an orphan drug designation application
Introduction

• Intent of the Orphan Drug Act
• Orphan drug:
  – Drugs (includes biologics) for the prevention, diagnosis, or treatment of diseases or conditions affecting fewer than 200,000 persons in the US
  OR
  – Drugs that will not be profitable within 7 years following approval by the FDA (not discussed further in this webinar)
• What are the benefits of obtaining orphan designation:
  – Tax credits for qualified clinical testing
  – Waiver of NDA/BLA user fees
  – Eligibility for 7-year marketing exclusivity ("orphan exclusivity") upon marketing approval
Application Content

For a complete list of required elements refer to [21 CFR 316.20(b)](https://www.fda.gov)

- Sponsor Template
- Basic elements:
  - Administrative information
  - Explaining what is the disease or condition
  - Providing sufficient scientific rationale
  - Determining the population estimate to support that the disease is rare
Administrative Information

• Statement that sponsor is requesting orphan drug designation for a rare disease or condition which is identified with specificity
• Contact information as specified under 21 CFR 316.20(b)(2)
• Descriptive name of the product
• Manufacturer for drug substance/drug product
Explaining the Disease or Condition

• Directly affects the population estimate
• Designation given to a drug for a disease or condition, **not** 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
Explaining the Disease or Condition

• Scientific understanding of what the disease is can evolve with new scientific findings

• Factors for determining a disease or condition include:
  – Mechanism of Action (MOA) of drug
  – Pathophysiology
  – Etiology
  – Treatment options
  – Prognosis
Explaining the Disease or Condition

- Key points:
  - Pneumonia in cystic fibrosis is a different disease than community acquired pneumonia
  - For lymphomas, the WHO classification stipulates the disease of record
  - Systemic sclerosis or systemic scleroderma is a different disease than localized scleroderma
  - The 5 groups of pulmonary hypertension in the WHO classification are different diseases
  - Generally, for infections, the site of infection determines the disease
Providing Sufficient Scientific Rationale

- Drug must demonstrate “promise” to treat, diagnose or prevent the disease/condition

- Provide:
  - Drug description and MOA relevant to disease/condition
  - Data: in vitro, in vivo, clinical studies relevant to drug and disease/condition
Scientific Rationale: General Tips

• Clearly explain when study drug was administered in relation to onset of disease or condition
  – Treatment: study drug administered after disease/condition developed
  – Prevention: study drug administered before disease/condition developed
• Do not include:
  – Safety/toxicology information
  – Pharmtox data
  – Data from use of the drug in other diseases/conditions
  – Data from use of a similar product in the disease/condition
Scientific Rationale: Drug Description and MOA

• Drug description (brief paragraph):
  • active ingredient(s)
  • drug class/type
  • structure
  • physical/chemical properties
  • route of administration/formulation

• MOA: Brief paragraph describing drug’s actions and its relevance to the disease/condition
Scientific Rationale: Data

• Data should support the rationale for using the drug in the disease or condition
• Data may include clinical study data, in vivo animal data, and in vitro data
• Be concise, descriptive and clear in how the data findings relate to the disease
Scientific Rationale: Clinical Data

• Provide strongest rationale for establishing medically plausible basis for expecting drug to be effective in disease/condition
  – Two adequate and well-controlled studies are not required
  – Provide details about the study (study design, treated population, inclusion/exclusion criteria, outcome measures, timing of treatment)
  – Case reports may be acceptable if presented with sufficient detail
Scientific Rationale: In Vivo Data

• If no clinical data, animal studies conducted in a relevant animal model of disease may be considered
  • Animal model need not perfectly recapitulate disease seen in humans
  • Provide details about the study (how the disease was created, symptom development timeframe, timing of treatment)
Scientific Rationale: In Vitro Data

• Considered with supporting information if no relevant animal model exists for disease and when there is no clinical data
• Clearly explain what the data means and how it relates to the disease
Same Drug

• Refer to 21 CFR 316.3(b)(14) for detailed definitions of what constitutes a “same drug”

• Must include a plausible hypothesis for clinical superiority
  • Note: The previously approved same drug need not have been granted orphan drug designation
Same Drug

• Examples of same drugs include:
  – Two monoclonal antibodies with the same complementarity determining regions (CDRs) or with only minor amino acid differences
  – Liposomal and non-liposomal preparations of the same active moiety
  – Pegylated and unpegylated proteins
  – Small molecules with the same active moiety but different salt or ester
Plausible Hypothesis for Clinical Superiority

• Required if “same drug” is approved for the same use for which the sponsor is requesting orphan drug designation
• Hypothesis for superior effectiveness, safety or a major contribution to patient care (MC-to-PC) over previously approved same drug
• Only a hypothesis is required at the designation stage
• To be eligible for the 7-year marketing exclusivity upon approval, sponsor must demonstrate that their drug is clinically superior to the previously approved same drug(s)
Plausible Hypothesis for Clinical Superiority: Common Pitfalls

• Inadequate detail to support the hypothesis
• Hypothesis must be more than just a theory
Plausible Hypothesis for Clinical Superiority: MC-to-PC

- What constitutes a major contribution to patient care
- 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 injectable
- 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
Orphan Subset

• See 21 CFR 316.3(b)(13)
• 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
Orphan Subset

• **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
Regulatory Status

• 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
Population Estimate

- See 21 CFR 316.20(b)(8)
- 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
- Do not:
  - Average prevalence/incidence rates
  - Simply note a prevalence/incidence rate
  - Simply note that the disease is rare because it was noted on a website associated with rare diseases
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
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/](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
General Tips

- 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
- Explain formulation or packaging for combination products
- 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
  - Separate references
General Tips

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 pages
Additional Website Links

- Office of Orphan Products Development
- Designating an Orphan Product
- Searchable Database for Designated Products
- Code of Federal Regulations
Orphan Drug Regulations and Resources

• 21 Code of Federal Regulations (CFR) Part 316
  – Subpart C – Designation of an Orphan Drug
  – Subpart D – Orphan Drug Exclusive Approval

• Proposed and Final Rules
OOPD Contact Information

• Still have questions?
  • Email us at orphan@fda.hhs.gov | Call us at 301-796-8660