ORPHAN PRODUCT DEVELOPMENT

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About Dr. Fermaglich

- Medical Officer in the Office of Orphan Products Development (OOPD)
  - Administer incentive programs to promote the development of products for rare diseases and participate in cross-agency rare disease initiatives

- MD, University of Kentucky College of Medicine
- Residency in Pediatrics, Children's National Medical Center, Washington, D.C.
- Masters in Health Administration (MHA), George Washington University in 2018

Disclosure

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration, or the Department of Health and Human Services
- The speaker has no relevant personal, professional or financial relationship(s) with respect to this presentation

Learning Objectives

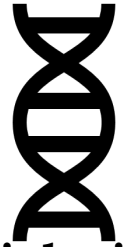
- Define an orphan product
- Describe why developing treatments for rare diseases is challenging, yet important to public health
- Review FDA's orphan drug designation process
- Explain FDA incentives to promote the development of orphan drugs

ORPHAN PRODUCT BASICS

What is an "Orphan Product"?

- Product that demonstrates promise for the diagnosis, treatment, or prevention of a **rare disease or condition** and includes:

Drugs



Biologics

Medical Devices

Medical Foods

What is a "Rare Disease"?

- Defined by law and is different for drugs/biologics and devices
  - Drugs/Biologics: **Disease that affects < 200,000 persons in the US** [1]
  - Devices: Disease with an incidence of ≤ 8,000/year in the US [2]

- Definition varies globally; for drugs/biologics:
  - EU: < 5 per 10,000
  - Japan: < 50,000 (4 per 10,000)

- Examples include Cystic Fibrosis, Duchenne's Muscular Dystrophy, Sickle Cell Disease, Amyotrophic Lateral Sclerosis (ALS), Pancreatic Cancer

1. SEC. 526 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT [21 U.S. Code 360bb]
2. 21 Code of Federal Regulations 814.102

Challenges to Rare Disease Drug Development

- Phenotypic diversity within a disorder adds to complexity, as do genetic subsets
- Small (often *very* small), widely-dispersed patient population
- Natural history of the disease is often not well understood
- Complexity in identifying the appropriate endpoints

DEVELOPMENT OF U.S. LEGISLATION ON RARE DISEASES

U.S. Historical Perspective

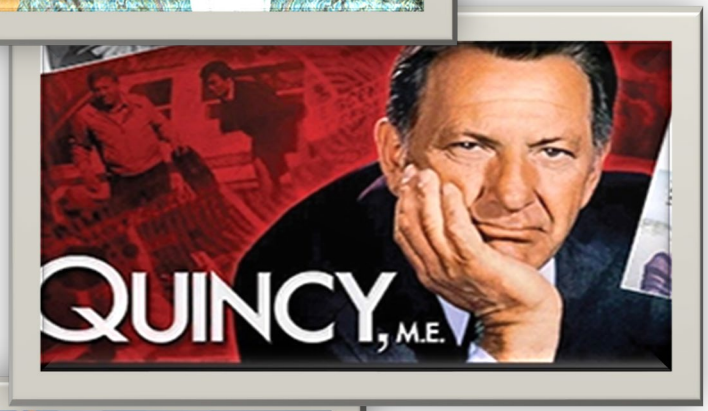
In the decade prior to 1983, only ~1 drug per year was independently developed by pharmaceutical companies specifically for rare diseases.

Industry was reluctant to invest in small markets, so legislation was needed to create incentives to promote drug development for rare diseases.

Patients were the driving force!

Abbey Meyers, a parent of a child with a rare disease was the driving force behind U.S. rare disease (orphan) legislation

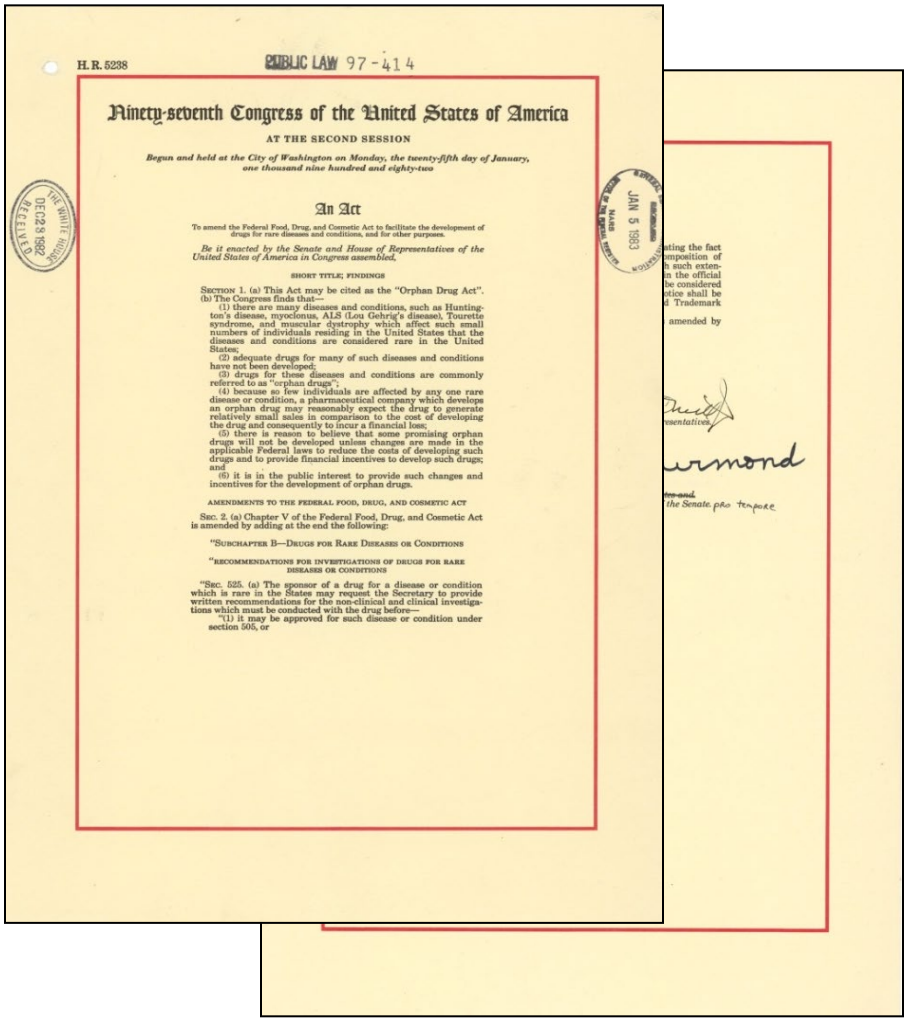
- Her son was taking an experimental drug which the sponsor discontinued manufacturing because it was not profitable



- She worked with other patient advocates to convince U.S. Congress to hold hearings on orphan drugs

- In 1981 **Congressman Waxman** introduced the Orphan Drug Act (ODA), which was signed into law on Jan. 4, 1983

Orphan Drug Act (ODA)



H. R. 5238 PUBLIC LAW 97-414

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

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:

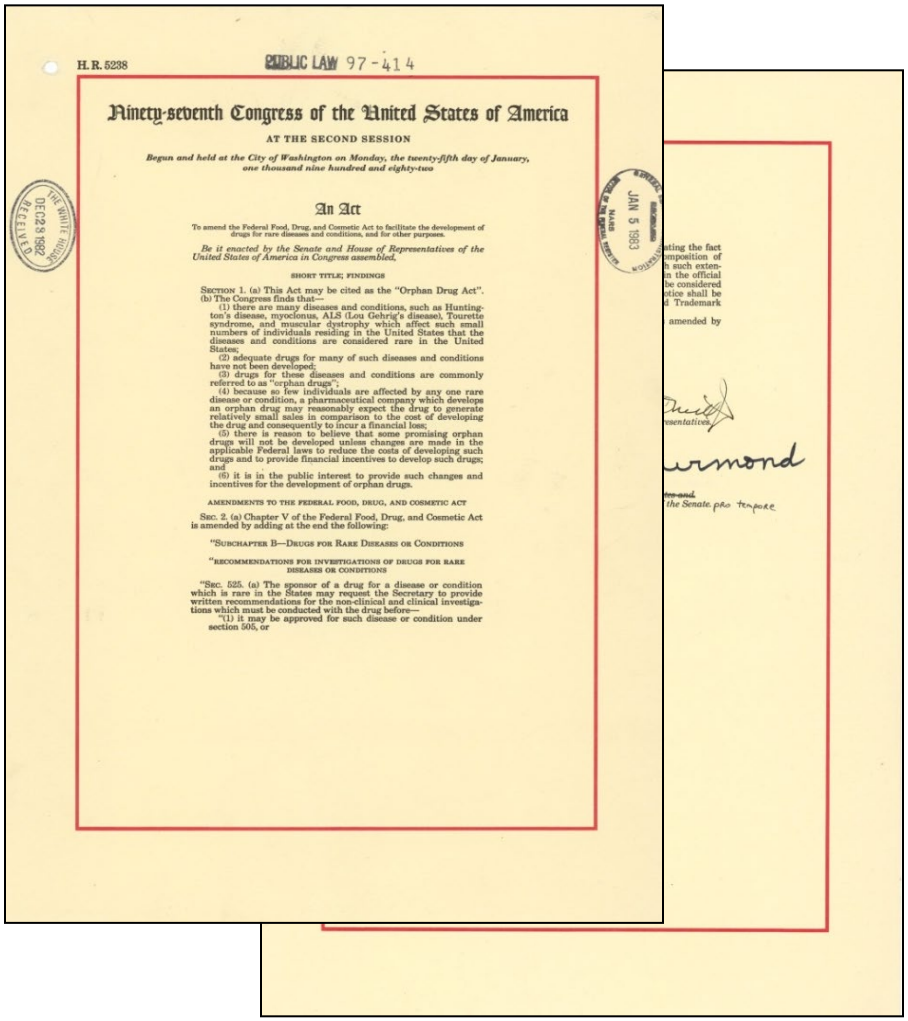
"SUBCHAPTER B—DRUGS FOR RARE DISEASES OR CONDITIONS

"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

- Defined **"rare disease"** for drugs and biologics
  - Disease/condition that affects < 200K people in the U.S.; or
  - Drug for a disease that affects > 200K people, but will not be profitable within 7 years of U.S. FDA approval

Orphan Drug Act (ODA)



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Created incentives for orphan drug development, including:

1. Orphan Drug Designation Program
2. Orphan Products Grants Program

(Note, since the ODA, other legislation has been passed to incentivize devices for rare diseases and therapies for rare pediatric diseases.)

ORPHAN DRUG DESIGNATION PROGRAM

Financial Incentives Associated With Orphan Drug Designation

1. **Tax credits** (currently 25%) to defray costs of conducting qualified clinical studies
2. Receive a **waiver** of marketing application fees
3. Potential eligibility for **7-year marketing exclusivity** ("*orphan exclusivity*") upon marketing approval

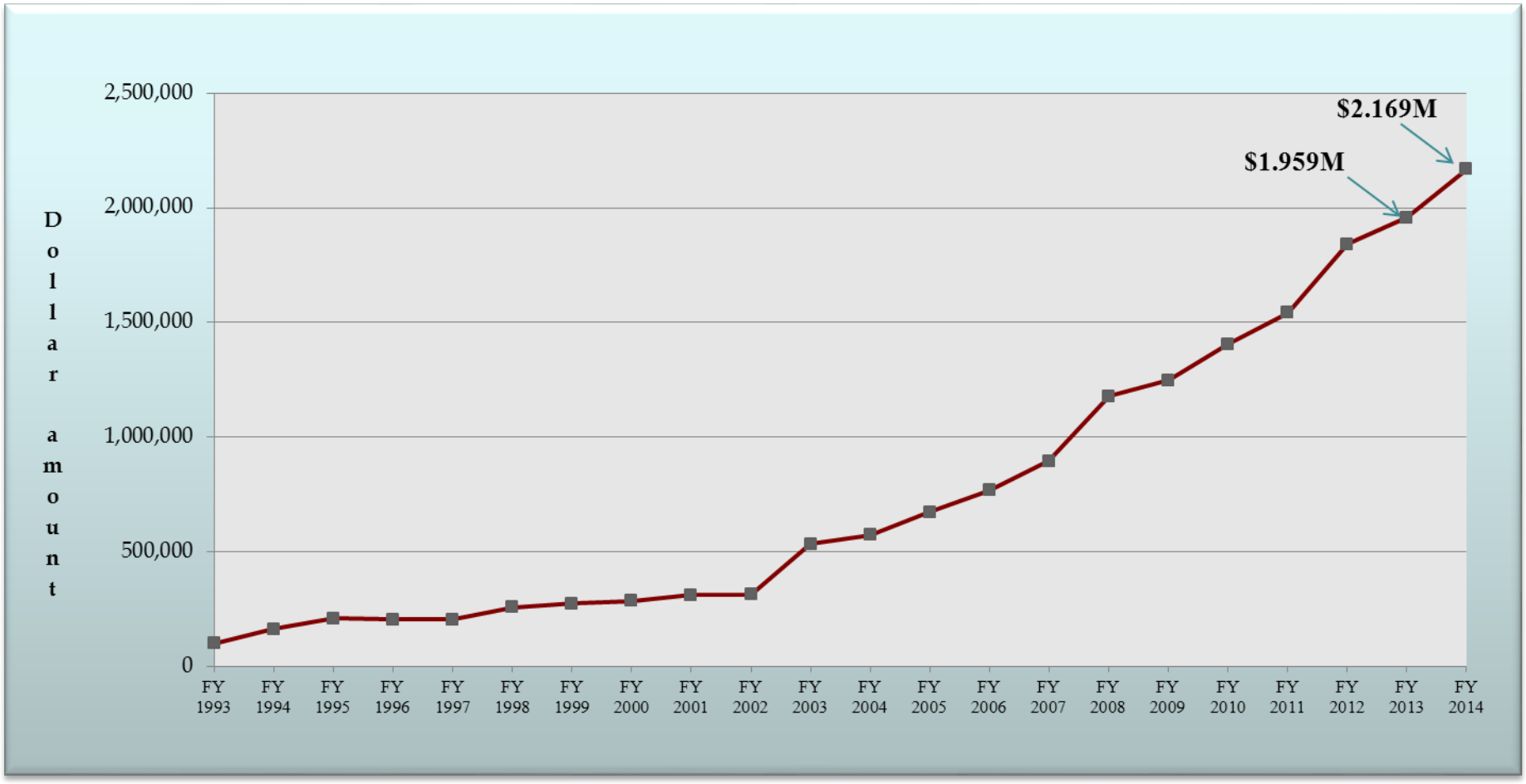
Cost of Clinical Trials

- In 2016, the median estimated direct costs of pivotal trials was $19 million

(Moore TJ et al. JAMA Int Med. 2018;178:1451-1457)

Potential to receive up to $4.75 million in tax credits with orphan drug tax incentives

Marketing Application Fees

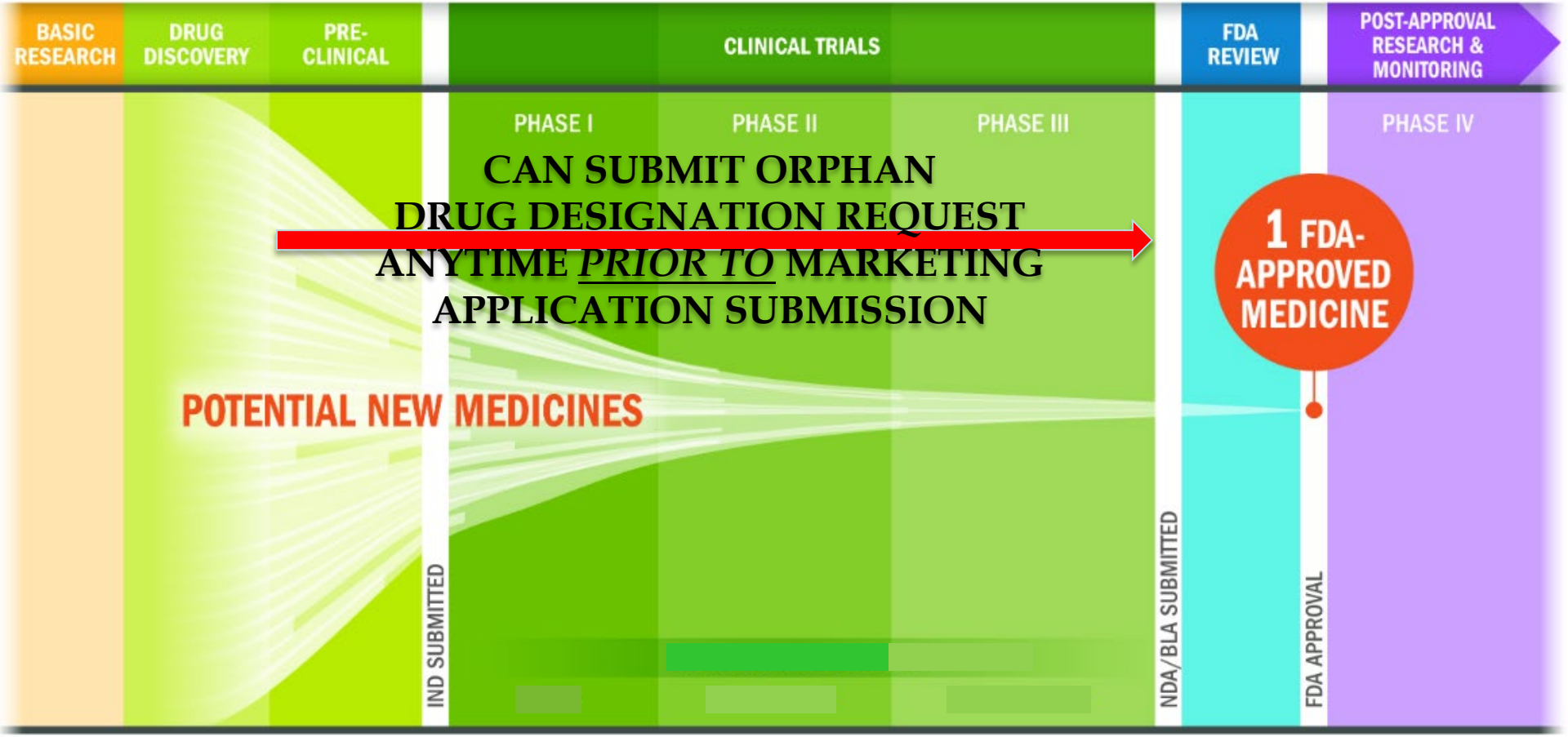


For FY22, marketing application user fees are $3,117,218

7-Year Market Exclusivity

- **FDA will not approve another "same drug" (i.e., active moiety or molecular structure) for that same use/indication by a different sponsor for 7 years**
- Example: if drug A has orphan exclusivity for treatment of cystic fibrosis, FDA could not approve another same drug A for **that disease**. However, FDA could approve other drugs for cystic fibrosis and could approve drug A for other diseases, including other rare diseases
- Exclusivity can be "broken" in cases of:
  - Drug shortage
  - Another drug is "clinically superior" to the approved drug

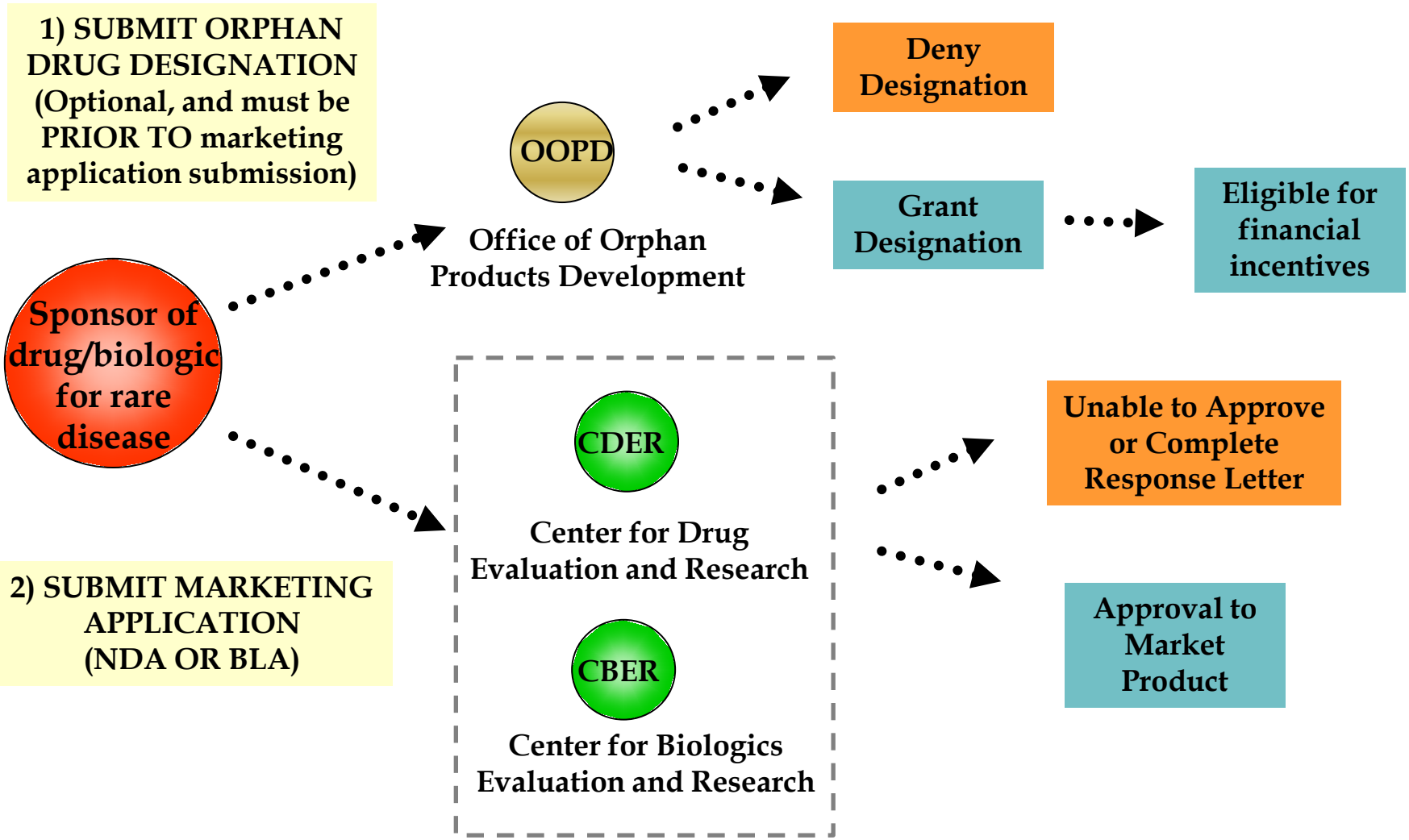
Drug Discovery Timeline



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).


1) SUBMIT ORPHAN DRUG DESIGNATION (Optional, and must be PRIOR TO marketing application submission)
OOPD
Office of Orphan Products Development
Deny Designation
Grant Designation
Eligible for financial incentives
Sponsor of drug/biologic for rare disease
CDER
Center for Drug Evaluation and Research
CBER
Center for Biologics Evaluation and Research
Unable to Approve or Complete Response Letter
Approval to Market Product
2) SUBMIT MARKETING APPLICATION (NDA OR BLA)

Review of a Designation Request

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

2. Is the disease rare (**population estimate**)?

3. Is there sufficient **scientific rationale** that demonstrates promise ("medical plausibility"[1]) that the drug/biologic will treat, diagnose or prevent the disease/condition at issue?

1. SEC. 526 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT [21 U.S. Code 360bb]

#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?

- 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
- Population estimate generally determined by **prevalence** in US - must be less than 200K
- **Incidence** only used for acute diseases with a duration of < 1 year that do not recur
- If there is a prevalence or incidence range, generally FDA uses the highest estimate as the most conservative population estimate

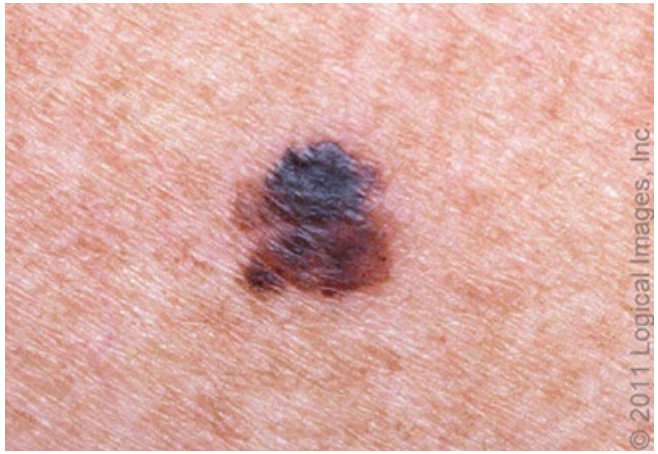
#2 cont'd – Is the Disease Rare?

- Examples of sources to determine prevalence/incidence:
  - Published literature
  - NCI's SEER database for rare cancers
  - 3 independent expert opinions (sponsor's last option)

- If disease/condition occurs in > 200K persons, can grant 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 Subset

- Prevalence of melanoma in 2017: 1,245,276
- Current standard of care for Stage I-IIA melanoma is curative surgical excision
- Prevalence of Stage IIB–IV melanoma: **129,424**
- >100 Drugs have been designated for Stage IIB–IV melanoma



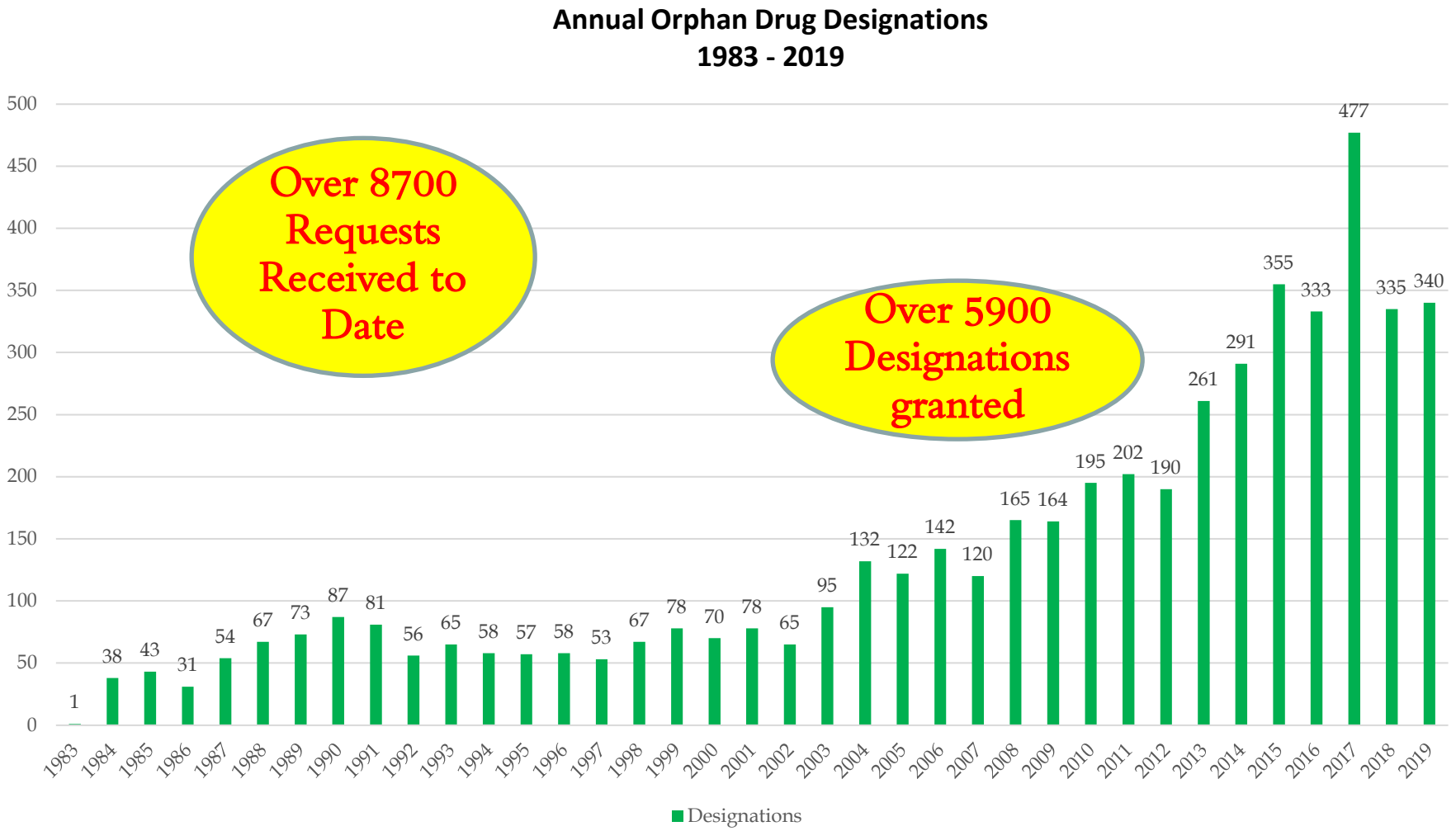
#3 – Is the Scientific Rationale Sufficient?

- Basis of evidence that the drug holds promise for being effective in treating/preventing/diagnosing disease
- Includes data from:
  - Clinical data, case study reports;
  - Animal models; **or**
  - *In vitro* data (with proposed mechanism of action and pathogenesis of disease when no adequate animal model is available)
- Data from adequate and well-controlled studies are **not** required

Clinical Superiority

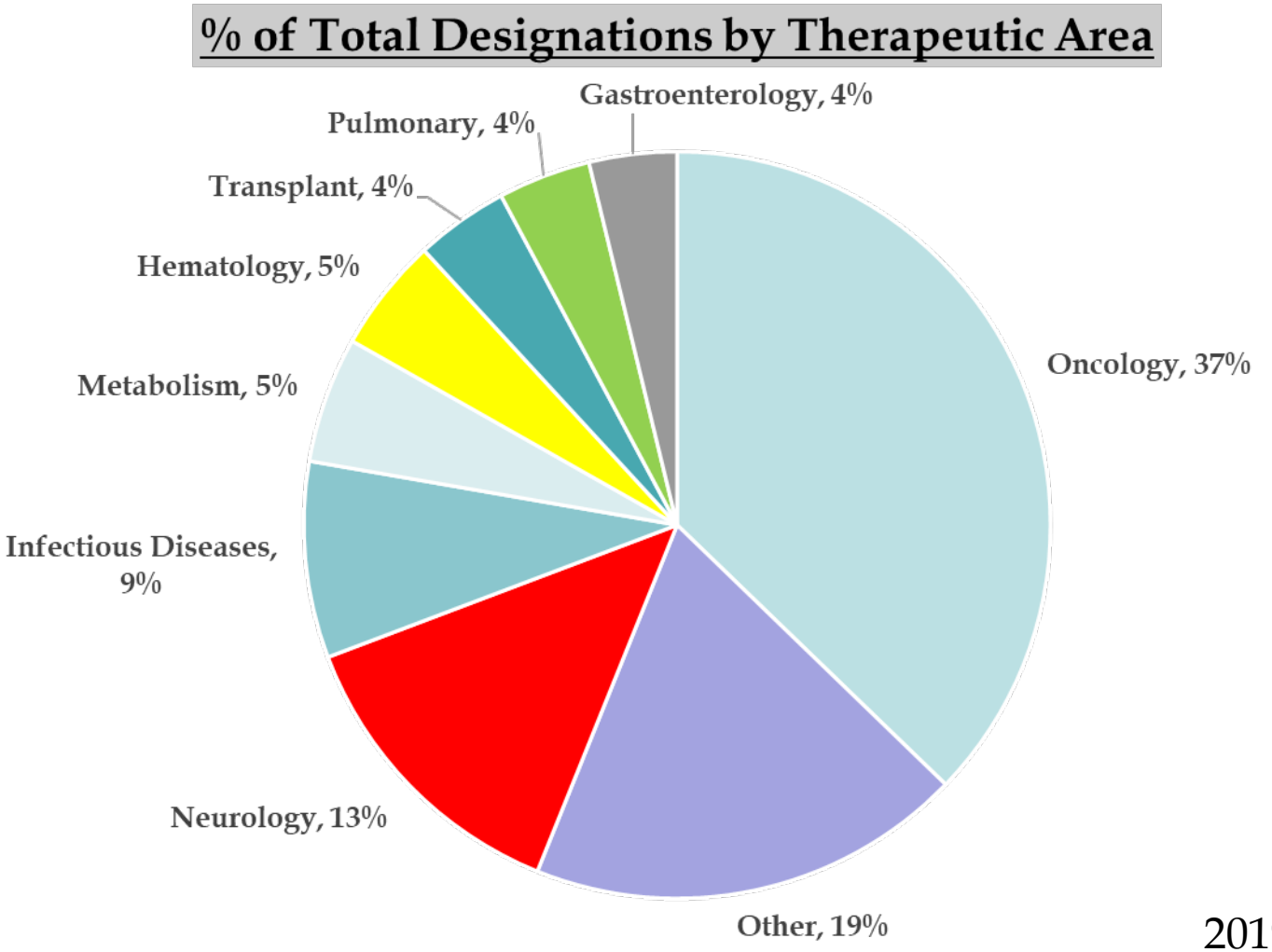
- When seeking designation of a drug that is the "same" as an already approved drug, sponsors must provide a **plausible hypothesis of clinical superiority**
  - "Same drug" defined in regulation; does not mean identical
    - i.e., small molecule with same active moiety but different salt or ester
      - Glycerol phenylbutyrate vs. sodium phenylbutyrate
  - "Clinical superiority" defined as greater safety, greater efficacy, or a major contribution to patient care

Orphan Drug Designation Data



Orphan Drug Approval Data

Orphan Drug Designation Data



2019 Data

Approval Standard

- To be approved, drugs need to be safe and have substantial evidence of efficacy
  - Generally means 2 well-controlled clinical trials
- Approval Standard for Orphan Drugs – Same standard of approval BUT…

" While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of users for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."

– 21 CFR 314.105(c)

OTHER OOPD PROGRAMS

OOPD Grants Programs

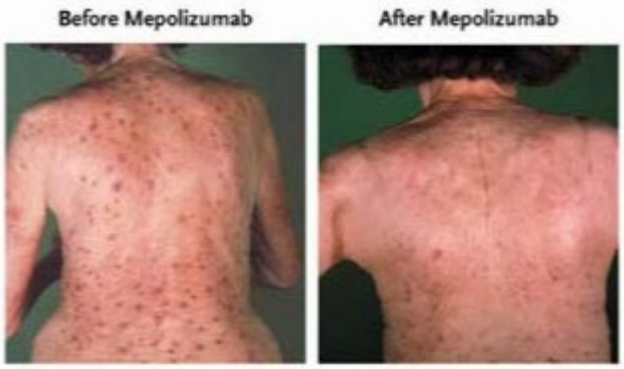
Clinical Trial Grants Program (~$15 million)

Supports clinical studies of products that address unmet needs in rare diseases or conditions or provide highly significant improvements in treatment or diagnosis

Natural History Grants Program (~$2 million)

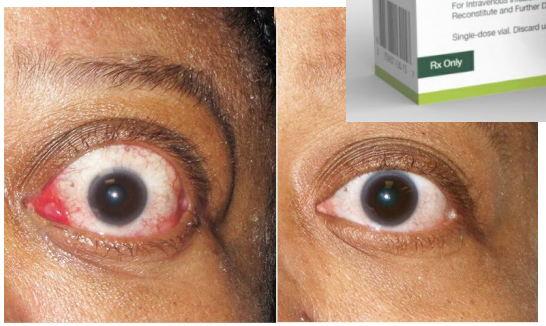
Supports studies that advance rare disease medical product development through characterization of the natural history of rare diseases/conditions, identification of genotypic and phenotypic subpopulations, and development and/or validation of clinical outcome measures, biomarkers and/or companion diagnostics

Examples of OOPD Grants



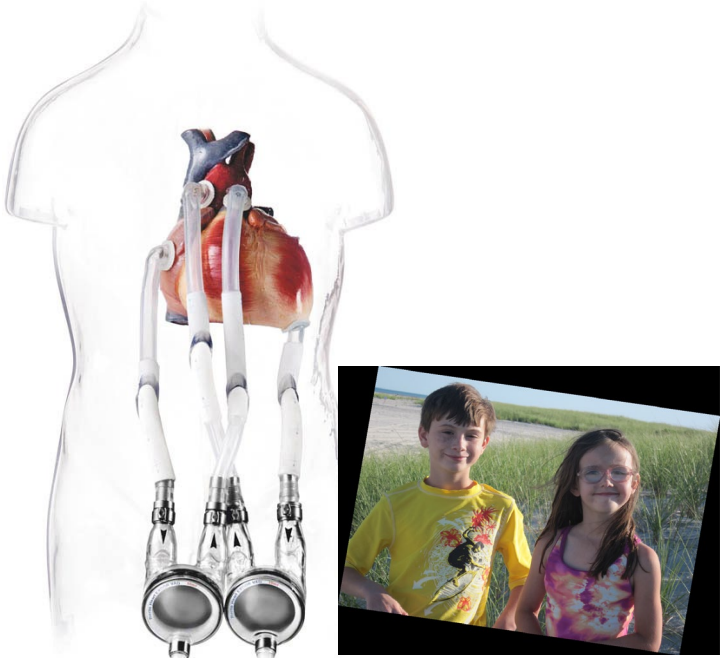
Nucala (mepolizumab) is a monoclonal antibody that works by reducing levels of eosinophils (a type of white blood cell) approved for Hypereosinophilic Syndrome (HES).
OOPD supported 2003-2006
Marketing approval 2020

Kalydeco® (ivacaftor), an example of personalized medicine, is the first available treatment that targets the defective CFTR protein which is the underlying cause of cystic fibrosis (CF).
OOPD supported 2007-2010
Marketing approval 2012 and subsequent approvals of Orkambi® (in 2018), and Trikafta®, Symdeko® (in 2019)



Patient's eye before/after Tepezza treatment

Tepezza® (teprotumumab) is a treatment for proptosis associated with thyroid eye disease.
OOPD supported 2014-2017
Marketing approval 2020



Berlin Heart Excor® Pediatric Ventricular Assist Device, used as a bridge to heart transplantation in children, is designed to vibrate rhythmically to assist patients who cannot pump enough blood with their own heart.
OOPD supported 2009-2012
Marketing approval 2011

Rare Pediatric Disease Priority Review Voucher (RPD PRV) Program

- Program intended to incentivize the development of therapies for rare pediatric diseases
- Basic Idea: If a sponsor receives approval of a **"rare pediatric disease product application,"** the sponsor is eligible to receive a PRV which can be redeemed, or transferred to another sponsor, to obtain priority review of another application that would otherwise be ineligible for priority review
- RPD designation does not guarantee voucher award upon approval

Device-Related Programs

- **Humanitarian Use Device (HUD) Designation**
  - HUD designation if treating or diagnosing a disease or condition affecting ≤ 8,000 individuals in the US/year [1]
  - Eligible to submit an HDE application, which allows a product to be approved based on a showing of safety and probable benefit

- **Pediatric Device Consortia Grant Program**
  - Funds Consortia (networks) that support pediatric device developers; not a direct research grant

1. 21 Code of Federal Regulations 814.102

Communicating with FDA

Resources for FDA to engage with patients and their advocates

- Patient-Focused Drug Development (PFDD)
  - FDA-led
  - Externally-led
- Patient Listening Sessions
- Dockets

Communicating with FDA

Please join us for FDA's **Rare Disease Day** on **3/4/2022** – Register **HERE**

Summary

- An orphan product is designed for the **diagnosis, treatment, or prevention of a rare disease or condition**
- Sponsors can apply for orphan drug designation **any time** during the drug development process **prior to submitting a marketing application**
- To be designated as an orphan drug, sponsors must provide evidence that:
  - The target disease/condition is rare (**POPULATION ESTIMATE**)
  - The proposed drug or biologic demonstrates "promise" to treat, diagnose or prevent the disease/condition (**SCIENTIFIC RATIONALE**)
- FDA incentives to promote the development of orphan drugs include **tax credits**, marketing application fee **waiver**, and conditional **7-year exclusivity**

Additional Resources

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

- Still have questions?
  - Email me at lewis.fermaglich@fda.hhs.gov

ADDITIONAL SLIDES

Approved Products Supported by OOPD Clinical Trials Grants

- Over 75 FDA approved products were at least partially funded through the OOPD Grants Program for over 85 indications
- ~10% of funded-studies have been used towards approval

- Triheptanoin (Dojolvitm) for long-chain fatty acid oxidation disorders (LC-FAOD)
- Teprotumumab (Tepezza) for Thyroid Eye Disease
- Cysteamine bitartrate (Procysbi) for Nephropathic Cystinosis
- Deferiprone (Ferriprox) for Iron overload in hematologic disorders requiring chronic transfusion therapy
- Ivacaftor (Kalydeco) for Cystic Fibrosis Subjects
- Dinutuximab (Unituxin) for Neuroblastoma
- Mepolizumab (Nucala) for Hypereosinophilia
- Sirolimus (Rapamune) for Lymphangioleiomyomatosis
- Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD) for Bridge to heart transplantation in children