FDA Orphan Drug Designation 101

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Worldwide Orphan Medicinal Designation Workshop
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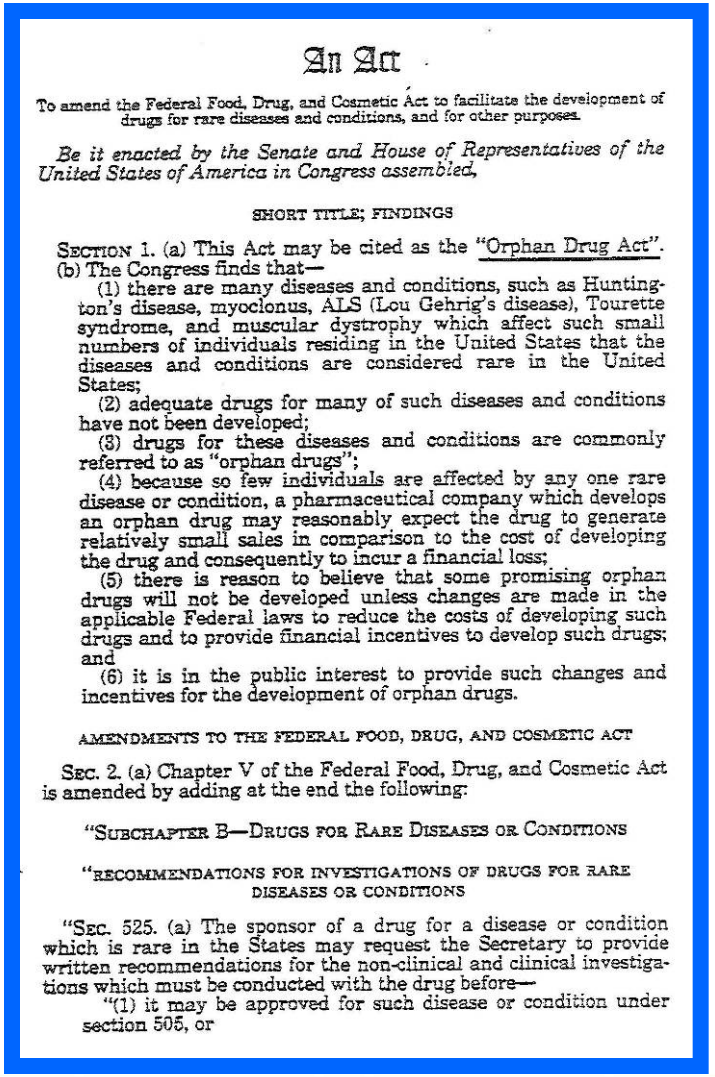
Overview

- The Orphan Drug Act (ODA)
  - Orphan Drugs
  - Rare Diseases
- Orphan Drug Designation Program
  - Requests
  - Review of Criteria
  - 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



An Act

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SHORT TITLE; FINDINGS

SECTION 1. (a) This Act may be cited as the "Orphan Drug Act".
(b) The Congress finds that—
(1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States;
(2) adequate drugs for many of such diseases and conditions have not been developed;
(3) drugs for these diseases and conditions are commonly referred to as "orphan drugs";
(4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;
(5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and
(6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

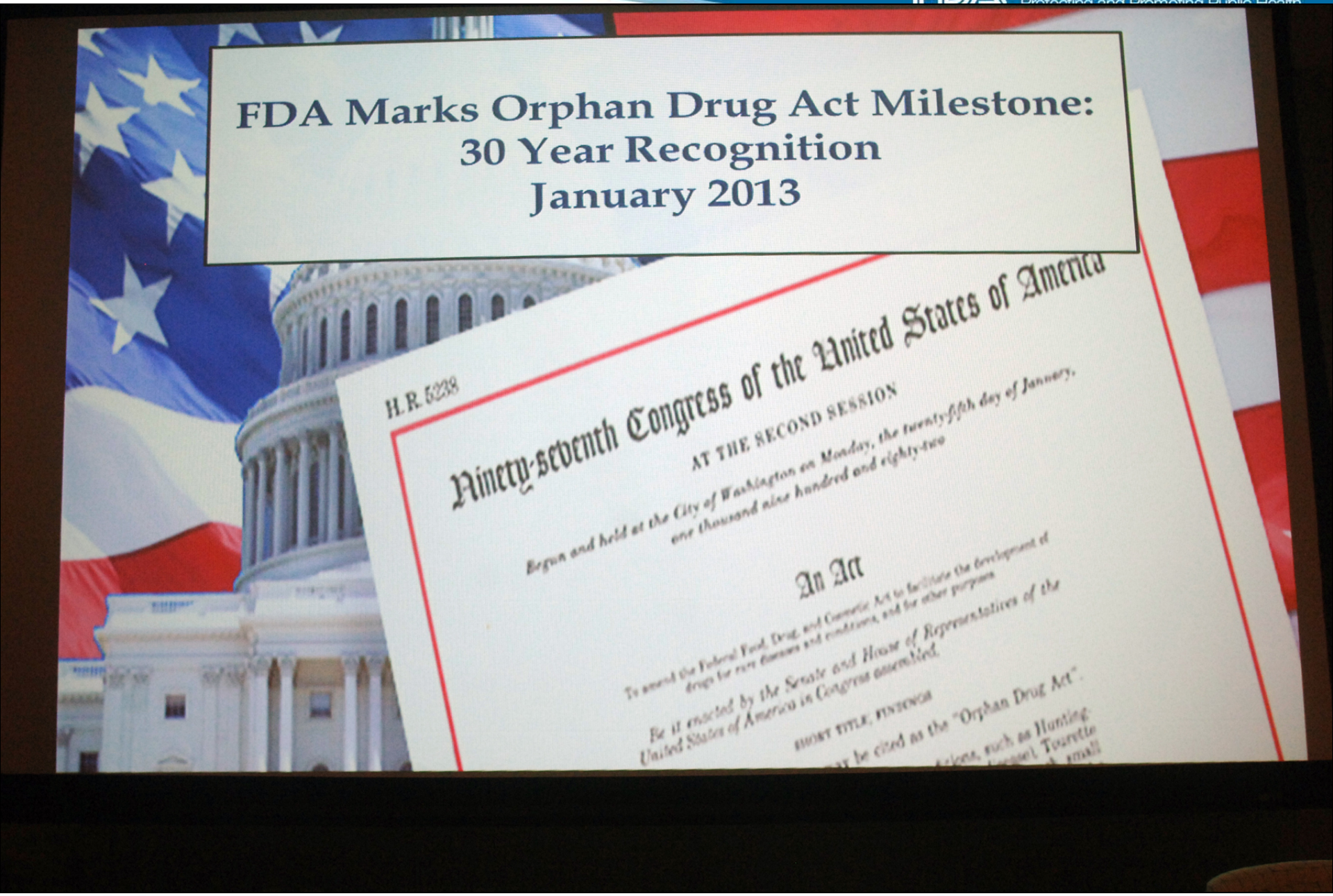
AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

SEC. 2. (a) Chapter V of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end the following:

"SUBCHAPTER B—DRUGS FOR RARE DISEASES OR CONDITIONS

"RECOMMENDATIONS FOR INVESTIGATIONS OF DRUGS FOR RARE DISEASES OR CONDITIONS

"SEC. 525. (a) The sponsor of a drug for a disease or condition which is rare in the States may request the Secretary to provide written recommendations for the non-clinical and clinical investigations which must be conducted with the drug before—
"(1) it may be approved for such disease or condition under section 505, or


FDA Marks Orphan Drug Act Milestone:
30 Year Recognition
January 2013
H.R. 5238
Ninety-seventh Congress of the United States of America
AT THE SECOND SESSION
Begun and held at the City of Washington on Monday, the twenty-fifth day of January, one thousand nine hundred and eighty-two
An Act

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

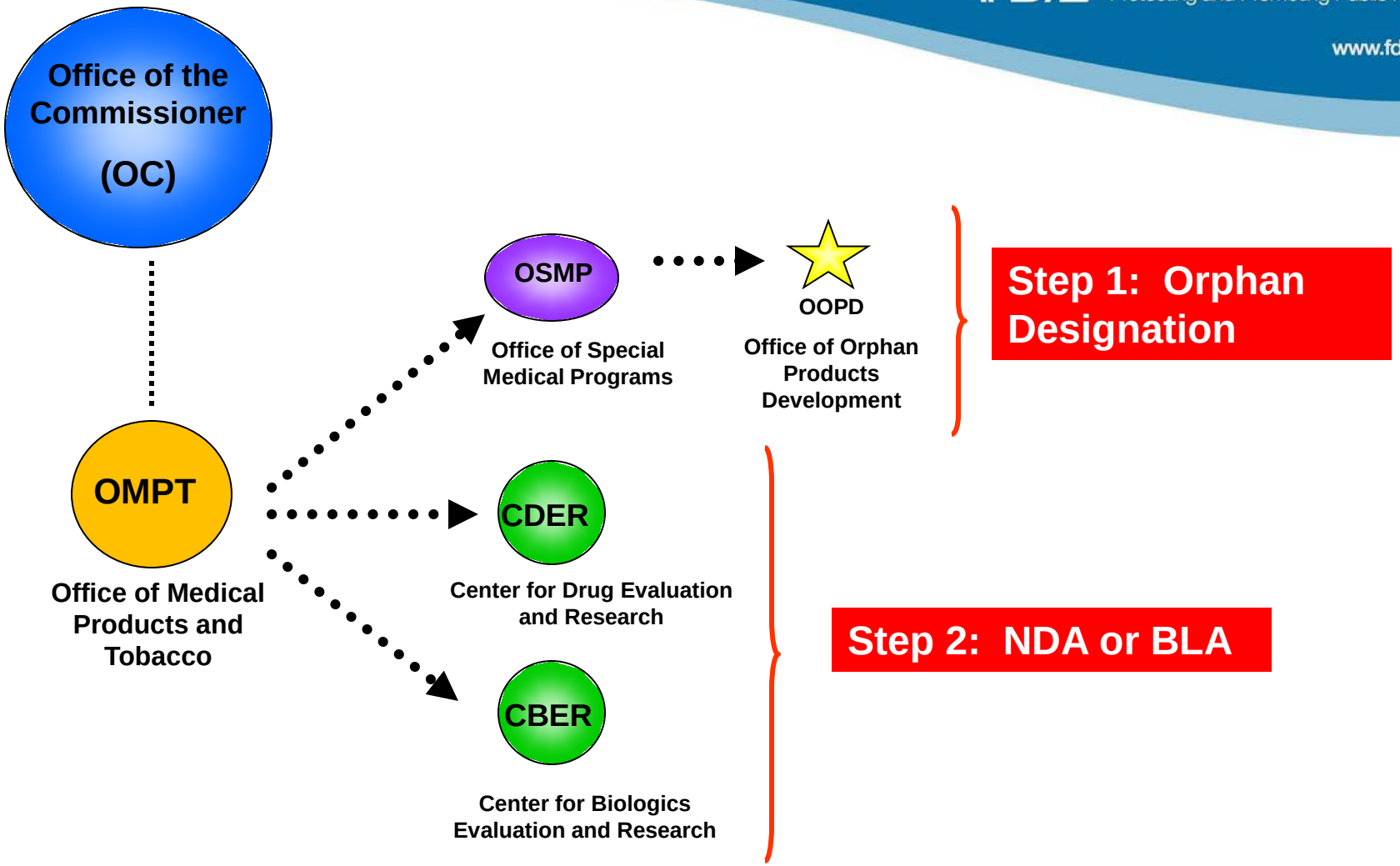
- If designated, eligible for the following **financial incentives**:
  - Tax Credits – 50% of clinical trials costs
  - Waiver of marketing application user fees – over $2 million
  - 7-year Marketing Exclusivity if first approved

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:

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM288864.pdf

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

Content and format of a request for orphan-drug designation

- (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
    - Detailed description of the drug
    - 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
  - 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:
  - Prevalence < 200K

    Or

  - 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

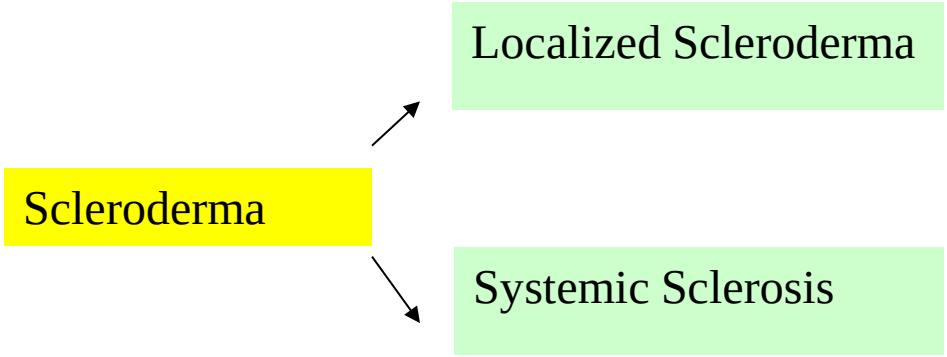
1. What is the **disease/condition**?

2. Is the disease rare (**prevalence**)?

3. Is there sufficient **scientific rationale** that demonstrates "promise" that the drug/biologic will treat, diagnose or prevent the disease/condition at issue?

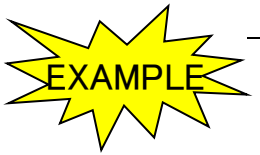
#1 – What is the Disease or Condition?

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

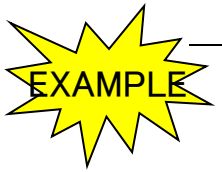


#2 – Is the Disease Rare?

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

→ ***Sickle cell disease***
  - **Exception** – For *acute* illnesses (duration < 1 year), use incidence


→ ***Necrotizing Soft Tissue Infections***
- For *diagnostic* claims, all who would be subjected to diagnosis per year 

→ ***Confirmatory Diagnostic for Anthrax***
- For *prevention* claims, everyone who is at risk of the disease is counted per year 

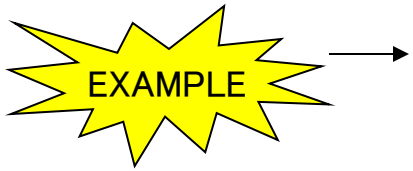
→ ***Prevention of corneal transplant rejection***

#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)

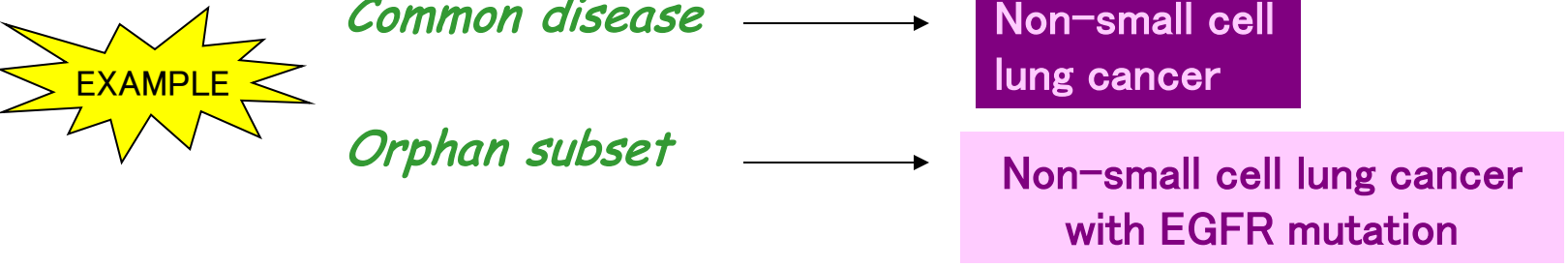
- If a range exists for the prevalence, apply the highest estimate



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



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 informatioin 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%
- *In-vitro* Study Data: 2%

Lev et al. 2012 Drug Discovery Today

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

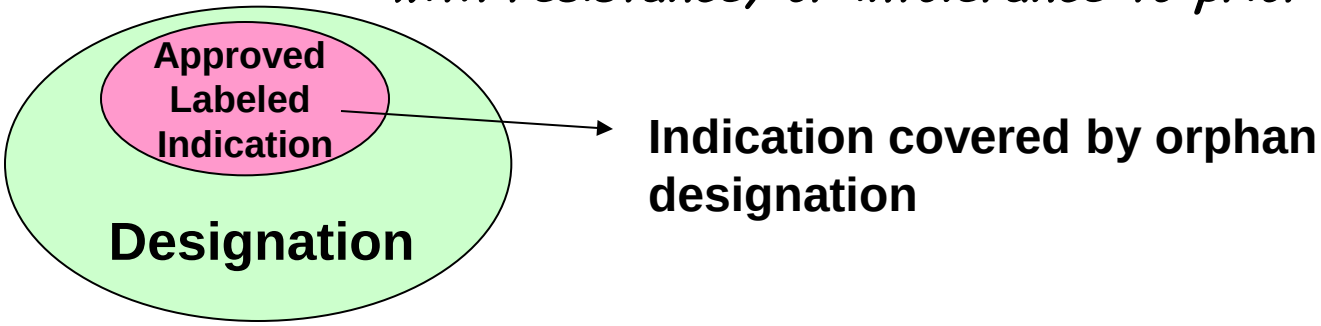
Designation vs. Labeled Indication

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

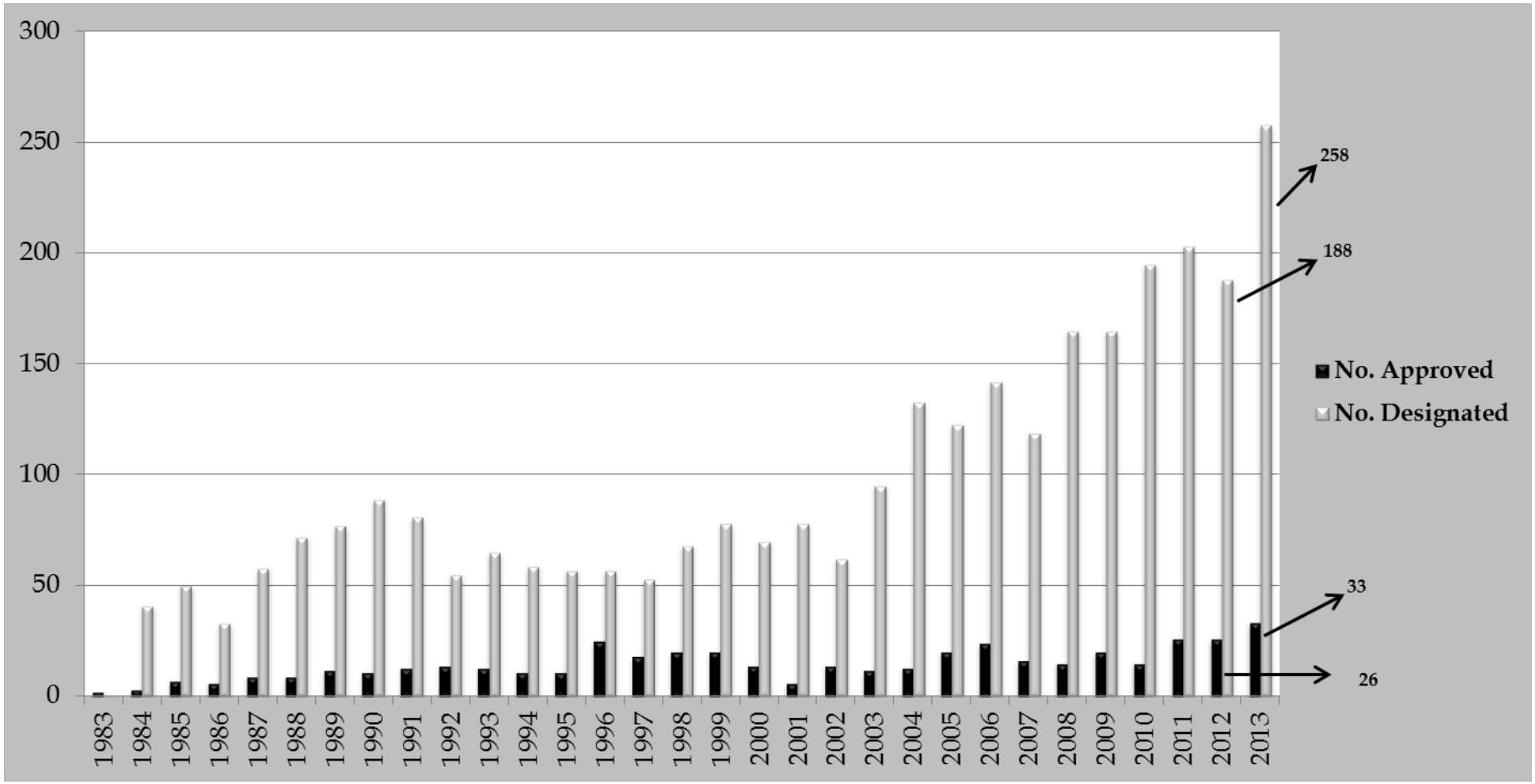
EXAMPLE

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

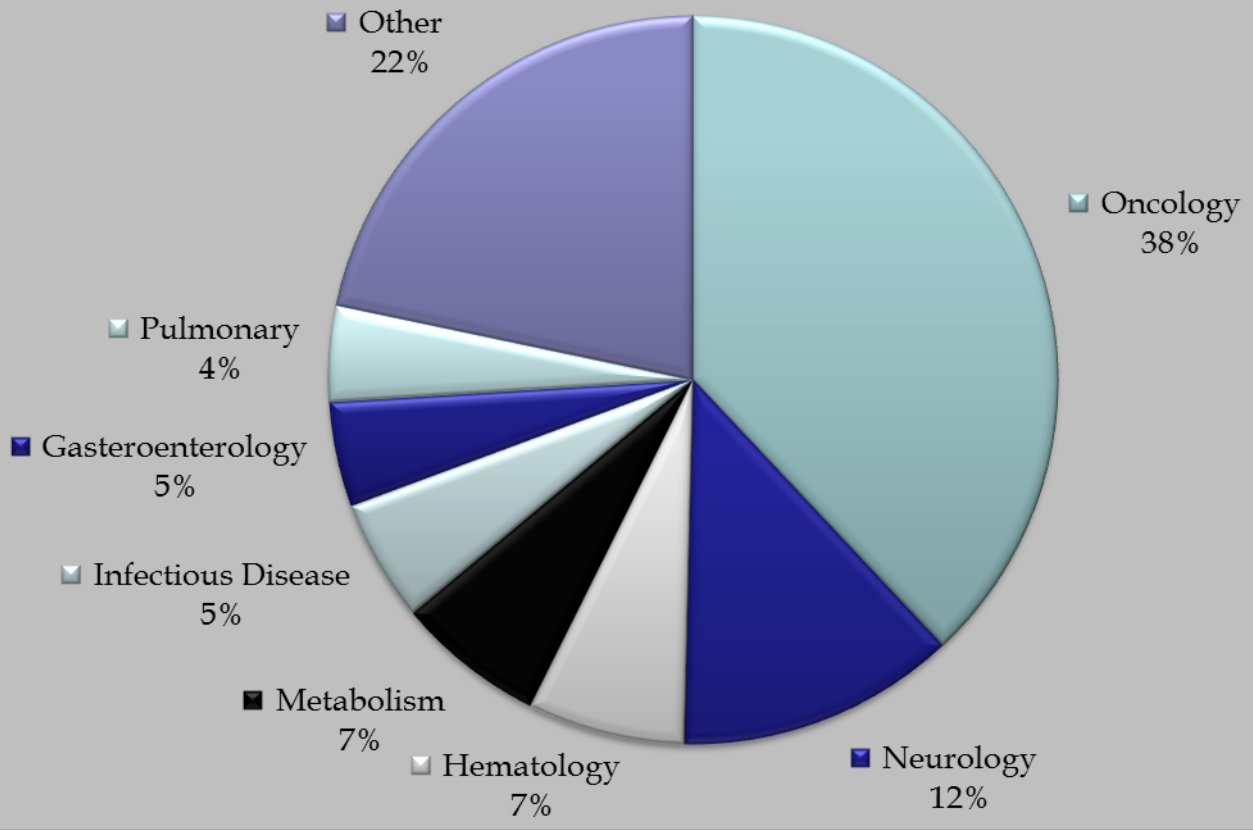
Approved Labeled Indication: *Bosutinib approved for the treatment of Philadelphia chromosome-positive (Ph+) CML with resistance, or intolerance to prior therapy*



Drug Designations and Approvals



Orphan Drug Designations 2013



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