



Regulatory Education for Industry (REdI): **FALL CONFERENCE 2016**

Silver Spring, MD | September 27-28, 2016

Welcome!

Capt. Brenda Stodart, PharmD

Captain, United States Public Health Service

Program Director

CDER Small Business and Industry Assistance

DDI | OCOMM | CDER | FDA

FDA Insights on Products for Rare Diseases and Pediatrics

**FDA Small Business
Regulatory Education for Industry (REdI)
September 27, 2016**

Eric Chen, MS

Director
Humanitarian Use Device
Designation Program
Office of Orphan Products
Development
Office of Special Medical
Programs

**Jonathan Goldsmith, MD,
FACP**

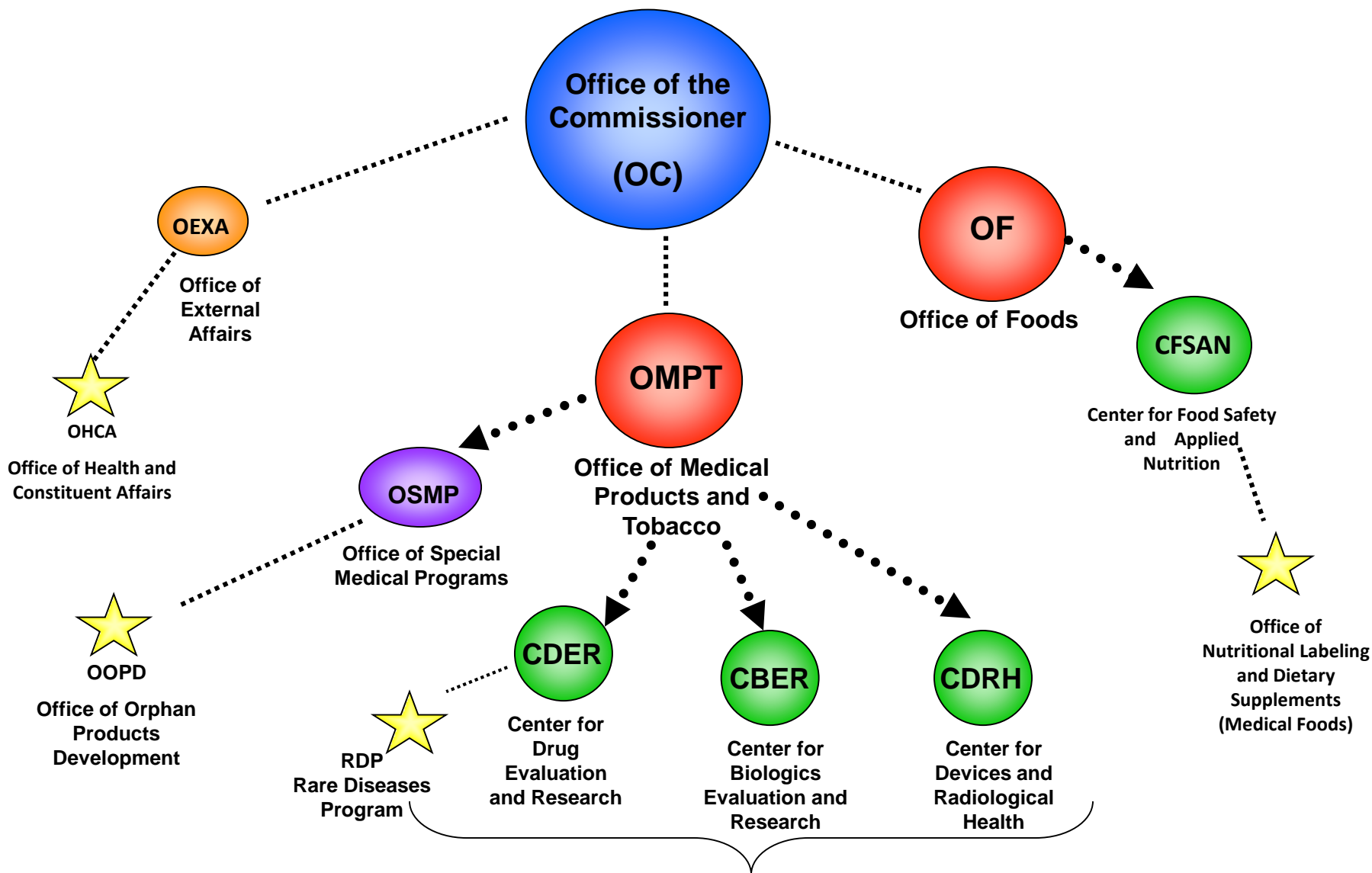
Associate Director
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**Vasum Peiris, MD,
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Populations
Center for Devices and
Radiological Health

Learning Objectives

- Describe FDA's focus on products for rare diseases and pediatrics
- Identify and learn about the different regulatory Centers and responsibilities
- Understand the unique regulatory pathways and flexibility that is available



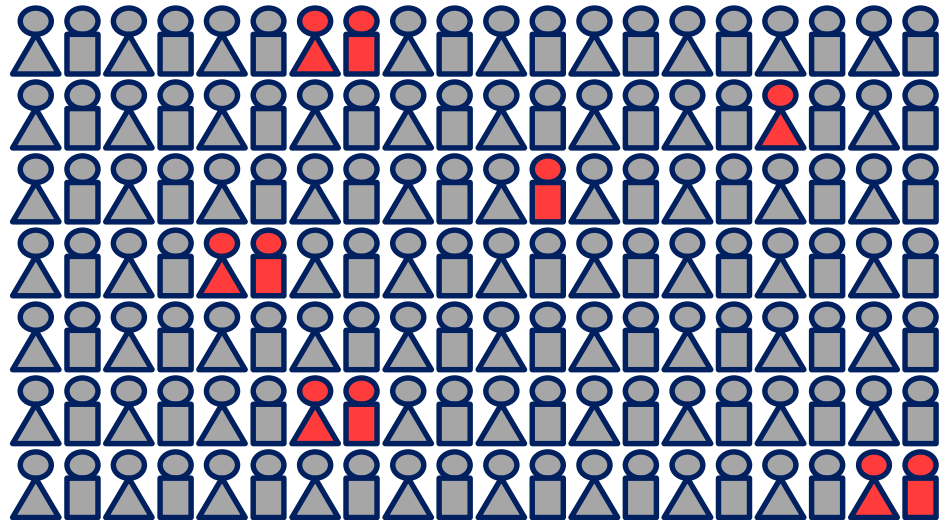
"The Review Divisions"

OOPD Mission Statement

*To promote the development of products, including drugs, devices, biologics, and medical foods, for the treatment, diagnosis and prevention of **rare diseases and conditions**.*

DESIGNATION PROGRAMS	GRANT PROGRAMS
Orphan Drug Designation	\$15M Orphan Product Grants
Rare Pediatric Disease Designation	\$3M Pediatric Device Consortia Grants
Humanitarian Use Device (HUD) Designation	\$2M Orphan Products Natural History Grants

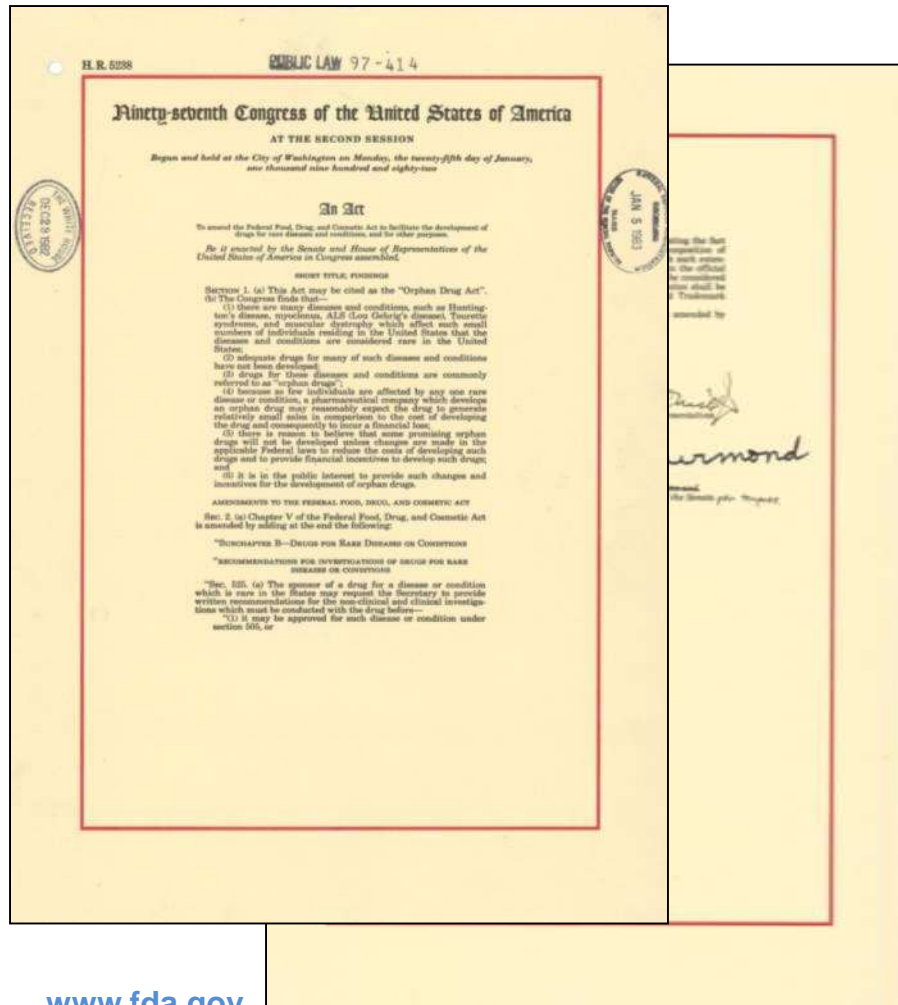
Rare Diseases and Challenges



- ~7,000 known rare diseases
- Only a portion have approved treatments
 - >500 orphan drug approvals (drugs & biologics)*
 - 69 Humanitarian Use Device approvals*

*as of 03/01/2016

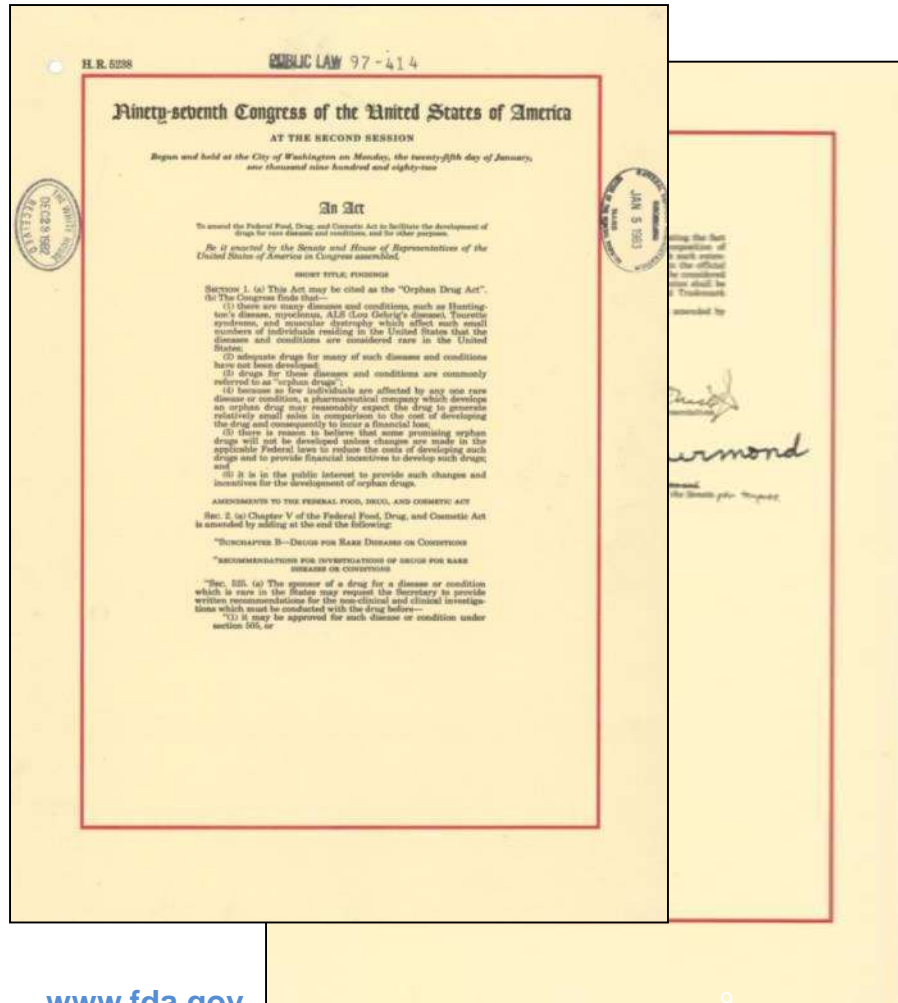
Orphan Drug Designation



The Orphan Drug Act in 1983 was created to motivate industry to develop drugs and biologics for rare diseases by providing **financial incentives**:

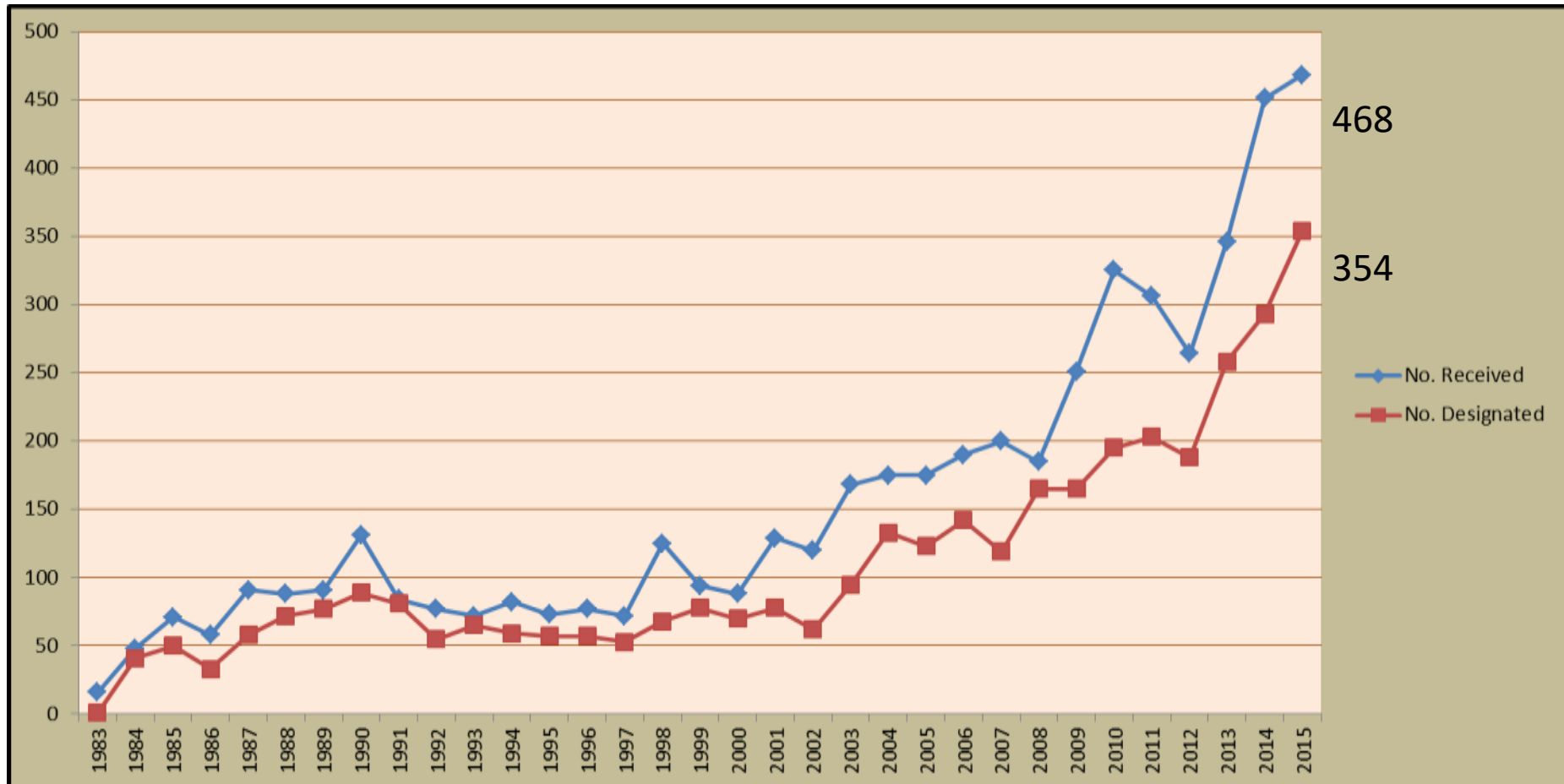
- Tax Credits for 50% of Clinical Trial Costs
- Waiver of Marketing Application User Fee: >\$2M
- Eligibility for 7-Year Marketing Exclusivity

Orphan Drug Act



- Defined **“rare disease”** for drugs and biologics
 - Disease/condition affects fewer than 200,000 people in the U.S.
- OR
- Drug will not be profitable

Statistics: Orphan Drug Designations



Rare Pediatric Disease Designation

- Created in 2012 to encourage development of treatments for “rare pediatric diseases (RPD)” of drugs and biologics
- **Basic Idea:**
 - A sponsor who receives approval gets a voucher for priority review of another application (that would otherwise be ineligible for priority review)

Rare Pediatric Disease Designation Routes

- **Two possible routes:**

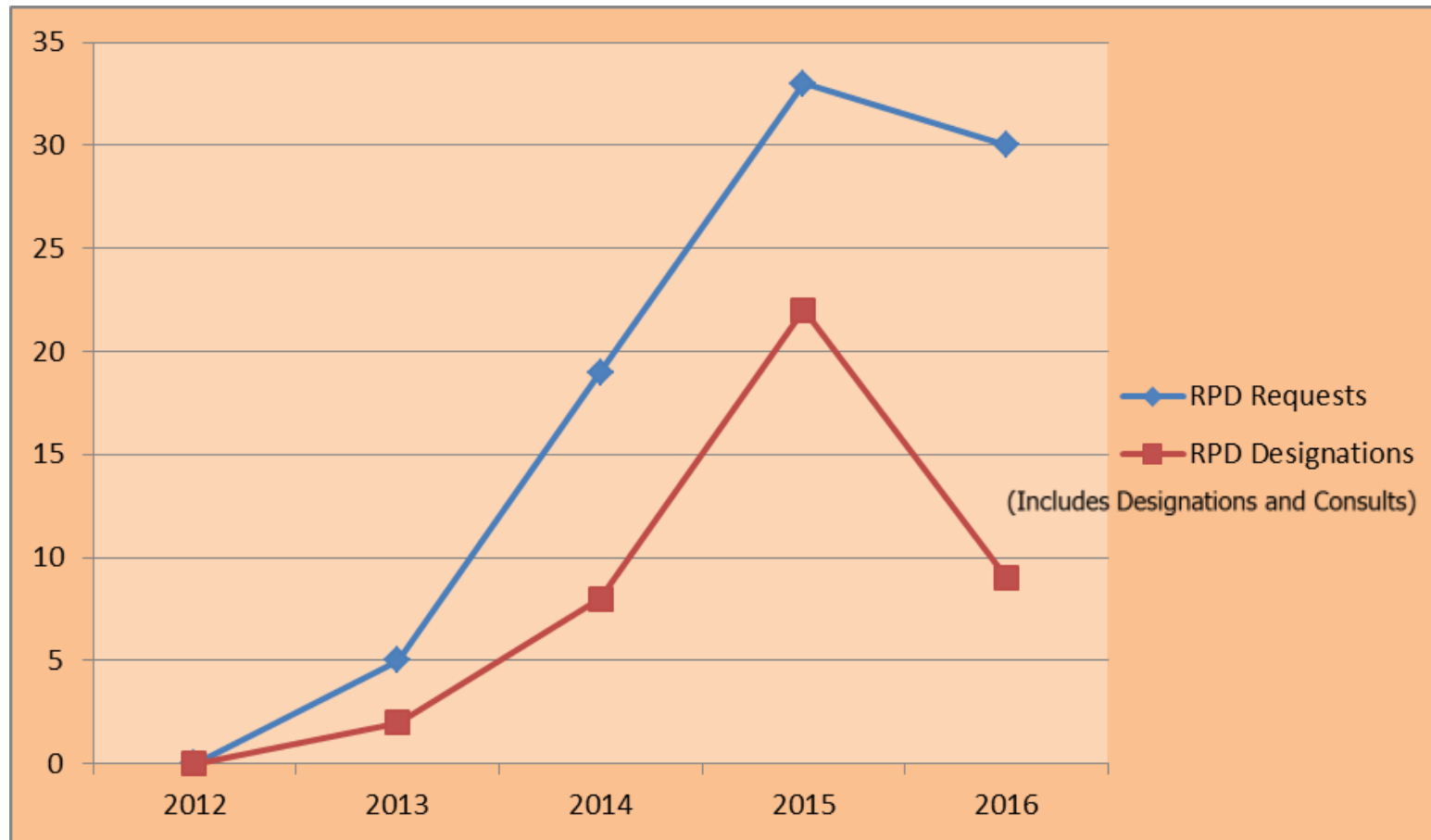
1. **Designation as a “rare pediatric disease”**

- Administered by OOPD
- Voluntary
- Not a pre-requisite to be eligible for a PRV

2. **Voucher eligibility determination**

- Administered by individual review divisions in CDER & CBER
- If designation not sought, OOPD consulted as to whether disease is a “rare pediatric disease”
- Whether a New Drug Application (NDA) or Biologics License Application (BLA) satisfies criteria for a “rare pediatric disease application”

RPD Requests and Determinations

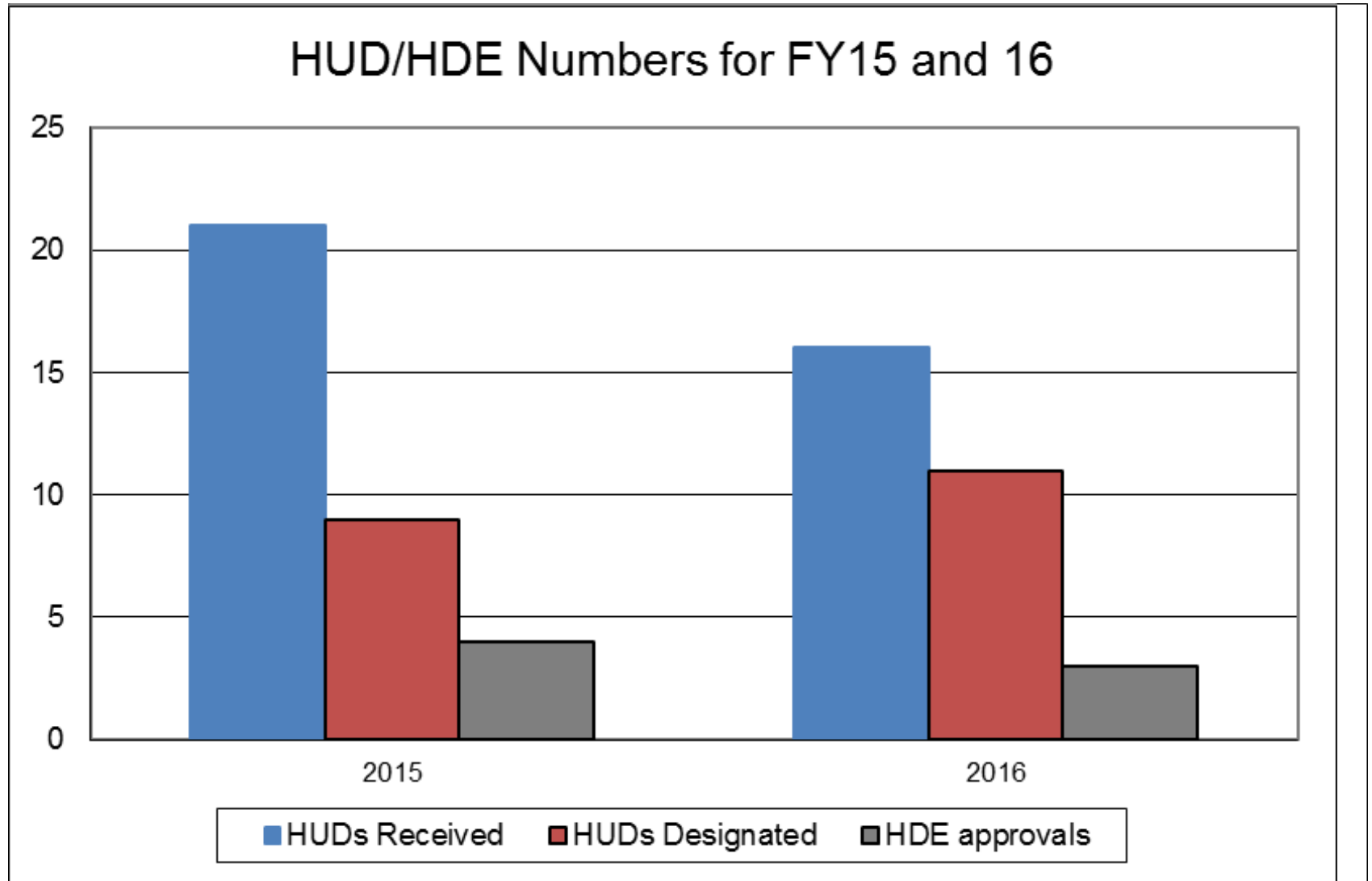


Data as of September 15, 2016

HUD/HDE

- **Humanitarian Device Exemption (HDE) Pathway**
 - 1990: Encourage the development of devices for rare diseases
 - General approval basis for medical devices: safe and effective
 - HDEs: safe and probable benefit
 - Fewer than 4,000 new patients per year
- **Restrictions on HUDs approved via HDE pathway**
 - Institutional review board approval at each facility
 - Prohibited from profit except for certain circumstances

HUDs and HDEs



Orphan Products (OPD) Grants

- Encourage clinical development of products for use in rare diseases or conditions
- Drugs, Biologics, Medical Devices or Medical Foods
- Grants funding for clinical trials
 - Usually 3 to 4 years
 - 60 to 85 ongoing grant-funded projects
 - Fund 10 to 15 new grants per fiscal year
- Website:
www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/ucm2005538.htm

Lack of Thorough Understanding of Rare Diseases

- Vast majority of rare diseases:
 - **Have:**
 - A name
 - Rough description of clinical manifestations
 - **Don't have:**
 - Thorough understanding of the natural history of the disease
 - Understanding of pathogenesis
 - Targeted treatments

A Rare Disease



The Black Box That Has A Name



"I'll give it to you straight — This disease is almost *impossible* to pronounce."

Objectives of OPD Natural History Grants Program



The ultimate goal is to support marketing approvals

- Help characterize natural history of a rare disease or condition
- Identify genotypic and phenotypic subpopulations
- Develop and/or validate clinical outcome measures, biomarkers, and diagnostics

[www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/
OrphanProductsNaturalHistoryGrantsProgram/default.htm](http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OrphanProductsNaturalHistoryGrantsProgram/default.htm)

Pediatric Device Consortia (PDC) Grants

- Goal
 - Support development of nonprofit consortia designed to stimulate projects for pediatric devices
- Types of Services and Referrals Provided:
 - Intellectual Property / Legal; Business Planning; Funding Advice; Regulatory Consulting; Preclinical and Clinical Study Planning; Prototyping and Design Services
- Consortia websites:
[www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/
PediatricDeviceConsortiaGrantsProgram/default.htm](http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/default.htm)

Questions?

For more information on OOPD's programs:

www.fda.gov/orphan

Still have questions?

- Email us at orphan@fda.hhs.gov OR
- Call us at 301-796-8660

CDER Perspectives on Drug Development for Rare Diseases

Jonathan Goldsmith, MD, FACP

Challenges for Rare Disease Drug Development (1)

- Rare diseases **natural history** is often poorly understood/characterized
- Diseases tend to be **progressive, serious, life-limiting and life-threatening** and **lack approved therapy**
- **Small populations** often restrict study design and replication

Challenges for Rare Disease Drug Development (2)

- **Phenotypic (disease presentation)** diversity within a disorder adds to complexity, as do **genetic subsets**
- Well defined and validated **endpoints, outcome measures/tools**, and **biomarkers** are often lacking
- Lack of **precedent** for drug development
- **Ethical** considerations for children in clinical trials

Pediatric Rare Diseases

- Most rare diseases are genetic and thus the affected pediatric population is a major focus
- Crucial Principle:
 - **best access** to safe and effective treatment is having an FDA-**approved** product on the market
- For diseases affecting children, this means substantial **evidence** to support **pediatric labeling**

Exclusivity to Promote Drug Development

- **Section 505(A) of Food and Drug Administration Modernization Act**
– **(FDAMA, 1997)**
- 6-month period of marketing (pediatric) exclusivity
AND
- 7 years of Orphan exclusivity
- Incentive to industry to study Pediatric indication(s) requested by the Agency.

Drug Approval Standard

Standard for approval of rare disease drugs and biological products is the same as for prevalent disease drugs:

Substantial Evidence of product effectiveness.

- The meaning of “safe” is not explicitly defined in the statutes or regulations that govern approval.

Substantial Evidence

“evidence consisting of **adequate and well-controlled (A&WC) investigations**... on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use...”

Kefauver Harris Amendment –FD&C Act § 505(d), 21 USC 355(d) (1962)

See Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998

Flexibility

- Regulations allow for **flexibility** and **scientific judgment**⁺ in applying the standard, and in determining the kind and quantity of data required to be provided for a particular drug
- Reliance on a **single A&WC study*** with confirmatory evidence is generally limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome.
 - Confirmation of the result in a second trial would be practically or ethically impossible.
 - It is critically important to consider proposals relying on a single trial early in planning

⁺Kefauver Harris Amendment –FD&C Act § 505(d), 21 USC 355(d) (1962)

As amended by Food and Drug Administration Modernization Act Sec 115 (1997)

*Described at 21 CFR 314.126

See Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, May 1998



Application of Flexible Clinical Development Programs

CDER NME approvals 1/1/2008 – 9/07/2016

Flexible Development Programs	Rare Approvals	Non-Rare Approvals
Use of ≥ 1 flexible development approaches*	78 (82%)	66 (35%)
Traditional development program**	17 (16%)	122 (65%)

*Flexible Development approaches are defined as approval supported by other than 2 AWC Studies and/or use of a novel end point

**Traditional Development defined as ≥ 2 AWC studies using endpoints with prior precedents

Expediting Rare Diseases Drug Development

- Programs have been developed to target serious diseases with unmet medical needs when a new treatment could provide meaningful clinical benefit

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

Expediting Rare Diseases Drug Development

- **Fast Track**
 - FDAMA 1997/FDASIA 2012
- **Breakthrough Designation**
 - FD&C Act/FDASIA 2012
- **Priority Review**
 - PDUFA 1992
- **Accelerated Approval**
 - 21CFR314 subpart H, 601 subpart E/FDASIA 2012



Expedited Clinical Development Programs

CDER NME approvals 2008-2016*

Expedited Programs	Number Rare (n = 109)	Number Non-Rare (n = 193)
Priority Review	82 (75%)	58 (30%)
Fast Track	59 (54%)	42 (22%)
Accelerated Approval	28 (26%)	3 (2%)
Breakthrough Therapy	20 (18%)	8 (4%)
Used any Expedited Program	94 (86%)	68 (35%)

*as of September 7, 2016



CDER Novel *Orphan* New Drug Approvals First Approvals in the US – CY 2014 -2016*



*as of September 7, 2016

Rare Pediatric Disease (RPD) Priority Review Voucher Program: Background

- 2012 FDA Safety and Innovation Act (FDASIA) [Section 908]
 - Provides an incentive to encourage the development of drugs and biologics for rare pediatric diseases
- Upon approval, the sponsor may be issued a voucher redeemable for a priority review for a ***subsequent*** application that may not have otherwise qualified for a priority review
- The incentive offers a shorter review clock for marketing applications, 6 months compared with the 10 months standard review time

Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry

www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf

Rare Pediatric Disease Priority Review Voucher Program

- OOPD reviews requests for Rare Pediatric Disease designation
 - 41 Designated/6 Denied/7 Under Review
- Voucher requests are managed by the OND RDP
 - 11 Voucher requests were submitted with an NDA or BLA
 - 6 Vouchers awarded, 3 denied and 2 pending review
 - Two PRV's have been redeemed
- Future (?)
 - Sunsets - 30 September 2016 although pending legislation may be extended to 31 December 2022 (for designation)/31 December 2027 (for redemption)

Rare Diseases: Common Issues in Drug Development

August 2015 (Draft Guidance)

- To assist sponsors of drug and biological products intended to treat or prevent rare diseases
- To help sponsors conduct more efficient and successful development programs

Rare Diseases: Common Issues in Drug Development Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

*Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submission comments to the Division of Dockets Management (HFA-005), Food and Drug Administration, 1010 Potomac Lane, rm. 1061, Rockville, MD 20850. 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 draft document, contact (CDER) Jonathan Goldsmith at 240-402-9639, or (CDER) Office of Communication, Outreach, and Development at 1-800-435-4709 or 240-402-9010.

*U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)*

*August 2015
Rare Diseases*

*11-0747-01
09/01/15*

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf

Rare Diseases: Common Issues in Drug Development

August 2015 (Draft Guidance)



- Adequate description and understanding of the disease's natural history
- Adequate understanding of the pathophysiology of the disease and the drug's proposed mechanism of action
- Nonclinical pharmacotoxicology considerations to support the proposed clinical investigation(s)
- Reliable endpoints and outcome assessment
- Standard of evidence to establish safety and effectiveness
- Drug manufacturing considerations

Rare Diseases: Common Issues in Drug Development Guidance for Industry

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

August 2015
Rare Diseases

CDER/CDER
2015.12

Thank you very much for your attention!

Send us a Question at:

CDERONDRareDiseaseProgram@fda.hhs.gov

Jonathan.Goldsmith@fda.hhs.gov

**Rare Diseases
Program/OND/CDER/FDA**

CDRH Perspectives on Device Development for Rare Diseases

**Vasum Peiris, MD, MPH
FAAP, FACC, FASE**

Pediatrics and Rare Diseases



Dexcom G4 PLATINUM
(Pediatric) Continuous
Glucose Monitoring
System



Lixelle® β 2-microglobulin
Apheresis Column

**Pediatric
Diseases**

**Rare
Diseases**



DLP Pediatric One-Piece
Arterial Cannulae



Berlin Heart Pediatric
Ventricular Assist Device



Argus® II Retinal
Prosthesis System

Patients are at the Heart of What We Do



CDRH Mission: To Protect and Promote the Public Health and Facilitate Medical Device Innovation



Vision: Patients in the U.S. have access to high-quality, safe and effective medical devices of public health importance first in the world

What is a Humanitarian Device Exemption (HDE)?

- A marketing application for a HUD
- Primary medical device submission type for rare diseases
- Exempt from the effectiveness requirements of Sections 514 and 515 of the FD&C Act
- Subject to certain profit and use restrictions

Section 520(m) of FD&C Act

Eligibility for HDE

1. Received HUD designation

AND

2. No legally marketed device for same disease or condition granted under:
 - Premarket notification (510(k))
 - Premarket approval (PMA)
 - *de novo*

Approval Threshold

Reasonable Assurance Safety

And

Probable Benefit*

*Exempt from requirement to establish reasonable assurance of effectiveness



Basis to Approve HDE

- Device use (**benefit**) outweighs risk of injury/illness (**safety**)
- Accounting for other available options:
 - currently available devices or alternative forms of treatment
 - their respective benefits and risks

Clinical Evidence

- **Evidence should include:**
 - summaries,
 - conclusions, and
 - results of **all** clinical experience or investigations
- Generally includes information on both safety and probable benefit

Limitations of Clinical Evidence

- **Rare disease/condition:**
 - Limited patient population available to study
 - smaller sample sizes
- **Lack of available comparable device**
 - no active control arm
 - no randomization

HDE Approval Package

Once a HDE is approved, FDA makes these documents publically available:

- **Approval Order**
- **Summary of Safety and Probable Benefit (SSPB)**
- **Labeling**
 - professional labeling
 - patient labeling (if applicable)
- **Consumer Information**
 - short, plain-language summary of the device and its intended use

HDE Approvals

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm

U.S. Department of Health and Human Services

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Protecting and Promoting Your Health

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Medical Devices

Home > Medical Devices > Products and Medical Procedures > Device Approvals and Clearances > HDE Approvals

HDE Approvals

- Listing of CDRH Humanitarian Device Exemptions

Listing of CDRH Humanitarian Device Exemptions

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

Click the small arrow at the top of each column to sort.

HDE Number Approval Date and Docket Number ↕	Device Name ↕	Company Name and Address ↕	Device Description / Device Indications ↕
H130006 12/18/15	FENIX™ Contenance Restoration System	Torax Medical, Inc. Shoreview, MN 55126	Approval for the FENIX™ Contenance Restoration System. This device is indicated for the treatment of fecal incontinence in patients who are not candidates for or have previously failed conservative treatment and less invasive therapy options (e.g. bulking agents, radiofrequency ablation, sacral nerve stimulation).

FDA Initiatives to Facilitate Pediatric Device Development

- **Early Feasibility Program (Guidance)**

www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf

- **Extrapolation (Guidance)**

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM444591.pdf

- existing clinical data in another studied population (such as adults, or a different pediatric subpopulation) may be leveraged (“extrapolated”) to support marketing approval and labeling of medical devices for use in pediatric patients

- **Expedited Access Program – Unmet clinical need (Guidance)**

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf

- **Pre-Post Market Balance (Guidance)**

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393994.pdf

- Conversion of HDE to PMA
- Potential PMA/HDE Approval - existing clinical data from standard of care device therapy

Device Development for PRDs

Recommendations

- **Meet with CDRH Review Division**
 - Pre-Submission meetings: Early and Often
 - Free
 - Take advantage of the Early Feasibility Program
 - Enhances Collaboration
 - **Determine appropriate clinical evidence needs**
 - » Extrapolation
 - » Clinical trial designs and endpoints
 - » Pre- post-market balance
 - **Identify least burdensome pathway to market**
 - » PMA, HDE, *de novo*, 510(k)
 - » Expedited Access Pathway

Leveraging Existing Clinical Data

Guidance: Extrapolation to Pediatric Uses of Medical Devices June 2016

- **Problem Statement:**
 - Despite recognized need, relatively few medical devices have pediatric-specific indications and labeling
- **Proposed Methods:**
 - leverage data from adult and other populations to augment what is known about a device's performance in pediatric patients
- **Potential Outcome:**
 - stimulate growth in the number of legally-marketed devices specifically indicated and labeled for pediatric patients

www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm444591.pdf

Strengthen the Clinical Trial Enterprise

Guidance: Premarket Assessment of Pediatric Medical Devices

March 2014

- Define the pediatric population and pediatric use for medical devices
- Identify the types of information needed to provide reasonable assurance of the safety and effectiveness of medical devices intended for use in the pediatric population
- Define the guiding principles and protections sponsors should consider for pediatric subjects in device clinical trials

www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089740.htm

Virtual Population

- 10 different models available, more than 200 tissues and organs
- Extensively used in regulatory submissions
 - MR Conditional pacemakers, spinal cord stimulator, orthopedic implants

obese male
1.78m, 120kg

female adult
1.60m, 58kg

Credit: Kainz et al

8 year old girl
1.35m, 30kg

6 year old boy
1.17m, 20kg

5-year-old girl
1.09m, 16kg

male elderly
1.73m, 65kg

male adult
1.74m, 70kg

11 year old girl
1.46m, 36kg

14 year old boy
1.65m, 50kg

8 year old boy
1.40m, 26kg

Providing Information about Pediatric Uses of Medical Devices

Pediatric Tracking Guidance, May 2014

- Helps promote communication with sponsors about unmet need
- Potential pediatric use information must be provided with
 - any request for a humanitarian device exemption (HDE), premarket approval application (PMA), or product development protocol (PDP)

www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm339162.htm

Expedited Access Pathway Program

- Guidance issued April 13, 2015; intended for breakthrough devices
www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393879.htm
- Eligible devices:
 - subject to a PMA or *de novo*
 - intended to treat or diagnose a **life-threatening or irreversibly debilitating** disease
 - address an **unmet need**
- Early, ongoing, and extensive interaction with review team, engagement by senior management, assignment of a case manager, and **collaborative creation of a Data Development Plan**
- Where appropriate, **some premarket data collection shifted to the postmarket setting for PMA devices**

Summary

- FDA is focused on products for rare diseases and pediatrics
- Each regulatory Center has their own requirements and responsibilities
- FDA has unique regulatory pathways and flexibility that are available products for rare diseases

Questions

Please complete the session survey:
surveymonkey.com/r/REdl-Plenary

Call To Action

- Consider whether your product may be used for patients with rare diseases or for pediatrics.
- Let's work together to help these much needed medical products to patients who need them!

