Office of Orphan Products Development: Financial Incentives for CDER Medical Products

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Learning Objectives

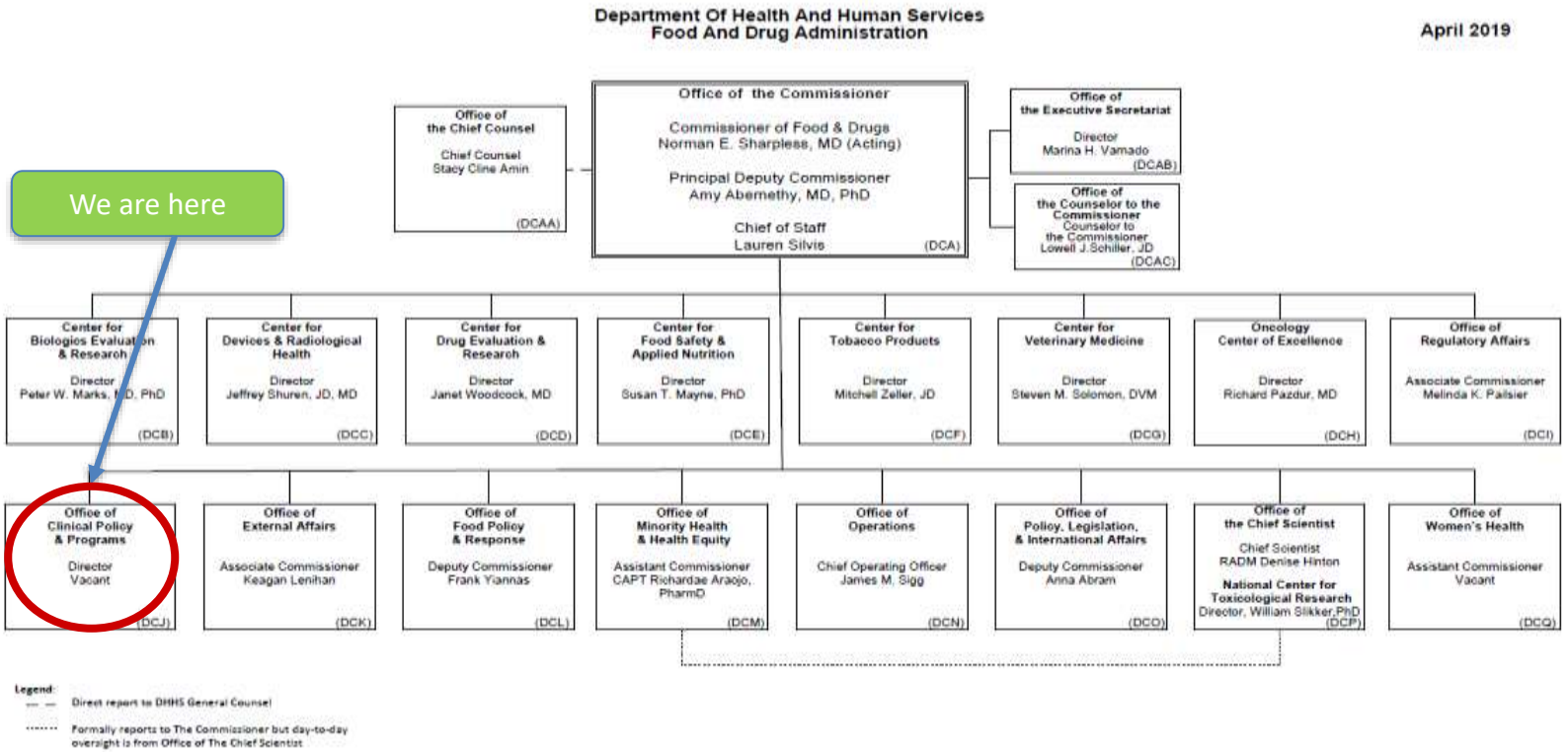
After completion of this activity, the participant will be able to:

- Describe the Office of Orphan Products Development (OOPD) Orphan Drug Designation program
- Describe the OOPD Rare Pediatric Disease Designation review program
- Describe the OOPD Clinical Trials and Natural History Grants Programs
- Navigate to OOPD webpage resources for these programs

Office of Orphan Products Development

- **Mission**: *To advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions*

Where in the FDA is OOPD?



Orphan Drug Act (ODA)

Created by Congress in 1983 to motivate industry to develop drugs and biologics for rare diseases by providing financial incentives

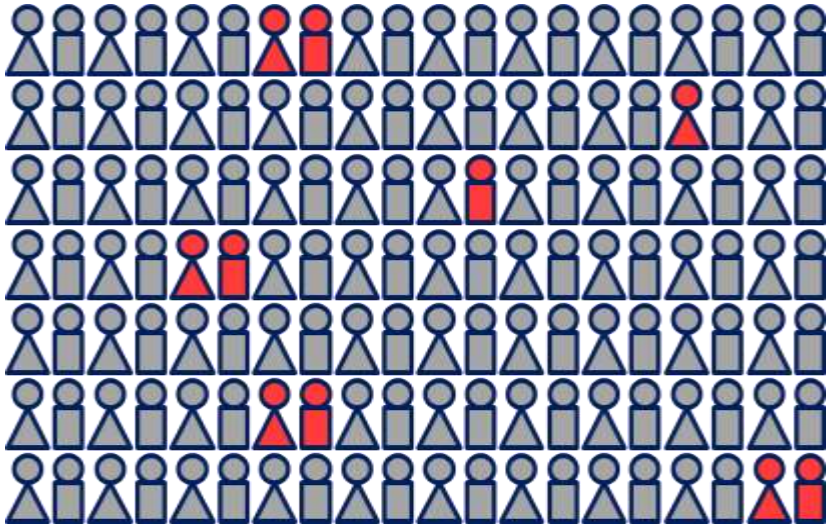
- Pre-ODA, fewer than 1 drug/year approved for rare diseases in the U.S.
- Since 1983, >780 approvals for > 250 rare diseases
- In 2018:
  - > 90 approvals for rare disease indications (highest # since ODA passed)
  - 58% of CDER's novel drug approvals were for rare diseases

What does “rare” and “orphan” mean?

- A **rare disease** is defined in the **Orphan Drug Act** as:
  - a disease/condition that affects <200,000 persons in the U.S., *or*
  - affects ≥200,000 persons in the U.S. but for which there is no reasonable expectation that the costs of developing and marketing the drug will be recovered from sales of the drug in the U.S.

- An **orphan drug** is a drug (or biological product) used for the prevention, diagnosis, or treatment of a rare disease in the U.S.

Rare Diseases



- More than 7,000 rare diseases
- Affect an estimated **30 million** Americans
- Examples: Cystic fibrosis, sickle cell anemia, amyotrophic lateral sclerosis, pancreatic cancer

OOPD Core Programs

Designation Programs	Grant Programs
Orphan Drug Designation Program	Orphan Products Clinical Trials Grant Program
Rare Pediatric Disease Designation Program	Pediatric Device Consortia Grant Program
Humanitarian Use Device Designation (HUD) Program	Orphan Products Natural History Grant Program

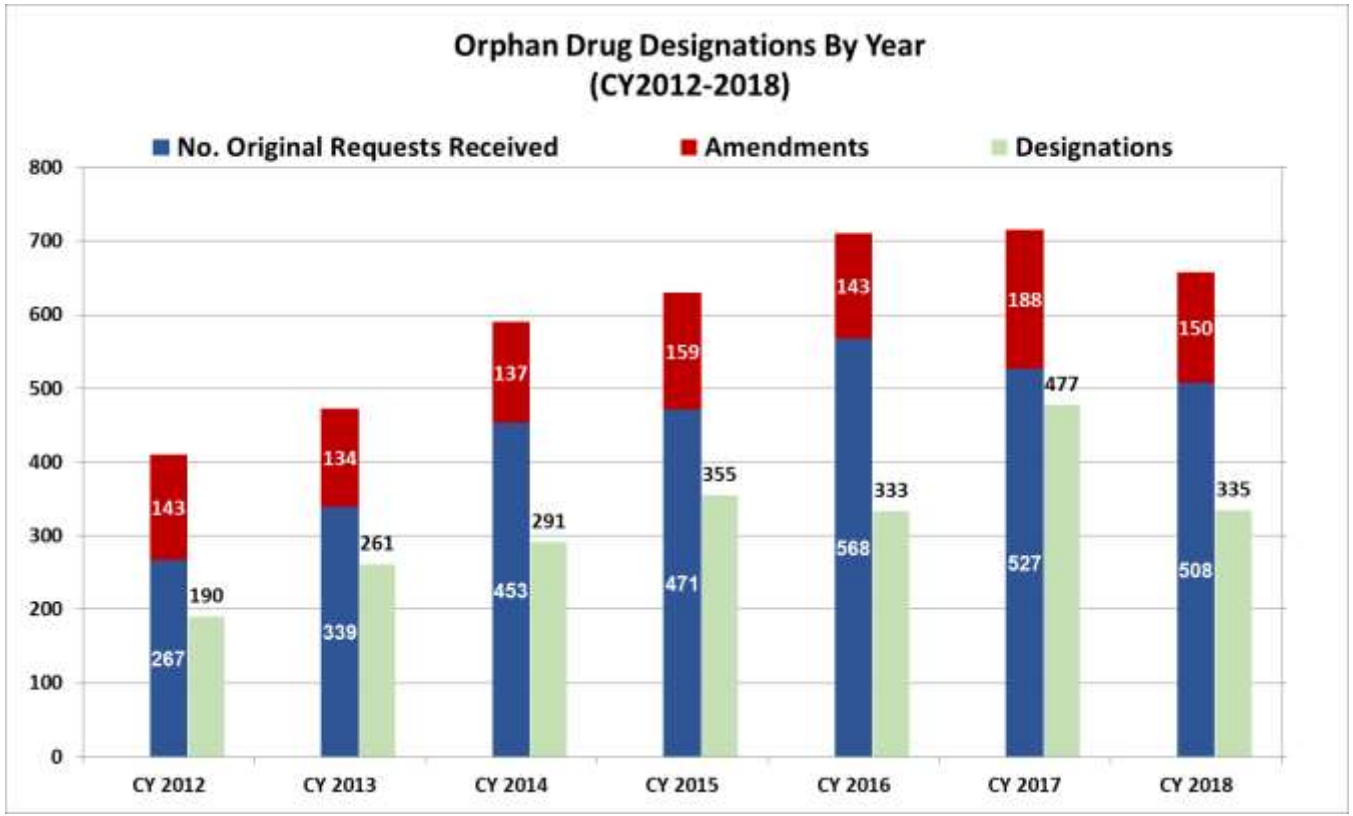
Orphan Drug Designation Program

Designation Programs
Orphan Drug Designation Program
Rare Pediatric Disease Designation Program
Humanitarian Use Device Designation (HUD) Program

Orphan Drug Designation Program

- ODA provides for FDA to designate a drug (or biologic) as a drug for a “rare disease or condition”
  - Drug must show promise for the prevention, diagnosis, or treatment of the rare disease or condition
  - Designation **not** given to proposed indication or how a sponsor may wish to study a drug
  - No fee for submitting designation request
  - Designation requests must be submitted **before** marketing application (NDA/BLA)
  - IND is not required

Orphan Drug Designation Trends



Since passage of ODA:

- >6,900 requests
- >4,800 designations

Financial Incentives for Orphan Drug Designation

- ✓ **Tax credits** up to 25% of qualified clinical trials costs
- ✓ **Waiver** of FDA User Fees
- ✓ Eligible to receive **7-years of marketing exclusivity**
- ✓ Orphan drug designation now associated with additional financial “incentives” under the Affordable Care Act (e.g., branded prescription drug fee, 340B drug discount pricing)

7-year Orphan Exclusivity

- Seven years of market exclusivity: FDA cannot approve same drug for same indication
  - if the drug is approved for an indication within scope of the orphan designation; *and*
  - the same drug has not been previously approved for the same indication
- Only to the first sponsor to receive approval for that drug for the orphan designated indication

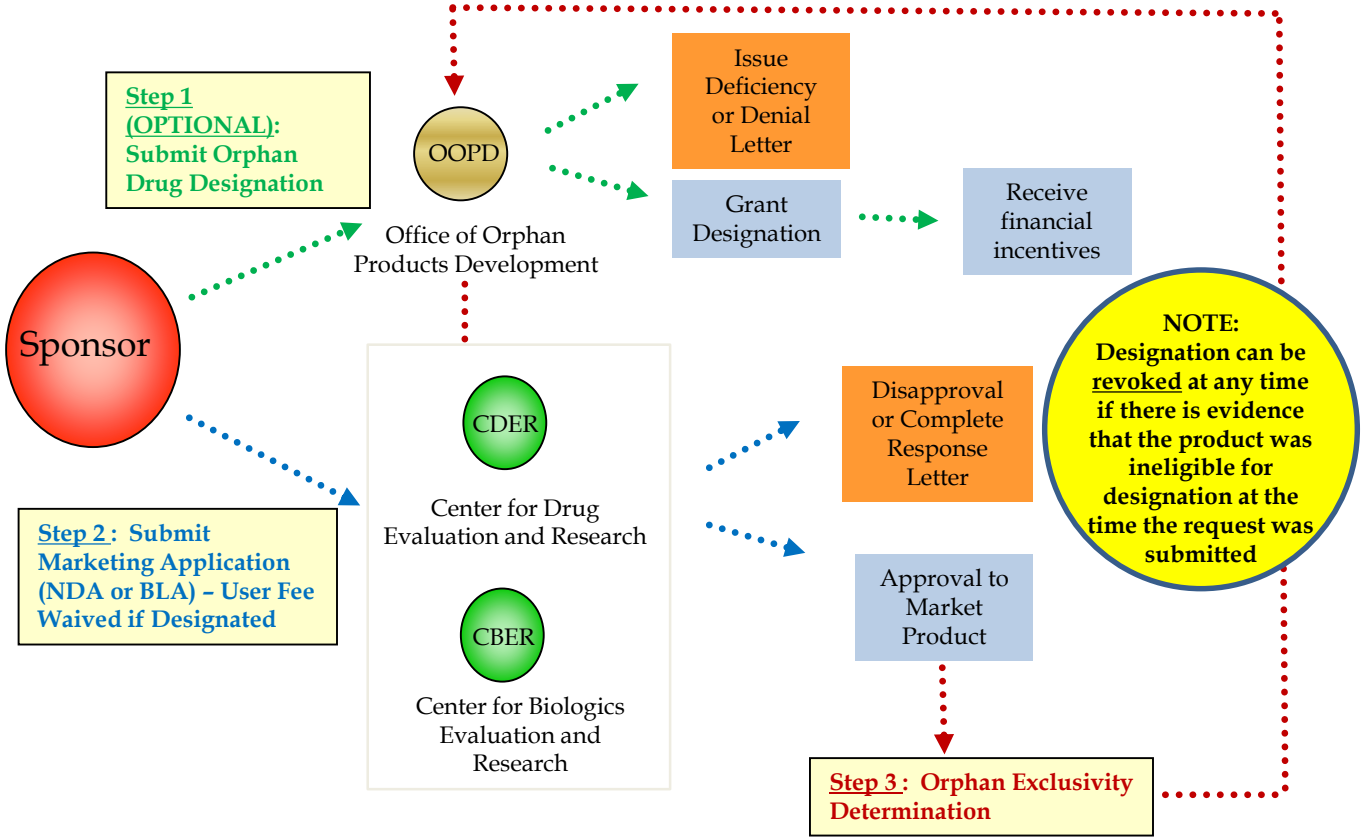
7-year Orphan Exclusivity

- Distinct from other exclusivities
- Determined by OOPD upon marketing approval
- OOPD sends letter to recognize exclusive approval per 21 CFR 316.34(a), then identified in Orange Book
- Exclusivity can be “broken” in cases of:
  - Drug shortage
  - Another drug is clinically superior to the approved drug

Orphan Drug Exclusivity

- One drug may receive multiple exclusivities under one orphan drug designation (ODD): e.g., Factor XIII

Orphan Drug Designation & Orphan Exclusivity



Review of a Designation Request

Five critical questions:

1. What is the disease or condition the drug is treating, diagnosing, or preventing?
2. Is this disease or condition rare?
3. If this disease or condition is not rare, is there orphan subset demonstration?
4. Is there a description of the drug and scientific rationale?
5. Is it "same drug" as a previously approved drug for same use?

What is the Disease?

What is the disease or condition the drug is treating, diagnosing, or preventing?

- Challenging and can evolve
- Depends on a number of factors, assessed cumulatively, including:
  - pathogenesis of the disease or condition;
  - course of the disease or condition;
  - prognosis of the disease or condition;
  - and resistance to treatment.

Is the Disease or Condition Rare?

"Rare disease" is generally defined by the Orphan Drug Act as:

- Disease or condition that affects <200,000 persons in the U.S.
  - ✓*Therapeutic drugs:* prevalence < 200,000
    - Prevalence: number of persons in U.S. who have been diagnosed as having the disease/condition at the time of the submission of the request
  - ✓*Vaccines, diagnostic, and preventative drugs:* number of persons drug will be administered to < 200,000 per year

Orphan Subset

If disease or condition occurs in > 200,000 persons (non-rare):

- Demonstration of an “orphan subset”: use of the drug appropriate in orphan subset due to one or more properties of the drug, but inappropriate in the remaining persons with such disease or condition
  - Drug toxicity
  - Mechanism of action
  - Previous clinical experience with the drug.
- “Orphan subset” must meet the regulatory threshold of 200,000 in the U.S.
- Cannot be considered without reference to the drug, specifically to the property(ies) of the drug

Drug Description & Scientific Rationale

- Description of the drug
  - Active moiety
- Scientific rationale: must establish a medically plausible basis for the use of the drug for the rare disease or condition
- What is scientific rationale based on?
  - Clinical data, case reports
  - Acceptable animal model(s) of human disease
  - *In vitro* data (with proposed mechanism of action and pathogenesis of disease when no adequate animal model of human disease exists)

Same Drug & Clinical Superiority

Is it “same drug” as a previously approved drug for same use?

- “Same drug” defined in 21 CFR 316.3(b)(14); does not mean identical.
    - *Small molecule* - contains same active moiety as previously approved drug.
    - *Macromolecules* - contains the same principal molecular structural features of previously approved drug. E.g.,: two protein drugs are same if the only differences were due to post-translational events, minor differences in amino acid sequences, different glycosylation patterns, etc.

- When seeking designation of a drug that is the “same” as an already approved drug for the same use, must provide a **plausible hypothesis** of clinical superiority

Same Drug & Clinical Superiority

- "Clinical superiority" (21 CFR 316.3(b)(3)):

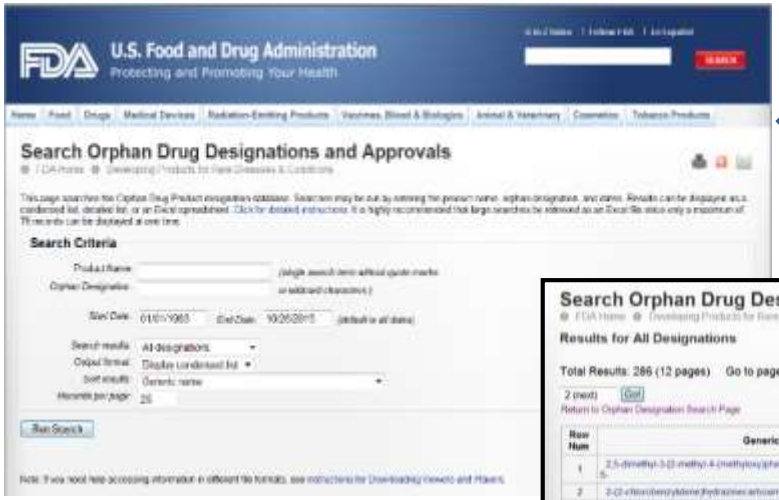
✓ **Greater effectiveness**

✓ **Greater safety**

✓ In unusual cases, a **major contribution to patient care**

- To get 7-years of market exclusivity, regulations require sponsors must **demonstrate** product is actually clinically superior

Resources: OOPD Public Database

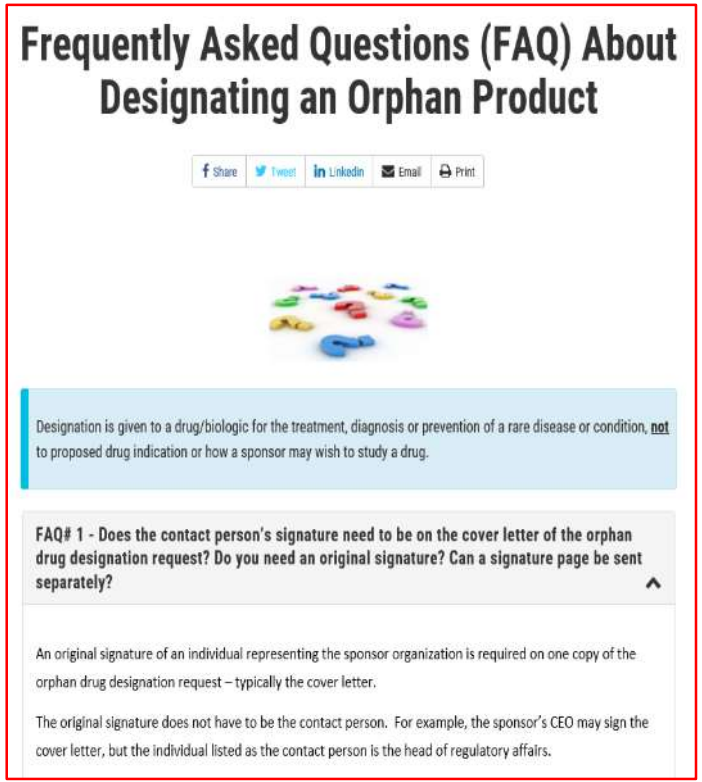


To search for orphan drug designations and approvals:

http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

For example, a search for all orphan drug designations to date yields…

Resources: Orphan Drug Designation Webpage and FAQs



Frequently Asked Questions (FAQ) About Designating an Orphan Product

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Designation 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.

FAQ# 1 - Does the contact person's signature need to be on the cover letter of the orphan drug designation request? Do you need an original signature? Can a signature page be sent separately?

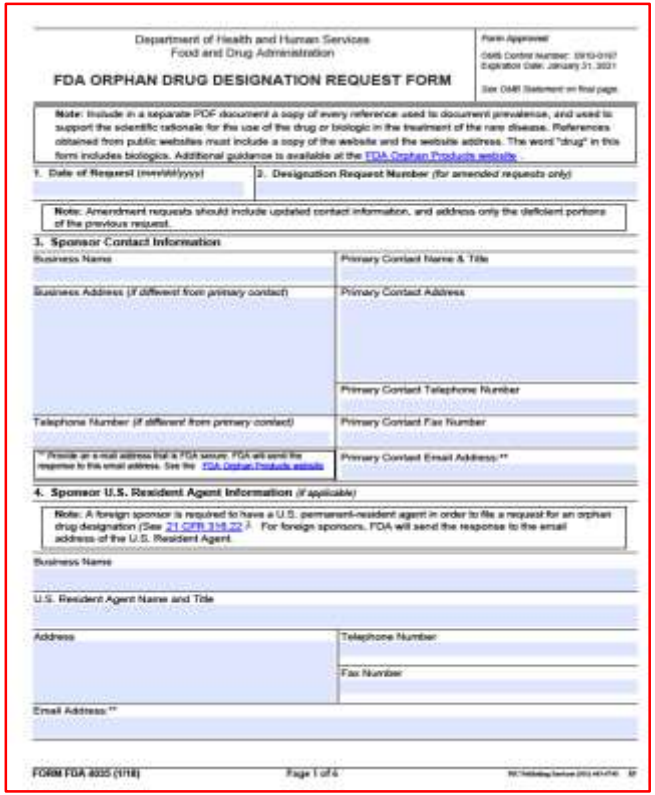
An original signature of an individual representing the sponsor organization is required on one copy of the orphan drug designation request – typically the cover letter.

The original signature does not have to be the contact person. For example, the sponsor's CEO may sign the cover letter, but the individual listed as the contact person is the head of regulatory affairs.

- ODD Program webpage
  - Several useful links, e.g. ODA & regulations
- FAQs

Resources: Orphan Drug Designation Request Form

- Form FDA 4035 (optional)
- Designed to assist sponsors in providing the required content **completely** and **succinctly**



Department of Health and Human Services
Food and Drug Administration

FDA ORPHAN DRUG DESIGNATION REQUEST FORM

Form Approved
OMB Control Number: 0910-0167
Expiration Date: January 31, 2021
See OMB Statement on final page.

Note: Include in a separate PDF document a copy of every reference used to document prevalence, and used to support the scientific rationale for the use of the drug or biologic in the treatment of the rare disease. References obtained from public websites must include a copy of the website and the website address. The word "drug" in this form includes biologics. Additional guidance is available at the FDA Orphan Products website.

1. Date of Request (mm/dd/yyyy)

2. Designation Request Number (for amended requests only)

Note: Amendment requests should include updated contact information, and address only the deficient portions of the previous request.

3. Sponsor Contact Information

Business Name

Primary Contact Name & Title

Business Address (if different from primary contact)

Primary Contact Address

Primary Contact Telephone Number

Telephone Number (if different from primary contact)

Primary Contact Fax Number

** Provide an e-mail address that a FDA server, FDA will send the response to this email address. See the FDA Orphan Products website.

Primary Contact Email Address:**

4. Sponsor U.S. Resident Agent Information (if applicable)

Note: A foreign sponsor is required to have a U.S. permanent-resident agent in order to file a request for an orphan drug designation (See 21 CFR 314.22). For foreign sponsors, FDA will send the response to the email address of the U.S. Resident Agent.

Business Name

U.S. Resident Agent Name and Title

Address

Telephone Number

Fax Number

Email Address:**

FORM FDA 4035 (1/18)

Page 1 of 4

Resources: Tutorial

- Addresses common issues found during the designation review process
- Provides general tips for submitting an orphan drug designation request (e.g. suggested page limits)

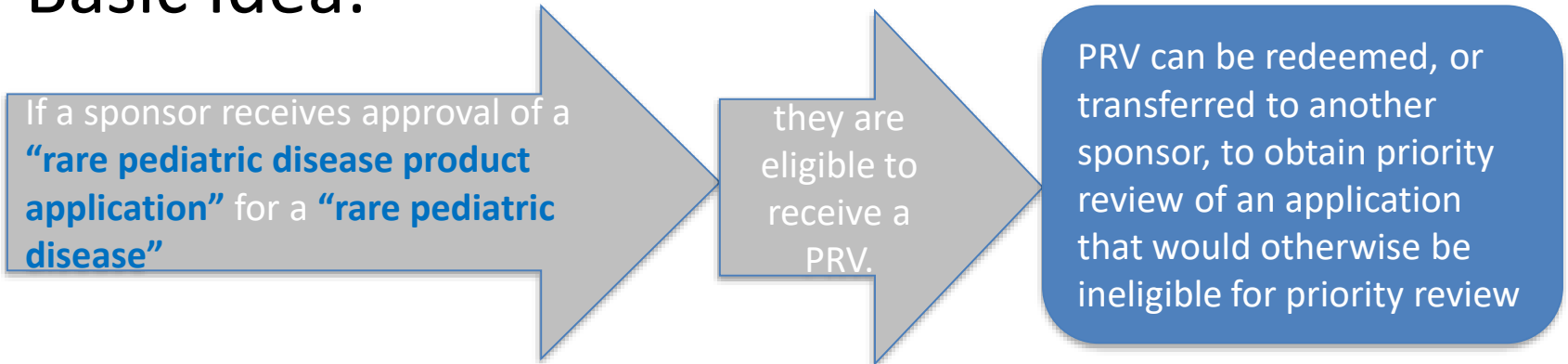
Rare Pediatric Disease Designation Program

Designation Programs
Orphan Drug Designation Program
Rare Pediatric Disease Designation Program
Humanitarian Use Device Designation (HUD) Program

Rare Pediatric Disease Priority Review Voucher (PRV)

- Created in 2012 under Section 529 of the FD&C Act to encourage development of drugs and biologics for “rare pediatric diseases”

- Basic Idea:



What is a Rare Pediatric Disease?

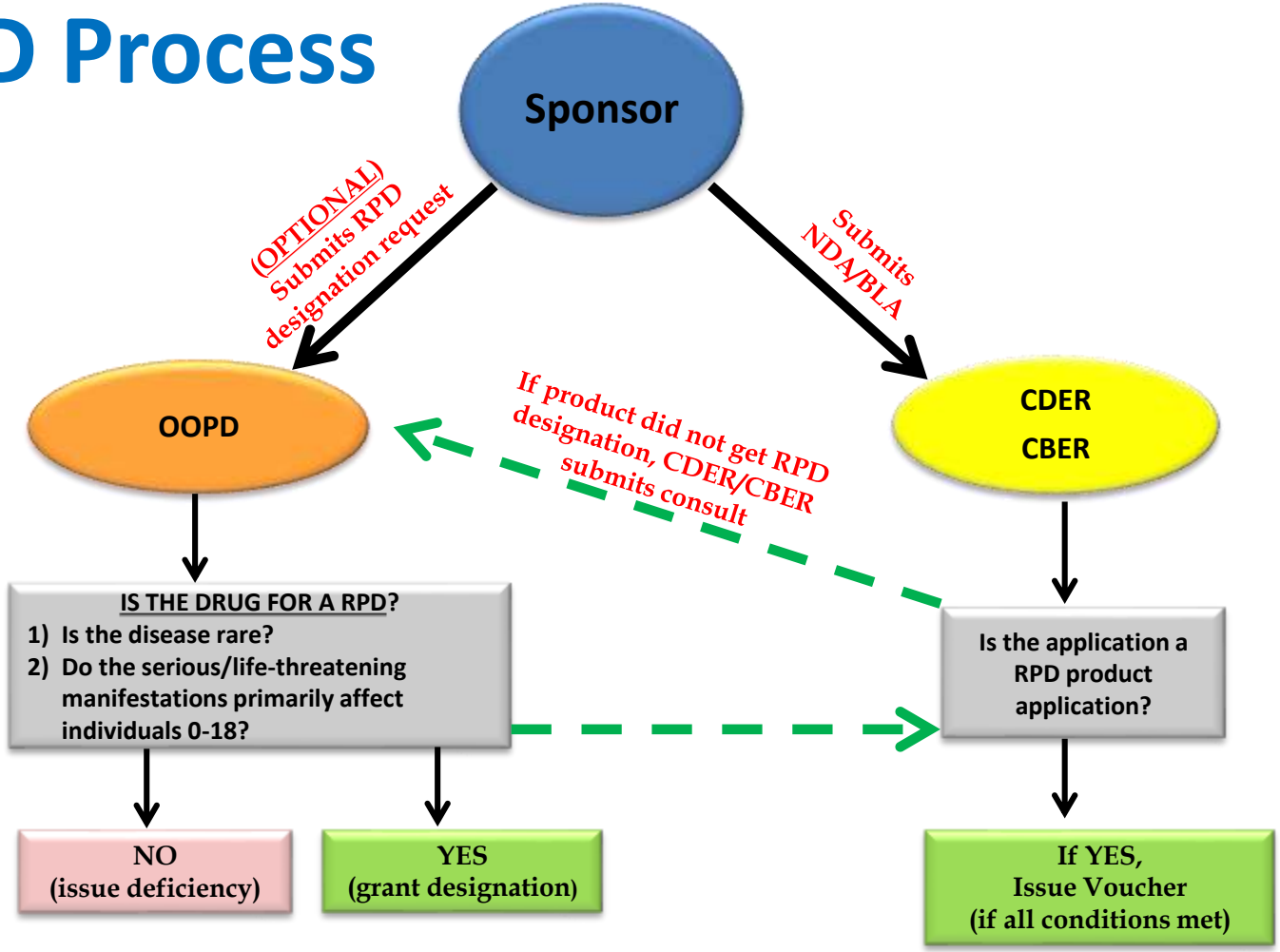
1. The disease is a rare disease or condition that affects:
   - <200,000 persons in the U.S. or
   - ≥200,000 persons and for which there is no reasonable expectation that the costs of developing and making the drug available in the U.S. can be recovered from sales of the drug in the U.S.

2. The disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years *(per the Advancing Hope Act of 2016)*.

Rare Pediatric Disease (RPD) Designation

- RPD designation is not required, nor sufficient, to receive a voucher.
- Requesting RPD designation in advance will expedite a sponsor's future request for a PRV.
- RPD designation requests must be submitted before FDA has filed the NDA/BLA for the drug for the relevant indication.

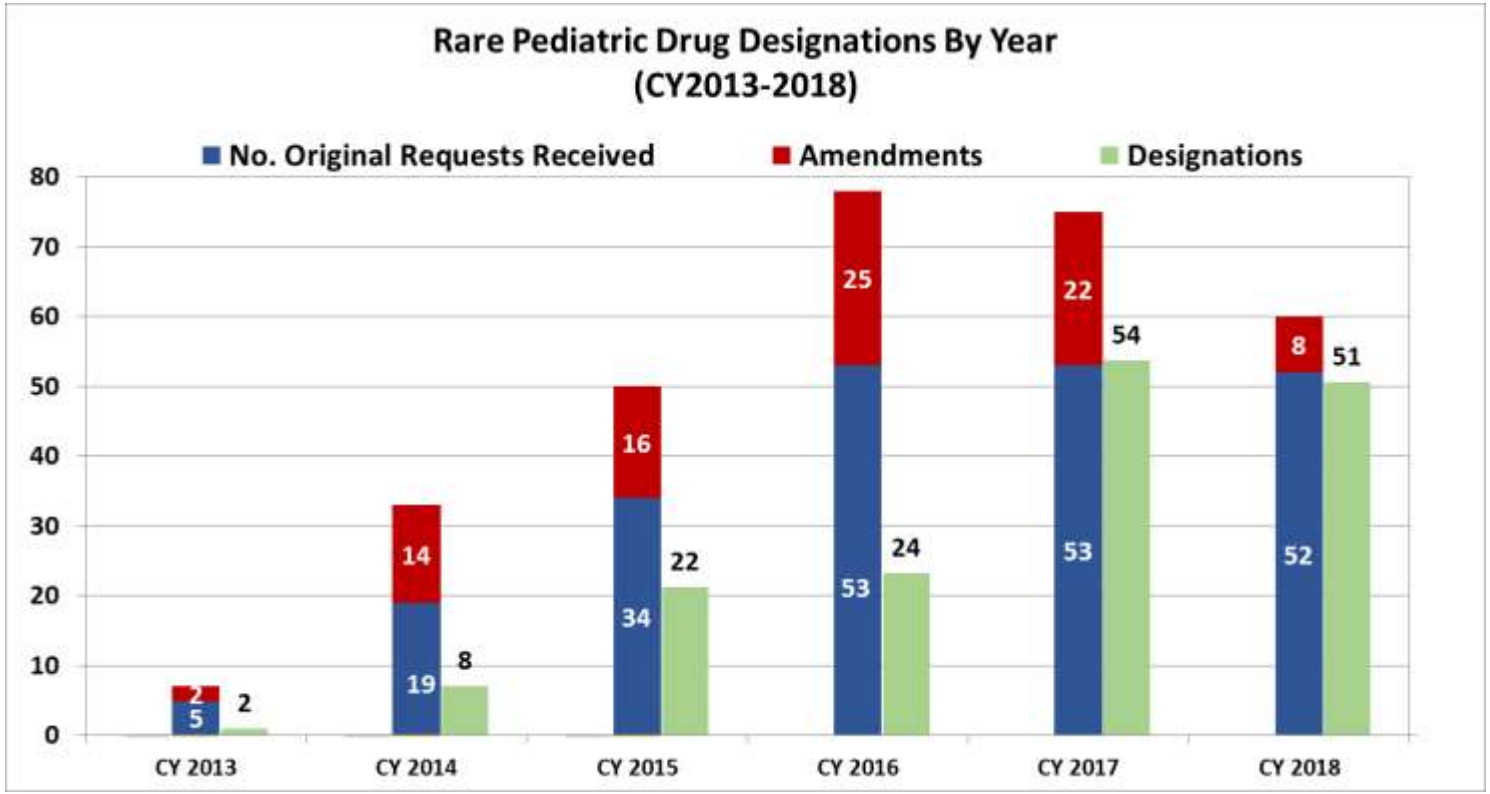
RPD Process


Sponsor
(OPTIONAL) Submits RPD designation request
Submits NDA/BLA
OOPD
CDER
CBER
If product did not get RPD designation, CDER/CBER submits consult
IS THE DRUG FOR A RPD?
1) Is the disease rare?
2) Do the serious/life-threatening manifestations primarily affect individuals 0-18?
Is the application a RPD product application?
NO (issue deficiency)
YES (grant designation)
If YES, Issue Voucher (if all conditions met)

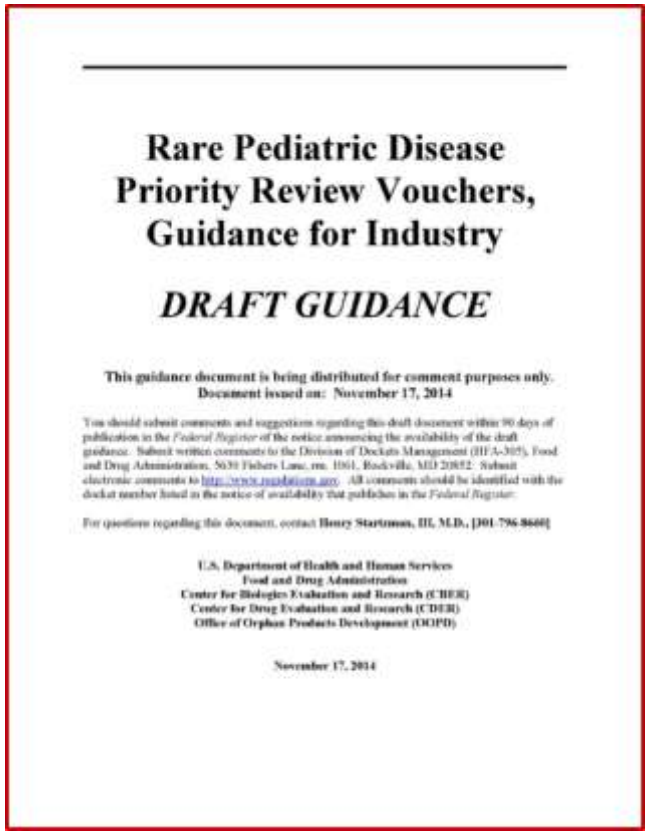
Review of RPD Designation Requests

- RPD designation requests should be submitted to OOPD.
- OOPD and the Office of Pediatric Therapeutics jointly conduct review of RPD requests.
- RPD designation requests should include similar information to orphan drug designation requests with emphasis on:
  - Is the disease or condition rare?
  - Do the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years?

RPD Designation Trends



RPD Resources



Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: November 17, 2014

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Henry Startsman, III, M.D., [301-796-8660]

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Office of Orphan Products Development (OOPD)

November 17, 2014

- Draft guidance: Rare Pediatric Disease Priority Review Vouchers, Draft Guidance for Industry (note: does not reflect changes made to the law by the Advancing Hope Act of 2016)

- OOPD RPD Program webpage

Orphan Products Clinical Trials Grants Program

Grant Programs
Orphan Products Clinical Trials Grant Program
Pediatric Device Consortia Grant Program
Orphan Products Natural History Grant Program

Orphan Products Clinical Trials Grants Program

Goal: Support **efficient** and **innovative** clinical trials for *products* that:

- address **unmet needs** in rare diseases/conditions or
- provide **highly significant improvements** in treatment or diagnosis

Products: drugs, biologics, devices, and medical foods

Disease or condition: <200,000 prevalence in U.S.

- Diagnostics and vaccines may be eligible if they will be administered to <200,000 people per year

Impact

- Since inception in 1983:
  - Received > 2,700 applications (~100/year)
  - Provided > $400 million to fund > 600 studies
  - Contributed to >60 products receiving marketing approval

- FY 2018 alone:
  - 79 grant applications received
  - Awarded 12 new clinical trial research grants
  - Totaling > $18 million funding over the next four years

Orphan Products Clinical Trials Grants Program

- OOPD Budget: ~$15.5 million/year
- Typically 60-85 ongoing grant-funded projects
- **Funding levels:**
  - No longer based on Phase of the study
  - Application budgets are not limited, but need to reflect the actual needs of the proposed project
  - Maximum project period is 4 years

Orphan Products Clinical Trials Grants Program

- **Eligibility**:
  - Foreign or domestic, public or private, for-profit or nonprofit entity
  - State and local units of government
  - Federal agencies may not apply
- Orphan drug designation is encouraged, but not required
- Funding dependent on scientific merits of application, availability of funds, and relevance to program priorities
- **Review:** Applications scored by panel of internal reviewers and external rare disease experts

Review Criteria

1. Rationale:

- The soundness of rationale in relation to the current understanding of the rare disease(s) and the likelihood the proposal will facilitate medical product development to address an unmet medical need in a rare disease(s) or provide highly significant improvements in treatment or diagnosis and assist or substantially contribute to market approval of the proposed product(s).

2. Study Design and Inclusion of Patient Input:

- The quality and appropriateness of the study design, research methodology, and data analyses to accomplish the specific aims of the proposed study. Patients and caregivers are highly encouraged to be involved in the planning of the design and development of these clinical studies. Their perspectives contribute to improved protocol design and medical product development through understanding of disease and treatment burden, impact on daily living and quality of life issues which may be otherwise overlooked.

3. Investigator(s):

- The qualifications of the Principal Investigator(s) (PIs), collaborators, and other support staff.

4. Infrastructure and Resources:

- The probability of success of the proposed project given the environment in which the work will be done.

5. Ability to Advance the Current Field:

- The ability of the project to shift current research or clinical practice paradigms towards future product development and to exert a significant influence on product development.

Orphan Products Clinical Trials Grants Program

- **Requirements:**
  - ✓ **Clinical study** of an orphan disease or condition
  - ✓ Study must advance information towards a market approval
  - ✓ Must have active IND (not on clinical hold)
  - ✓ Good Clinical Practices
  - ✓ Human Subjects Assurance from Office of Human Research Protections (OHRP) "Federal-Wide Assurance or FWA"
  - ✓ IRB approval
  - ✓ Confirmation that drug product is sufficiently available

- Next application due date: **June 25, 2019**
  - Registrations required prior to submitting a grant application can take 6 weeks or more (e.g. eRA Commons, Data Universal Number System [DUNS])

Resources: Clinical Trials Grants

- OOPD Clinical Trials Grants program webpage
  - Contains many useful links such as:
    - FAQs
    - Information on how to apply for funding
    - Previous webinars and presentations
    - Searchable database for funded grants (past & present)

Orphan Products Natural History Grants Program

Grant Programs
Orphan Products Clinical Trials Grant Program
Pediatric Device Consortia Grant Program
Orphan Products Natural History Grant Program

What is a Natural History Study?

- **Natural History of a disease**: the natural course of a disease from the time immediately prior to its inception, progressing through its pre-symptomatic phase and different clinical stages to the point where it has ended without external intervention

- **Natural History Studies:** track the course of disease over time, identifying demographic, genetic, environmental, and other variables that correlate with its development and outcomes

Orphan Products Natural History Grants Program

Goal: Support **efficient** and **innovative** studies that advance rare disease medical product development:

- through characterization of the natural history of rare diseases/conditions with **unmet needs**.
- exert a **significant and broad impact** on a specific rare disease or multiple rare diseases with similar pathophysiology.

- Ultimately, to assist in marketing approval

Orphan Products Natural History Grants Program

- First call for applications in 2016
  - 89 applications received; 83 responsive
  - $6.3 million awarded to 4 grants over 2 – 5 years.
  - Two additional grants co-funded by NIH (Therapeutics for Rare and Neglected Diseases program) and FDA
- Second cycle: Application deadline was Jan. 10, 2019
  - 31 applications received
  - Panel: June 24, 2019
  - Funding by: Sept. 30, 2019

Orphan Products Natural History Grants Program

- **Eligibility**:
  - Foreign or domestic, public or private, for-profit or nonprofit entity
  - State and local units of government
  - Federal agencies may not apply
- Funding dependent on scientific merits of application, availability of funds, and relevance to program priorities
- **Review:**
  - All applications scored by external rare disease experts and internal regulatory/technical experts
  - Those with best scores will go to panel which includes patient reps and statistical reviewers

Orphan Products Natural History Grants Program

- ✓ Review criteria: very similar to Clinical Trials Grants program
- ✓ OOPD Budget: ~$2 million/year
- ✓ **Funding levels:**
  - Application budgets are no longer limited but need to reflect the actual needs of the proposed project
  - Maximum project period:
    - Prospective NH Studies: 4 years
    - Retrospective NH Studies: 2 years
- ✓ Next deadline for applications: TBD

For more information see OOPD's Natural History Grants program webpage

10 Hints for Submitting Grant Applications

1. Start as early as possible, plan carefully, write clearly and objectively

2. Read the Request for Applications (RFA) and instructions carefully (not just for deadlines)

3. Use the Grant Writing Tips from NIH Extramural Programs

4. Panel reviewers are busy, so say things in fewer words if possible

5. Establish good relations with FDA review divisions via IND process. They do not score the application, but are invited to the panel as a resource.

10 Hints for Submitting Grant Applications (cont'd)

6. Call OOPD for clarifications: 301-796-8660

7. Call Grants Management for budget help: Dan Lukash (240-402-7596)

8. If you do not have expertise for issues, provide letters of collaboration for the needed expertise

9. Use outside readers improves the quality of the proposal

10. Don't be discouraged – read summary statements and address all critiques to improve the study

OOPD Contact Information

For more information on OOPD programs go to:
www.fda.gov/orphan

Still have questions?

Email us at orphan@fda.hhs.gov

Call us at 301-796-8660

Challenge Question

1: A sponsor can submit an Orphan Drug Designation request

a) any time prior to approval of their marketing application
b) any time prior to submission of the marketing application
c) whether or not they have an IND for the drug application
d) b *and* c

Challenge Question

2: Organizations that are eligible to apply for an Orphan Products Clinical Trials Grant include:

a) Foreign or domestic entities

b) For-profit and non-profit entities

c) State and local units of government

d) All of the above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