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)

- 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/)
    - 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
  - 2012 Final Rule – 78 Fed. Reg. 35117 (Jun. 12, 2012)
  - 2011 Proposed Rule - 76 Fed. Reg. 64868 (Oct. 19, 2011)
  - 1992 Final Rule - 57 Fed. Reg. 62076 (Dec. 29, 1992)
  - 1991 Proposed Rule - 56 Fed. Reg. 3338 (Jan.29, 1991)

OOPD Contact Information

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION