FDA Orphan Drug Designation 101

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Overview

• The Orphan Drug Act (ODA)
  o Orphan Drugs
  o Rare Diseases

• Orphan Drug Designation Program
  o Requests
  o Review of Criteria
  o Benefits
The Orphan Drug Act (ODA)

- Decade prior to 1983 – only ~1 drug/year independently developed by pharmaceutical sponsors

- Legislation needed to promote rare disease drug development

- The Orphan Drug Act signed into law on Jan. 4, 1983
FDA Marks Orphan Drug Act Milestone: 30 Year Recognition
January 2013
Basic Definitions

• What is an **orphan drug**?
  – Drug (or biological product) intended for use in a rare disease or condition (21 CFR 316.3 (b) (10);
    • Note: Being an orphan drug is not synonymous with having orphan drug designation

• What is a **rare disease**?
  – Disease/condition that affects <200K people in the US
Actions Pertinent to Orphan Drugs

1. Designation
2. New Drug Application (NDA)/Biological Licensing Application (BLA) Approval
Orphan Drug Designation

• In general, a Drug/biologic may be “designated” by the Office of Orphan Products Development if it is to prevent, treat, or diagnose a disease/condition that occurs in < 200,000 people in U.S.

Benefits of Orphan Drug Designation

• If designated, eligible for the following financial incentives:
  o Tax Credits – 50% of clinical trials costs
  o Waiver of marketing application user fees – over $2 million
  o 7-year Marketing Exclusivity if first approved
NDA/BLA Approval

• Marketing Approval of a new drug filed under section 505(b) of the Federal Food, Drug, and Cosmetic Act

• OR

• Marketing Approval of a biologics license submitted under section 351 of the Public Health Service Act
For Complete FDA Organizational Chart see:
When to Submit an Orphan Designation Request

- No IND is required
Content and format of a request for orphan-drug designation

• (1) Statement that the sponsor requests orphan-drug designation for the rare disease or condition.
Content and format of a request for orphan-drug designation

• (2) Identify the sponsor and the drug
• (3) Describe the rare disease or condition, the proposed use of the drug, and the reasons why such therapy is needed.
Content and format of a request for orphan-drug designation

• (4) Provide
  o Detailed description of the drug
  o Scientific rationale for its use
Content and format of a request for orphan-drug designation

• (5) If SAME DRUG as an already approved drug for the same rare disease or condition, with or without orphan exclusivity, designation would be inappropriate
  
    o Explain why clinically superior
Content and format of a request for orphan-drug designation

• (6) If the request is for an orphan subset of a common disease, explain why some property of the drug or biologic would limit use of the product to the subset
Content and format of a request for orphan-drug designation

• (7) Summary of the regulatory status and marketing history
Content and format of a request for orphan-drug designation

• (8) Documentation:
  o Prevalence < 200K

  Or

  o No reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales
Review of a Designation Request

1. What is the \textit{disease/condition}? 

2. Is the disease rare (\textit{prevalence})? 

3. Is there sufficient \textit{scientific rationale} that demonstrates “promise” that the drug/biologic will treat, diagnose or prevent the disease/condition at issue?
#1 – What is the Disease or Condition?

- Determine the disease/condition that would be treated, diagnosed or prevented by the drug/biologic
- Challenging and can evolve

Disease/Condition:
- Scleroderma
  - Localized Scleroderma
  - Systemic Sclerosis
#2 – Is the Disease Rare?

- For *Treatments*, determined by prevalence of the disease in US, so prevalence must be less than 200K
  - ** EXAMPLE:** *Sickle cell disease*

  - **Exception** – For *acute* illnesses (duration < 1 year), use incidence
    - ** EXAMPLE:** *Necrotizing Soft Tissue Infections*

- For *diagnostic* claims, all who would be subjected to diagnosis per year
  - ** EXAMPLE:** *Confirmatory Diagnostic for Anthrax*

- For *prevention* claims, everyone who is at risk of the disease is counted per year
  - ** EXAMPLE:** *Prevention of corneal transplant rejection*
#2 – Is the Disease Rare? (cont.)

- Sponsor must demonstrate prevalence
  - Must provide a specific number; not enough to say that the disease occurs in <200K persons

- Examples of sources to use to calculate prevalence:
  - Published literature
  - Registries
  - SEER database for rare cancers
  - 3 Independent expert opinions (last option)

- If a range exists for the prevalence, apply the highest estimate

**EXAMPLE**

*Myasthenia gravis*

*Prevalence: ~43,500 – 63,500*
#2 – Is the Disease Rare? (cont.)

- If disease/condition is common (i.e., occurs in > 200K persons in the US), can grant orphan designation for use in an “orphan subset”.
  - Subset of all persons with the disease or condition who would only be expected to benefit from the drug

**EXAMPLE**

- **Common disease**: Non-small cell lung cancer
- **Orphan subset**: Non-small cell lung cancer with EGFR mutation
Orphan Subsets

• No to “salami slicing”
  – Example: A drug proposed to be used to treat breast cancer patients refractory to first-line treatment
    • No, unless there is some property of the drug (e.g., toxicity) that would restrict its use
  – Example: A drug that will only be tested for those patients that meet clinical trial inclusion criteria
    • No
Orphan Subsets

• Yes to orphan subsets
  – Example: A drug (monoclonal Ab) that will act against a surface antigen found only in a rare subset of breast cancer cases and would not act in breast cancer cases without the surface antigen.
    • Yes
  – Example: A drug that targets a specific genetic mutation found in only a small subset of colon cancer cases
    • Yes
#3 – Is the Scientific Rationale Sufficient?

• Required – Evidence that the drug holds promise for being effective in treating/preventing/diagnosing disease

• Includes information from:
  - Clinical data, OR
  - Animal models, OR
  - In vitro data (with proposed MOA and pathogenesis of disease when no adequate animal model exists)
Key Statement

- The scientific rationale is best supported by clinical data; however, in the absence of human data, the application for orphan drug designation may be satisfactorily supported with preclinical data using a relevant animal model for the human disease.
Recent Analysis of Accepted Scientific Rationale presented by Sponsors over one year.

- Clinical Experience: 66%
- Animal Study Data: 32%
- \textit{In-vitro} Study Data: 2%
After Designation Request Is Submitted…

• Typical review cycle ~ 90 days

• Will either receive:
  – Designation Letter OR
  – Deficiency Letter

• Once designated, sponsor is required to submit annual reports until drug is approved
Designation vs. Labeled Indication

- Often the approved labeled indication is **narrower** than the designation because we designate for the disease, not for the indication.

**Designation:** Bosutinib designated for the treatment of chronic myelogenous leukemia (CML)

**Approved Labeled Indication:** Bosutinib approved for the treatment of Philadelphia chromosome-positive (Ph+) CML with resistance, or intolerance to prior therapy

- Indication covered by orphan designation
Drug Designations and Approvals

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The chart illustrates the number of drug designations and approvals from 1983 to 2013. The y-axis represents the number of designations and approvals, ranging from 0 to 300. The x-axis lists the years from 1983 to 2013.

Key observations:
- 1983: 33 designations and approvals
- 2013: 256 designations and approvals
- 188 designations and approvals in 2012
- 26 designations and approvals in 1983

The chart shows a significant increase in both designations and approvals over the years.
Orphan Drug Designations 2013

- Oncology: 38%
- Other: 22%
- Neurology: 12%
- Hematology: 7%
- Metabolism: 7%
- Infectious Disease: 5%
- Gastroenterology: 5%
- Pulmonary: 4%
Final Rule

- Amends 1992 regulations (21 CFR 316)
- Effective August 12, 2013
- Amendments intended to clarify certain regulatory language and add areas of minor improvement regarding orphan drug designation and orphan drug exclusivity
Final Rule

• If the sponsor who originally obtained orphan exclusive approval of the drug for only one indication within a designated disease subsequently obtains approval of the drug for one or more additional indications within that same orphan disease or condition, FDA will recognize orphan-drug exclusive approval, as appropriate, for those additional indications.
Final Rule

• Clarifies that submission by a sponsor of a marketing application for the drug for the orphan indication does not prevent another sponsor from submitting a request for orphan designation of the same drug for the same orphan use.
Questions?

For more information on OOPD’s programs, check out www.fda.gov/orphan

More questions?
Email us at orphan@fda.hhs.gov, OR
Call us at 301-796-8660