

ORPHAN PRODUCT DEVELOPMENT

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- No Conflicts of Interest
- Although statements are vetted, these statements are mine and not the formal opinion of the FDA

Objectives

- To describe FDA incentives to promote the development of orphan drugs, with a specific focus on orphan drug designation as an incentive
- To briefly describe FDA's focus on rare disease collaborations

“Orphan Products” may be:

- In the United States:
 - Drugs –
 - Biologics –
 - Medical Devices –
 - Medical Foods –

Development of U.S. legislation on rare diseases

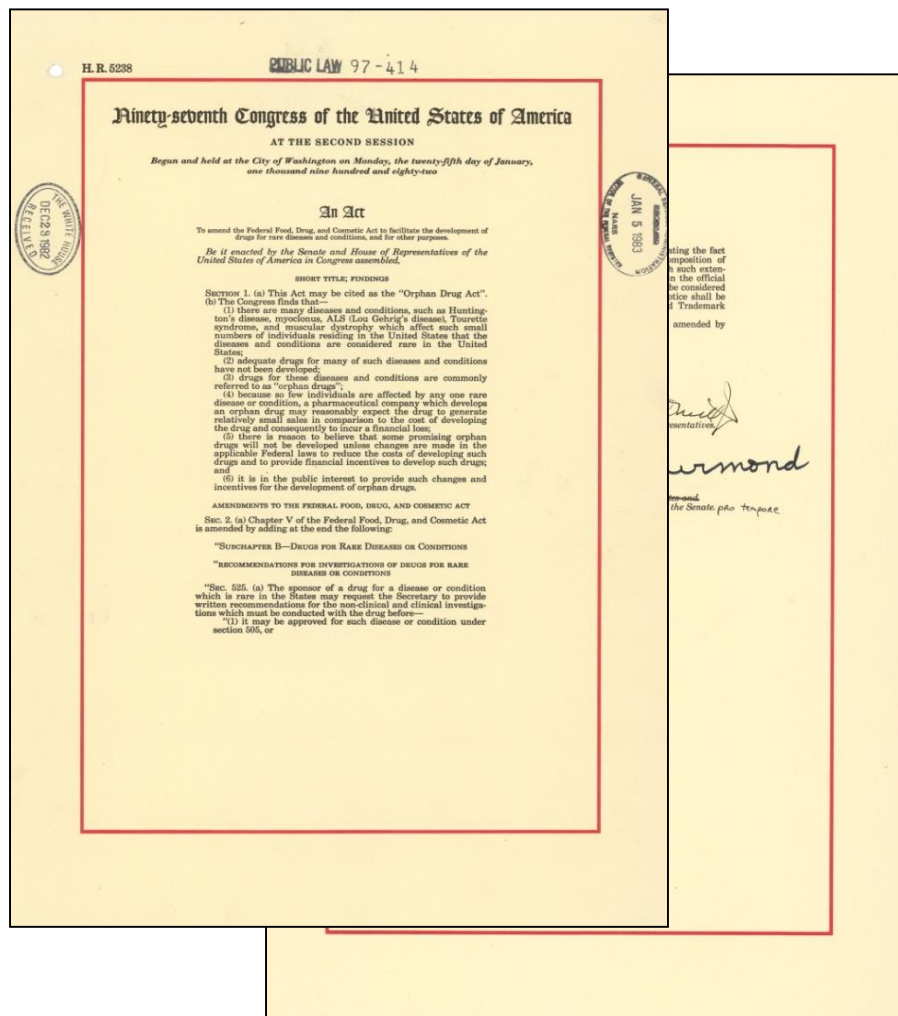
U.S. Historical Perspective

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

Industry was reluctant to invest in small markets so legislation was needed to create a market and promote drug development for rare diseases.

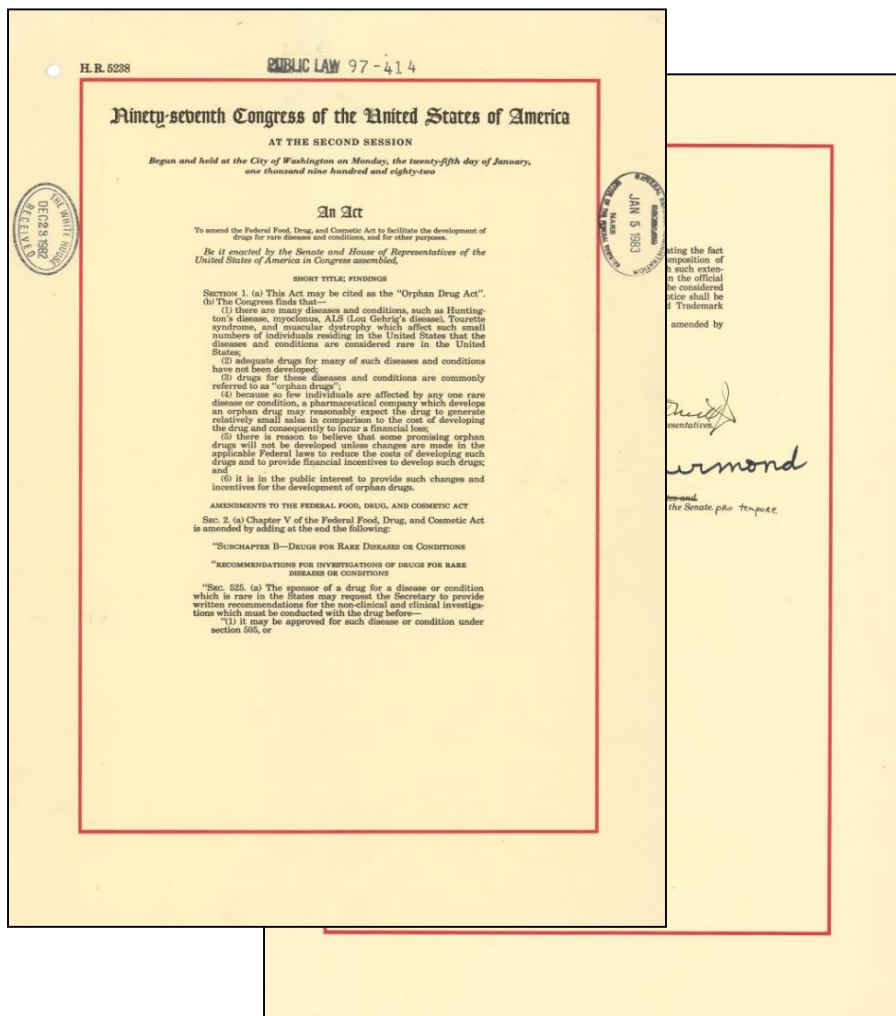
Patients were the driving force!

Orphan Drug Act (ODA)



- Defined “rare disease” for drugs and biologics
 - Disease/condition that affects < 200K people in the U.S.; or
 - Drug that will not be profitable

Orphan Drug Act (ODA)



Created incentives for orphan product development, including:

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

(Other legislation fir DEVICES therapies for RARE PEDIATRIC DISEASES

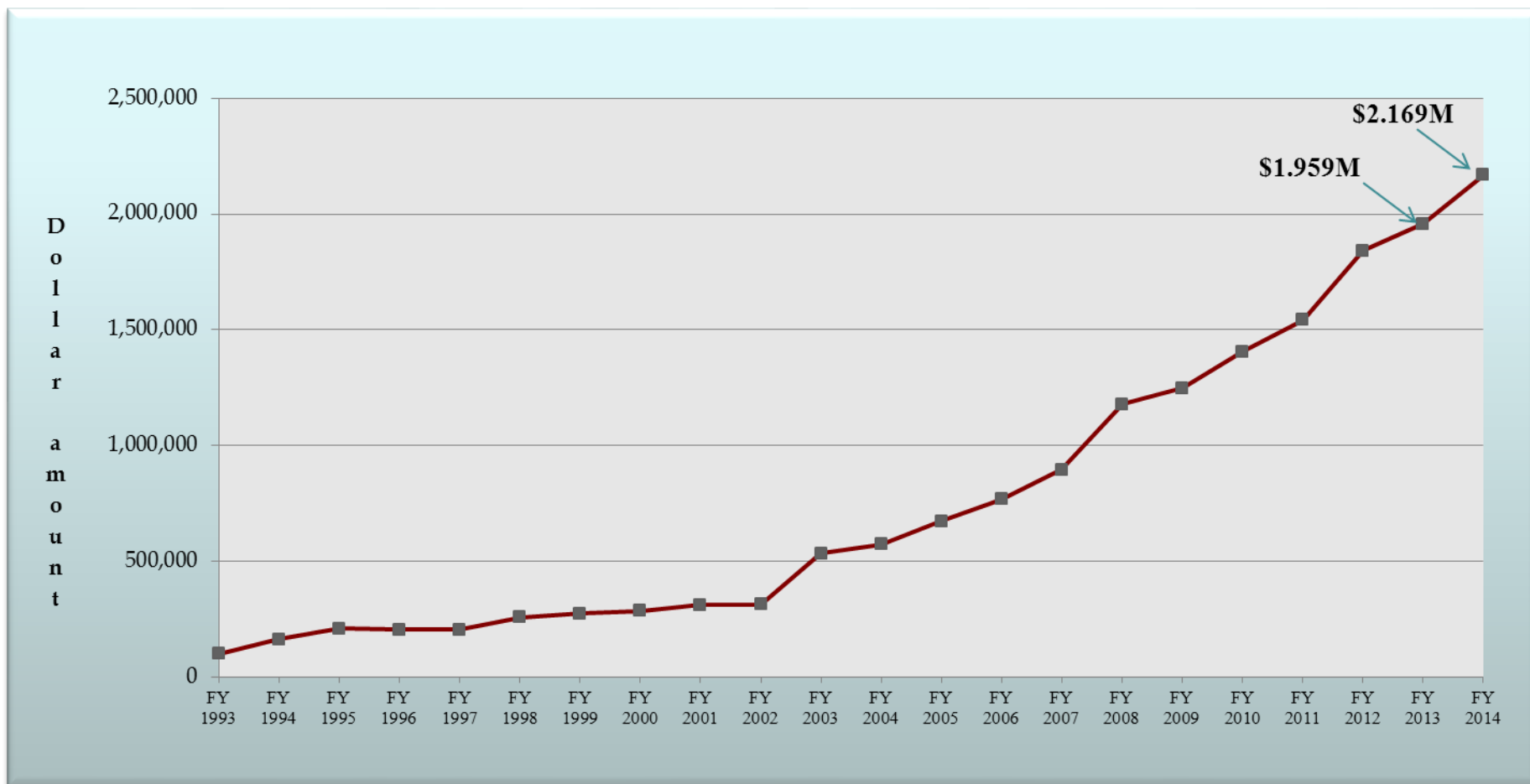


ORPHAN DRUG DESIGNATION PROGRAM

Financial Incentives Associated With Orphan Drug Designation

1. Receive 50% of clinical trials costs in **tax credits**
2. Receive a **waiver** of marketing application fees
3. May be eligible to receive **7-years of marketing exclusivity**

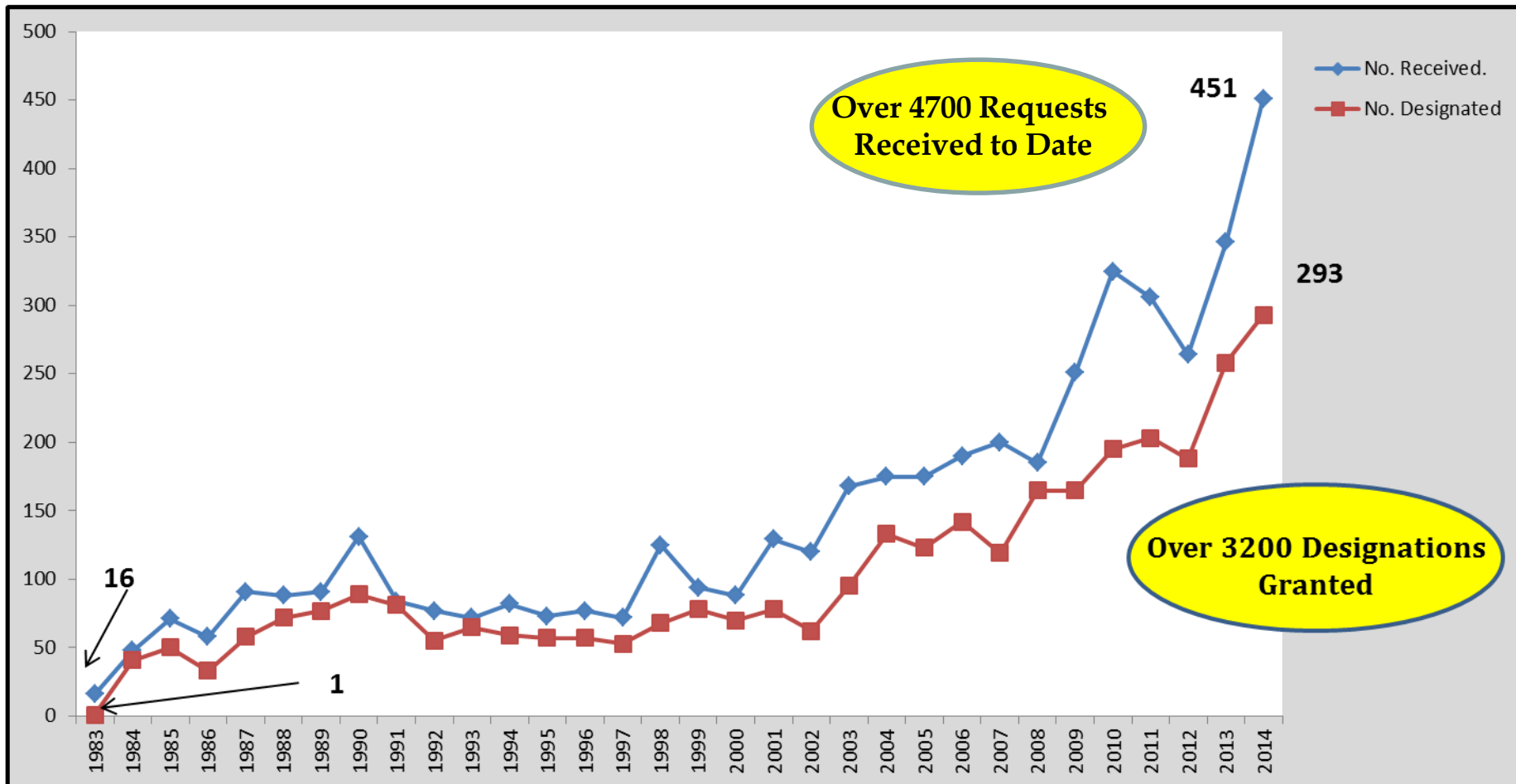
Marketing Application Fees



7-Year Market Exclusivity

- Exclusivity goes to the first sponsor of a designated orphan drug to receive approval for that designated orphan drug/disease
- FDA will not approve another “same drug” for the same indication for 7 years
- Exclusivity can be broken in cases of:
 - Drug shortage
 - Another drug is clinically superior to the approved drug
- Originally thought to be less important as an ODA incentive; now considered to be one of the biggest drivers of orphan drug development

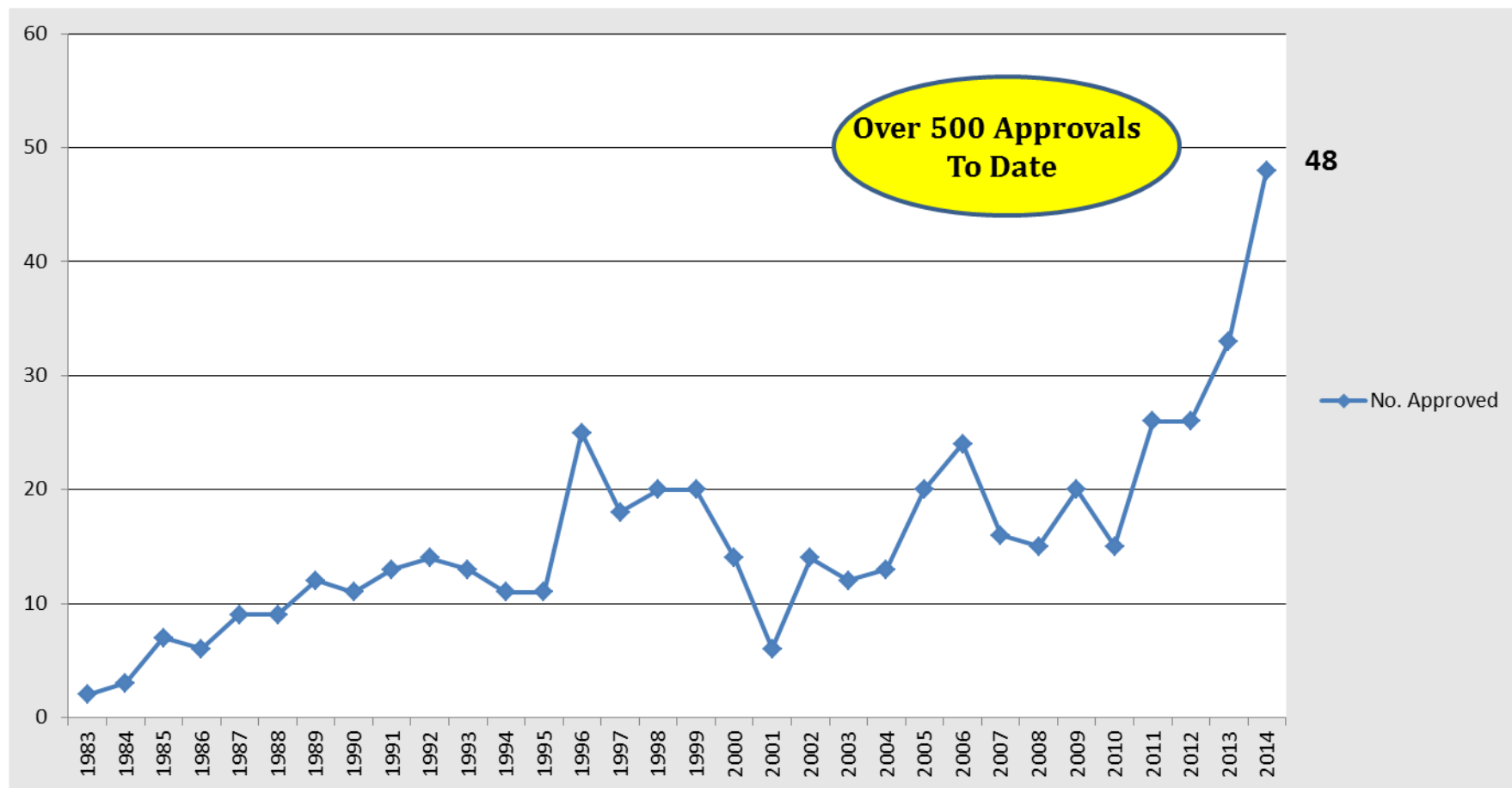
Orphan Drug Designations



Marketing Approval Standard

- Approval Standard for Drugs – Substantial evidence of safety and effectiveness
 - Generally means 2 well-controlled clinical trials
- Approval Standard for Orphan Drugs – Same standard of approval
- BUT...FLEXIBILITY regarding small populations such as orphan populations

Orphan Drug Approvals





OTHER OOPD PROGRAMS

Orphan Product *Grants* Program

- Fund clinical development of rare disease products
- Annual Budget ~ \$15 million
 - Phase I trials – Fund up to \$250,000/year for up to 3 years as of FY15
 - Up from \$200K/year for 3 years
 - Phase II & III trials – Fund up to \$500,000/year for up to 4 years as of FY15
 - Up from \$400K/year for 4 years

Orphan Product Grants Program

Very successful program to date

- Received over 2100 grant applications
- Funded 650 studies

- ~ 10% of orphan product approvals have received funding support by the OOPD Grants Program

Examples of OPD Grants



Scorpion antivenom

a biologic agent for the treatment of neurotoxicity from scorpion stings. Scorpion stings - an estimated 5,000 deaths annually worldwide.



Kalydeco™ (ivacaftor),

An example of personalized medicine-

The first available treatment that targets the defective CFTR protein which is the underlying cause of cystic fibrosis



Berlin Heart Excor® Pediatric Ventricular Assist Device,

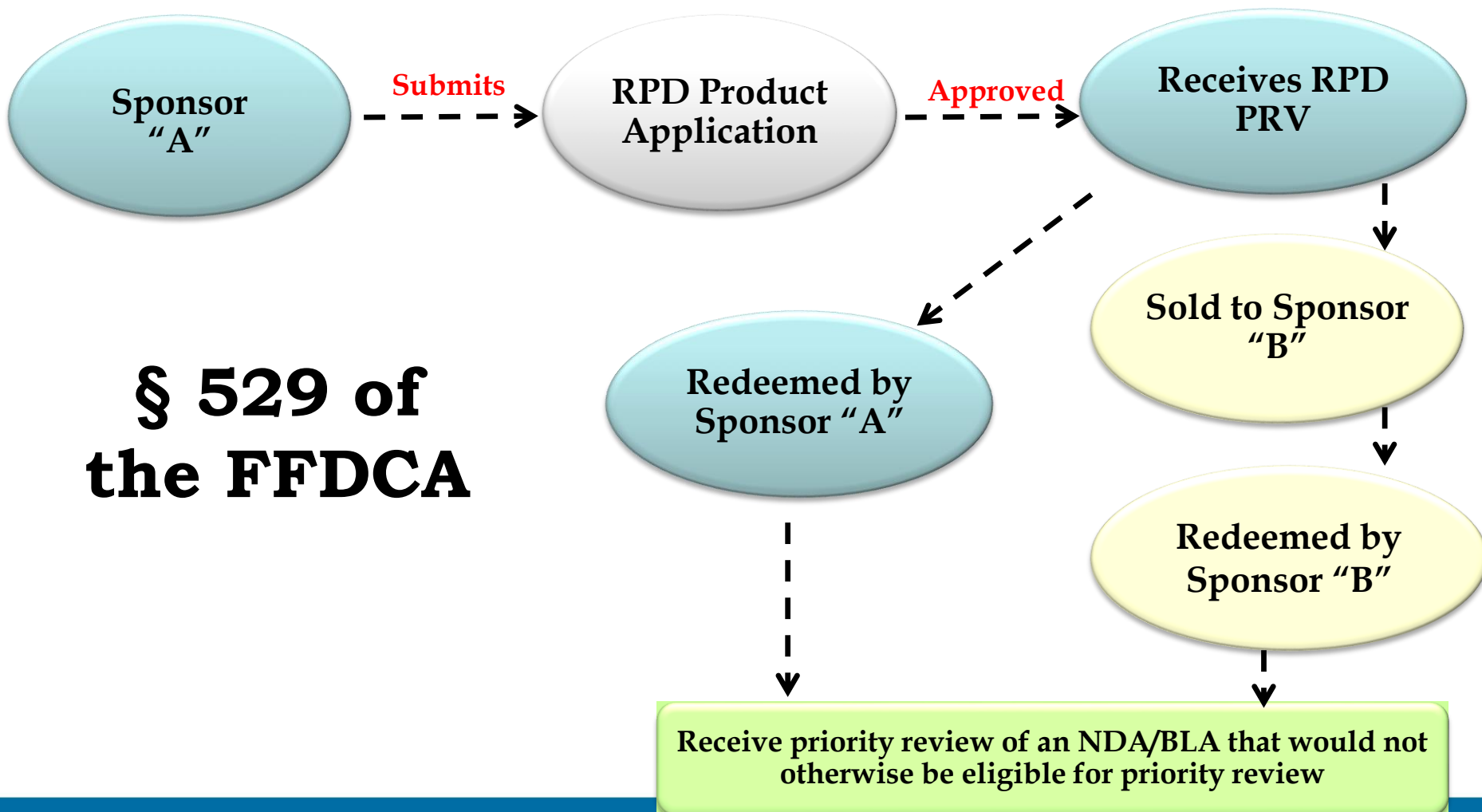
Used as a bridge to heart transplantation in children,

Designed to vibrate rhythmically to assist patients who cannot pump enough blood with their own heart.

Priority Review Voucher (RPD PRV) Program Rare Pediatric Disease Determination:

- 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

Rare Pediatric Disease Priority Review Voucher Program in a Nutshell



**§ 529 of
the FFDCA**

RPD Requests and Designations

	R	D
2012	0	0
2013	5	3
2014	19	8
2015*	16	8

RPD PRVs Granted

Drug	Vimizim (elosulfase alpha)
Company	BioMarin
Approval Date	February 14, 2014
Expedited Pathways	Priority Review Fast Track

Approved Indication
(in shorthand)

MPS IVA (Morquio A syndrome)

Progressive skeletal disease

Affects ~ 800 people in the U.S.

Majority are severely affected and survive only until late childhood/early adolescence

RPD PRVs Granted

Drug	Unituxin (dinutuximab)
Company	United Therapeutics
Approval Date	March 10, 2015
Expedited Pathways	Priority Review
Approved Indication <i>(in shorthand)</i>	Neuroblastoma

Rare brain tumor but is the most common cancer diagnosed within the first year of life

Children in the high risk group have a 5-year survival rate of 30%

RPD PRVs Granted

Drug	Cholbam (cholic acid)
Company	Asklepiion Pharmaceuticals
Approval Date	March 17, 2015
Expedited Pathways	Priority Review
Approved Indication <i>(in shorthand)</i>	Bile acid synthesis disorders due to single enzyme defects and peroxisomal disorders

Inability to produce bile acids, leading to malabsorption of fats and fat-soluble vitamins and fatal liver injury

Affects ~ 1600 people in the U.S. (for both)

RPD PRVs Granted

Drug	Uridine triacetate (Xuriden)
Company	Wellstart Threapeutics Corporation
Approval Date	September 4, 2015
Expedited Pathways	Priority Review
Approved Indication <i>(in shorthand)</i>	Uridine replacement Therapy in pediatric patients with hereditary orotic aciduria

Affects ~ Affects 8people in the U.S.

Sunset Provision

- Statute sets the program to sunset **one year after** the 3rd voucher has been issued
 - GAO to evaluate the program and issue a report one year after 3rd voucher is issued

**Since the 3rd voucher was issued in March 2015,
the program is set to sunset in March 2016**

Device-Related Programs

- Humanitarian Use Device (HUD)
 - HUD designation for diagnosis or treatment of a disease or condition affecting <4,000 individuals in the US/year
 - Eligible to submit a Humanitarian Device Exemption (HDE) application, which allows a qualified product to be approved based on a showing of **safety** and **probable benefit**

Device-Related Programs

- Pediatric Device Consortia (PDC) Grants
- Support consortia to promote pediatric device development
 - Provide targeted advisory and consultative services, with ability to award small amounts of discretionary funds to advance medical device projects

- Types of PDC Services and Referrals Provided:

- Intellectual Property / Legal
- Business Planning
- Funding Advice (Grant-writing and direction to potential sources)
- Regulatory Consulting
- Preclinical and Clinical Study Planning
- Reimbursement Counseling

PDC Grants Program

- Funded 8 consortia, a total of \$3.54M, in 2015
 - ~\$21.4 M spent on PDC to date
- Provided advice on development of >570 pediatric medical devices. Funding advice provided by the consortia have resulted in **\$ 65 Million raised** to advance PDC projects



<http://www.bme.umich.edu/news/all-news/hollister-and-green-use-3-d-splint-to-save-another-life>

FDA focus on rare disease collaboration

- Cross-Agency examples
 - Office of New Drugs Rare Disease Program
 - Rare Disease Council
- FDA-NIH NCATS partnerships
- International Rare Disease Partnership examples
 - EMA monthly meetings and other activities
 - IRDiRC
 - ICORD

Additional Resources

- For more information on OOPD programs and links to other rare disease resources:
www.fda.gov/orphan
 - links to regulations and guidance documents
 - link to [searchable drug designations and approvals](#)
 - link to [searchable grants funded by OOPD](#)
 - Also includes a link to “Educational Resources”

Contact Information

Questions?

- Email us at orphan@fda.hhs.gov OR
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