Hosted by
Professional Affairs and
Stakeholder Engagement (PASE)

CDER

RARE DISEASES 2017

30th Oct

Public Workshop

Register TODAY

8 AM. TO 5PM.

CDER-Rare-Diseases-Public-Workshop.Eventbrite.com

Strategies, Tools, and Best Practices for Effective Advocacy in Rare Diseases Drug Development

WO I Building 31 (Great Room)

Strategies, Tool, and Best Practices for Effective Advocacy in Rare Diseases Drug Development

FDA White Oak Campus

Building 31, Great Room (A, B, C)

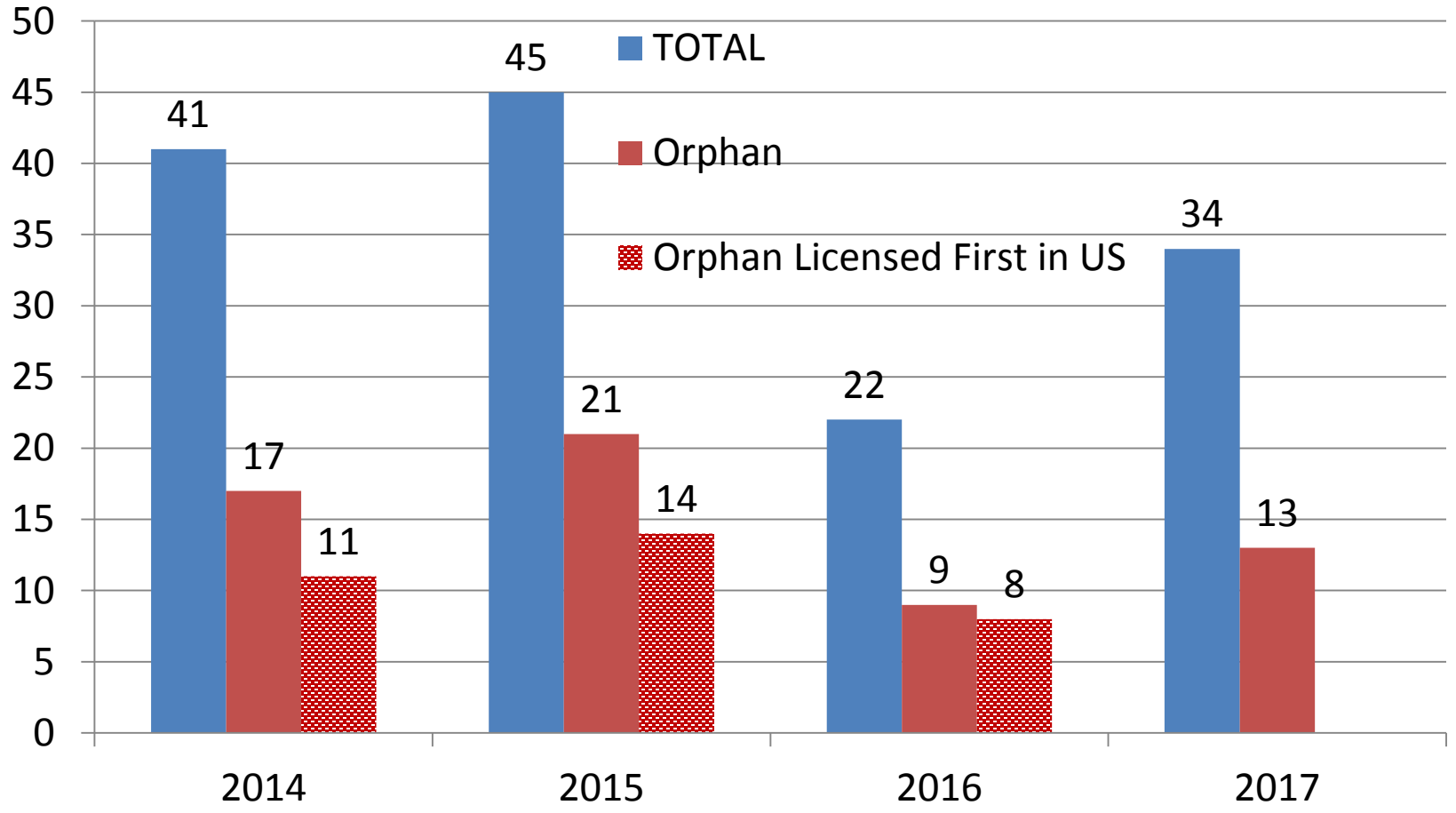
WELCOME & INTRODUCTIONS

Welcome and Introductions: Francis Kalush, Ph.D.
Global Genes Introduction: Meredith Cagle, M.P.H.
FDA Opening Remarks: Douglas Throckmorton, M.D.

Welcome & Introductions

FRANCIS KALUSH, PH.D.

CDER Novel Orphan Drug Approvals CY 2014 -2017*



* as of 07 October 2017

Global Genes Introduction

MEREDITH CAGLE, M.P.H.

Global Genes®

Allies in Rare Disease

Our Mission:
To eliminate the challenges of rare disease

Presented by: Global Genes

Patient Engagement Team

Meredith Cagle
Director, Patient Engagement

Kendall Davis
Sr. Manager, Corporate and Foundation Alliances

Amy Grover
Sr. Manager, Patient Engagement

Ashley Yee
Sr. Manager, Education Programs

Our Mission:
To Eliminate the Challenges of Rare Disease Globally

- We develop resources and tools to help equip patient advocates to become successful ACTIVISTS for their disease
- We are building a globally connected network, a platform for collaboration and success
- We fund Science and Technology innovations that will broadly impact patients within their lifetime

THIS IS WHY GLOBAL GENES WAS FOUNDED

OVER **7,000** RARE DISEASES IDENTIFIED

RARE DISEASE AFFECTS MORE THAN **350** MILLION PEOPLE WORLDWIDE

APPROXIMATELY **30%** OF CHILDREN WITH THESE DEBILITATING DISEASES WILL NOT LIVE TO SEE THEIR 5TH BIRTHDAY.

APPROXIMATELY 80% OF RARE DISEASES ARE GENETIC. **80%**

ONLY **5%** OF RARE DISEASES HAVE AN FDA APPROVED DRUG

50% OF PEOPLE AFFECTED BY RARE DISEASE ARE CHILDREN

Global Genes®

Advocacy to Activism

WHAT WE DO

WE EDUCATE & BUILD AWARENESS

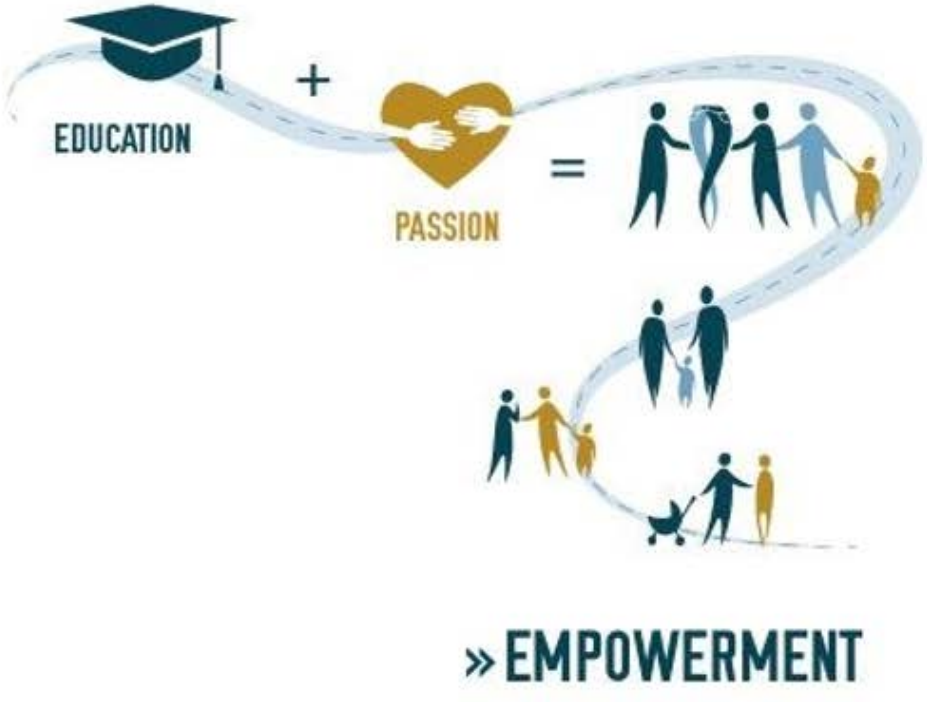
- Developing tools to aid rare disease advocates
- Equipping patients to become successful disease activists

WE COLLABORATE AND EMPOWER

- Building bridges between patients, advocates, clinicians and corporate partners

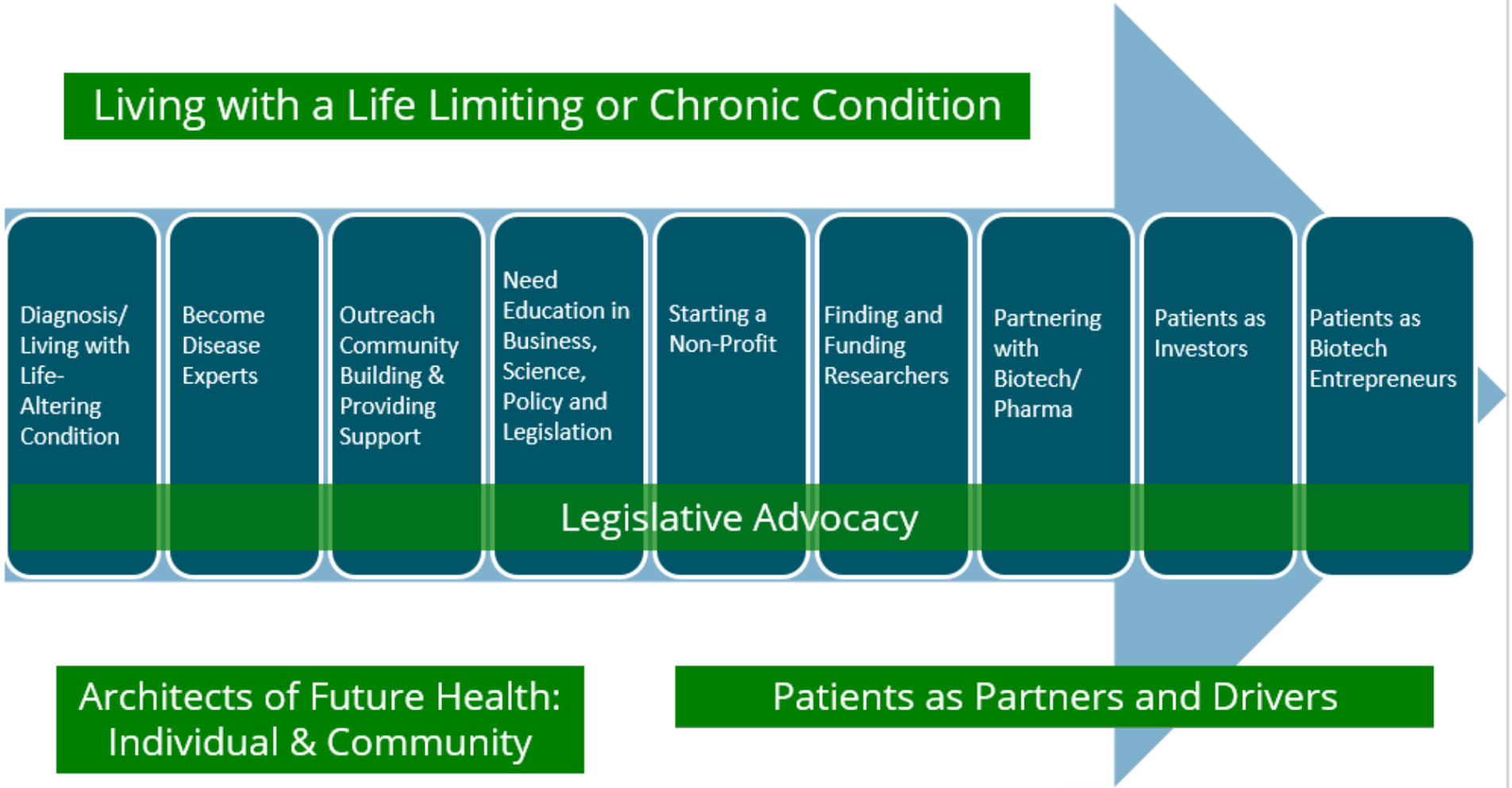
WE FOSTER INNOVATION

- Funding research that impacts rare disease patients in their lifetime



Global Genes®

RARE Patients Responsibilities - Landscape



Global Genes®

Expectations for Today's Meeting

THANK YOU!

Global Genes®

Allies in Rare Disease

www.globalgenes.org

FDA Opening Remarks

DOUGLAS THROCKMORTON, M.D.


30TH
OCT
CDER
RARE
DISEASES
Public Workshop
8 AM.
TO
5PM.

WHAT IS THE FDA AND WHO IS INVOLVED WITH RARE DISEASES ENGAGEMENT?

Moderator: *Francis Kalush, Ph.D.*
Introduction To FDA: *Heidi Marchand, Pharm. D.*
FDA Orphan Medical Product Designation Program: *Gayatri Rao, M.D., J.D.*
CDER Divisions Working With Rare Diseases: *Jonathan Goldsmith, M.D.*
Professional Affairs And Stakeholder Engagement Within CDER:
John Whyte, M.D., M.P.H.

Moderator:

FRANCIS KALUSH, PH.D.

Introduction to the FDA

HEIDI MARCHAND, PHARM.D.

FDA Overview and Introduction

Heidi C. Marchand, PharmD
Office of Health and Constituent Affairs
October 30, 2017

FDA's Public Health Mission

- Ensure the safety, effectiveness, and security of human and animal drugs, biological products and medical devices
- Ensure the safety of foods, cosmetics, and radiation-emitting products
- Regulate tobacco products

1906 Pure Food and Drug Act

A NAUSEATING JOB, BUT IT MUST BE DONE
(President Roosevelt takes hold of the investigating muck-rake himself in the packing-house scandal.)

Impact of *The Jungle*

Meat Inspection Act

Required federal inspection of meat and required the Agricultural Department (USDA) to set standards of cleanliness in meatpacking plants

Pure Food and Drug Act

Banned the sale of impure or falsely labeled food or drugs

FDA's Product Centers

FDA Commissioner-Dr. Scott Gottlieb

Our preference is for patient groups to interface directly with the review programs. –October 2017

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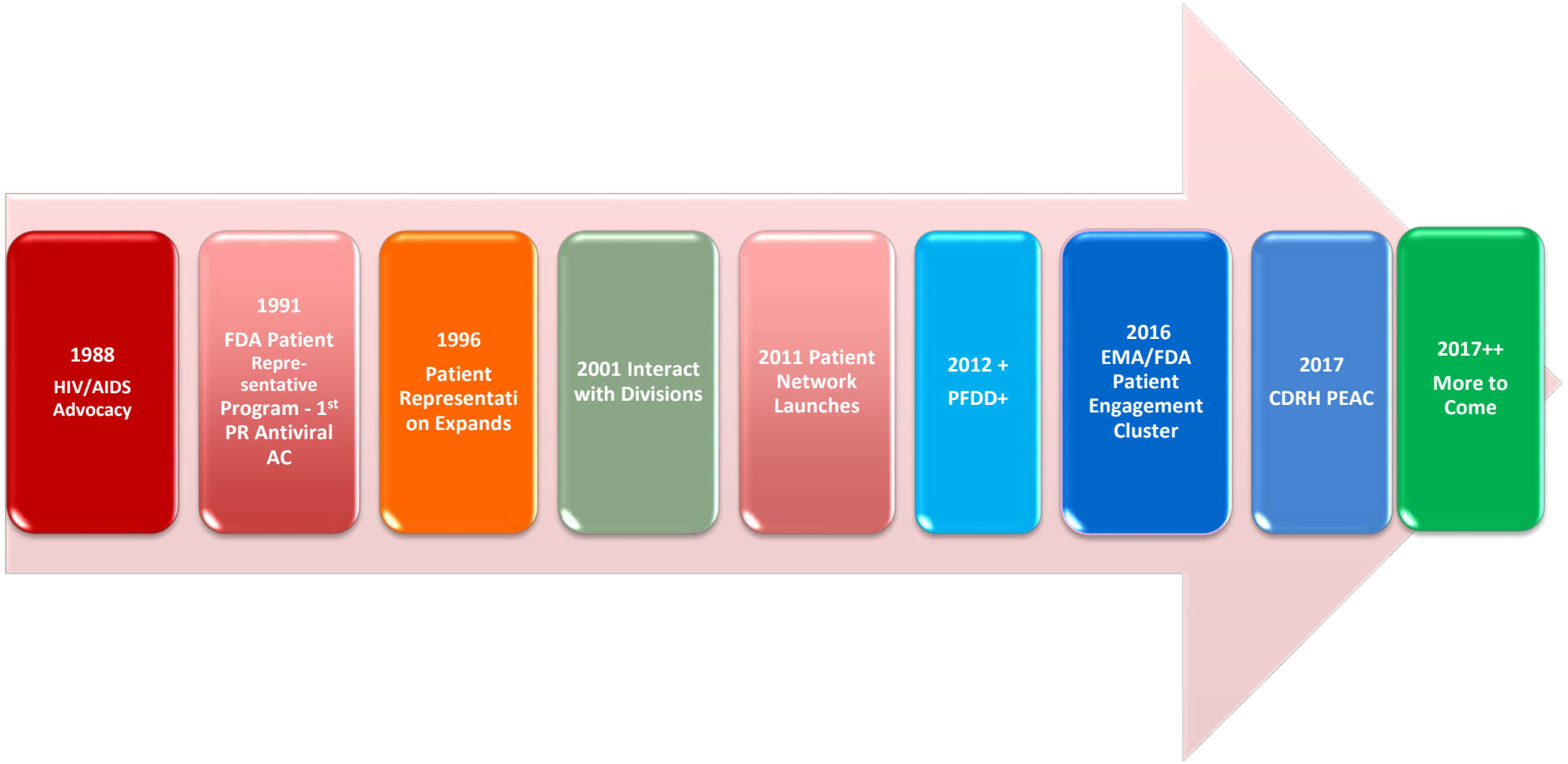
FDA Patient Involvement Milestones



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Patient-Oriented Offices and Staff

Office of the Commissioner

- Office of Health and Constituent Affairs
- Office of Orphan Products Development
- Office of Women's Health
- Office of Minority Health

Human Therapeutic Centers

- Drugs
  - Professional Affairs and Stakeholder Engagement
  - Rare Disease Program
  - Patient Focused Drug Development
- Biologics
- Devices
  - Patient Engagement Advisory Committee

Why is the Patient Voice Important?

- Provide insight on issues, problems, and/or questions that are important to patients and family members
- Patients have a vested interest diversity of opinions
- Varied perspectives, both in terms of risk tolerance and potential benefit
- The human element (judgment vs. empirical data)

Ultimately, patients are the focus of all of FDA's activities

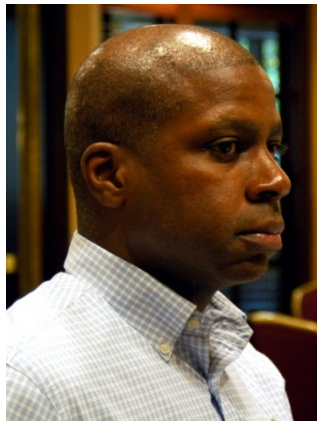
What Value Can Patient Engagement Add?

- Better designed trials
- Faster recruitment and improved retention
- Cutting time and cost of product development
- Help develop meaningful endpoints and measurements
- Contribute valuable data – patient and natural history registries
- Medical products that better reflect outcome and quality of life measures most important to patients

FDA Patient Representative Program

- Began in 1990s
- Patients having an active role on FDA Advisory Committees and consultations with review divisions
- Patient voice represented in important discussions about regulatory decision-making
- Presence at the table

FDA Patient Representatives



- Patients with a disease/condition
- Primary caregivers to patients (i.e., spouse, parent, family member, friend)
- Members of patient/community advocacy groups
- Special Government Employees

Patient Representatives

201 Reps | 300 diseases/conditions | 60 assignments/year

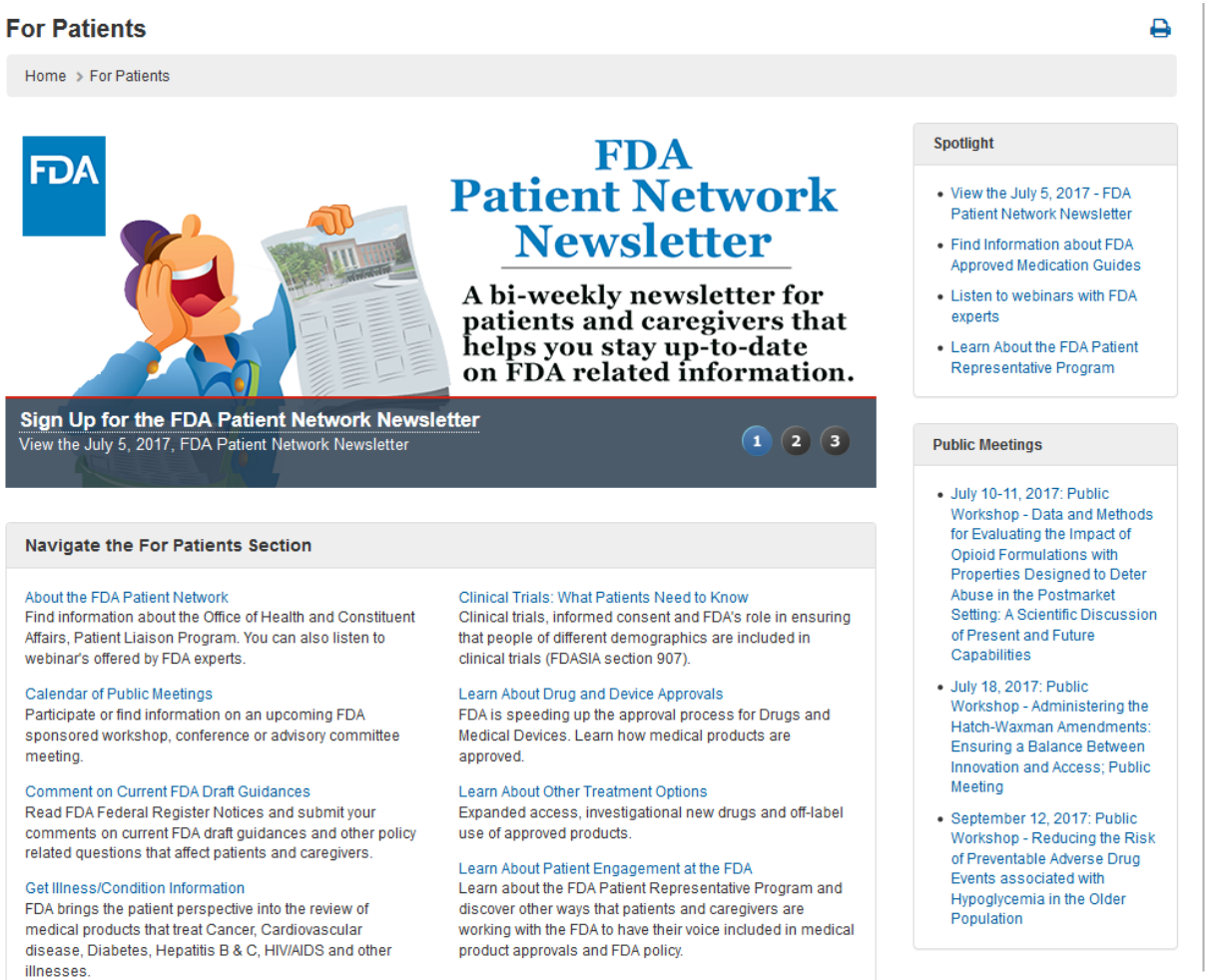
- AIDS/HIV
- Alzheimer's Disease
- Asthma
- Cancer (various)
- Cardiovascular disease
- Cerebral Palsy
- Crohn's disease
- Cystic Fibrosis
- Depression
- Diabetes
- Duchenne Muscular Dystrophy
- Fabry Disease
- Hepatitis B
- Hepatitis C
- Hypertension/Cardiovascular Disease
- Infantile Spasms
- Lung Transplantation
- Lupus
- Macular Degeneration
- Major Depressive Disorder
- Multiple Sclerosis
- Neuropathy
- Lysosomal Acid Lipase
- Obesity/Weight Control
- Parkinson's Disease
- Pompe Disease
- Polio
- Sickle Cell Disease
- Short Bowel Syndrome
- Temporomandibular joint (TMJ) disorder
- Urea Cycle Disorder

FDA Patient Network

- Webpage
- Webinars &
  In-person Meeting's
- Twitter
- Bi-weekly Email
  Newsletter

FDA Patient Network- Webpage

- About the FDA Patient Network
- Calendar of FDA Public Meetings
- Comment on Current FDA Draft Guidances
- Get Illness/Condition Information
- Clinical Trials: What Patients Need to Know
- Learn About Drug and Device Approval
- Learn About Other Treatment Options
- Learn About Patient Engagement at FDA



www.fda.gov/ForPatients

FDA Patient Network- Newsletter

- Medical Product Safety
- Drug Shortages and Discontinuations
- Medical Product Approvals
- Opportunities to Comment
- Announcements
- Upcoming Public Meetings
- Consumer Updates
  Food Safety
- Pet Health
  Tobacco Products

Patient Network News

from the FDA Office of Health and Constituent Affairs

Volume 7 | Number 14 | July 5, 2017

Medical Product Safety

No medical product safety issues to report.

Comunicaciones de la FDA sobre la seguridad de los medicamentos en español

Descargo de responsabilidad: La FDA reconoce la necesidad de proporcionar información importante sobre seguridad de los medicamentos en idiomas distintos al inglés. Hacemos lo mejor posible para proporcionar versiones en español precisas y oportunas de nuestras Comunicaciones de Seguridad de Medicamentos. Sin embargo, en caso que existiera discrepancias entre las versiones en inglés y la de español, la información contenida en la versión en inglés es la que se considera como versión oficial. Si tiene alguna pregunta, por favor contáctese con Division of Drug Information en druginfo@fda.hhs.gov.

Comunicaciones de la FDA

MedWatch — *Your FDA gateway for clinically important safety information and reporting serious problems with human medical products.*

Report a Problem | Safety Information | Stay Informed

Drug Shortages and Discontinuations

FDA knows the major public health consequences that can result from drug shortages. These shortages occur for many reasons including manufacturing and quality problems, delays and discontinuations. When issues are discovered, FDA works closely with the company to address risks involved to prevent harm to patients. FDA also considers the impact a shortage would have on patient care and access and works with the company to restore supplies while also ensuring safety for patients. More information

Drug Shortages Voluntarily Reported by Manufacturers During the Past 2 Weeks:

- Cromolyn Sodium Inhalation Solution, USP
- Pantoprazole (Protonix) Powder for Injection

Resources for You

FDA Patient Network

The FDA Patient Network contains a series of webpages, webinars and presentations on topics related to patient engagement, FDA regulations, understanding medical product (Drugs, Biologics, and Devices) approval and medical product safety updates. Take me to the FDA Patient Network or take me to FDA Webinars.

FDA Basics

Each month, different centers and offices at FDA will host an online session where the public can ask questions to senior FDA officials about a specific topic or just listen in to learn more about FDA. More |

Educational Videos

FDA Food Safety and Modernization Act: An FDA Primer

The Rulemaking Process: An FDA Primer

What is Regulatory Science

Taking Acetaminophen Safely

healthfinder.gov

Welcome to healthfinder.gov, a government Web site where you will find information and tools to help you and those you care about stay healthy. More information / más información

FDA Email Updates

Sign up for one of the FDA disease specific e-mail list that delivers updates, product approvals, safety warnings, notices of upcoming meetings, and notices on proposed guidances.

Ocular Disease

B and C

Sign up for other email updates from the FDA - see other email updates.

Office of Health and Constituent Affairs

PatientNetwork@fda.hhs.gov

www.FDA.gov/ForPatients

Submit Comments Through the Federal Register

Participate in an FDA Sponsored Public Meeting

About Clinical Trials – Information for Patients

For Patients

Home > For Patients > Clinical Trials: What Patients Need to Know

Clinical Trials: What Patients Need to Know

- What Patients Need to Know About Institutional Review Boards
- Glossary of Terms
- Clinical Research Versus Medical Treatment
- What Are the Different Types of Clinical Research?
- Informed Consent for Clinical Trials

Resources for You

- NIH Clinical Research Trials and You
- Good Clinical Practice
- Interactive Patient Education Tutorial On Clinical Trials
- Protecting America's Health Through Human Drugs
- Protection of Human Subjects of Research
- Get to Know ClinicalTrials.GOV (webinar)

Clinical Trials: What Patients Need to Know

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

en español

Learn more about clinical trials and find a trial that might be right for you. Clinical trials are voluntary research studies conducted in people and designed to answer specific questions about the safety or effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments. It is important to remember that the FDA does not conduct Clinical Trials.

Search for a Clinical Trial

Enter a word or phrase, such as the name of a medical condition or intervention.
Example: Cancer AND Los Angeles or expanded access AND compassionate use

Search

Learn More About Clinical Trials

- Clinical Research Versus Medical Treatment
  Understand the differences between clinical research and medical treatment and what those difference for you. Find answers to your questions about clinical trials, such as why they are done, who should c participating, and issues to consider before joining a trial.
- What are the Different Types of Clinical Research
  Understand the different types of research and the four clinical trial phases, such as their purpose and how many people participate in each of the phases.
- Informed Consent for Clinical Trials
  Understand what informed consent is and the questions you need to know before signing informed consent.
- Diversity in Clinical Trial Participation
  It is important to test drugs and medical products in the people they are meant to help. Learn about FDASIA 907 and how FDA works to make sure that people of different ages, races, ethnic groups, and genders are included in clinical trials.
- What is an Institutional Review Board
  Understand what Institutional Review Boards are, who is on them and who they protect.
- Sexual and Gender Minorities
  ...ions for the Review of Inclusion on the Basis of ... Research

For Patients

Home > For Patients > Clinical Trials: What Patients Need to Know > Informed Consent for Clinical Trials

Informed Consent for Clinical Trials

Informed Consent for Clinical Trials

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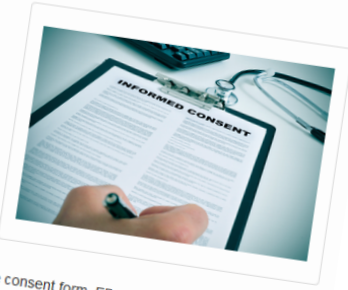
en español

On this page you will find information on:

- What is Informed Consent
- Before enrolling in a clinical trial, the following information must be given to each potential research subject
- When Appropriate, one or more of the following elements of information must also be provided in the informed consent document
- A potential research subject must have an opportunity to
- Informed consent may not include language that



To many, the term *informed consent* is mistakenly viewed as the same as getting a research participant's signature on the consent form. FDA believes that obtaining a research participant's verbal or written informed consent is only part of the process. Informed consent involves providing a potential participant with:

- adequate information to allow for an informed decision about participation in the clinical investigation.
- facilitating the potential participant's understanding of the information.
- an appropriate amount of time to ask questions and to discuss with family and friends the research protocol and whether you should participate.
- obtaining the potential participant's voluntary agreement to participate.
- continuing to provide information as the clinical investigation progresses or as the subject or situation requires.

To be effective, the process must provide sufficient opportunity for the participant to consider whether to participate. (21 CFR 50.20.) FDA considers this to include allowing sufficient time for participants to consider the information and providing time and opportunity for the participant to ask questions and have those questions answered. The investigator (or other study staff who are conducting the informed consent interview) and the participant should exchange information and discuss the contents of the informed consent document. This process must occur under circumstances that minimize the possibility of coercion or undue influence. (21 CFR 50.20.)

What is Informed Consent?

As new medical products are being developed, no one knows for sure how well they will ... will find. Clinical trials are used to answer questions such as:

- Are new medical products saf...

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Training Webinars Lead by FDA Experts

For Patients

Home > For Patients > About the FDA Patient Network

About the FDA Patient Network

- Learn About FDA Advisory Committees
- **Listen to Webinars and View Presentations Given by FDA Experts**
- Patient Liaison Program - Office of Health and Constituent Affairs
- Patient Liaison Team - Office of Health and Constituent Affairs

Resources for You

- View FDA Basics Webinar Series

Listen to Webinars and View Presentations Given by FDA Experts

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Through our webinars and presentations, the Office of Health and Constituent Affairs brings information to you on many topics related to patient engagement, medical product (Drugs, Biologics, Devices) approval and medical product safety updates.

You can listen to past webinars or view recent presentations from FDA experts. It is as easy as downloading the presentations, watching the webinar or reading the transcript.

If you would like to talk with the Office of Health and Constituent Affairs about ways your organization can engage with the FDA or if you have suggestions for future webinars, please email the Patient Network at patientnetwork@fda.hhs.gov

FDA Providing New Grants for Natural History Studies in Rare Diseases

For more information please visit The Office of Orphan Products Development.

Webinar Library

2017 - 2014

2013 - 2012

2013

FDA's Role in ClinicalTrials.gov
September 17, 2013

This webinar provides an overview of the Office of Good Clinical Practice and the FDA's responsibilities with ClinicalTrials.gov.

Listen to Webinar | Transcript

FDA Facebook

https://www.facebook.com/FDA/?fref=ts

FDA Patient Network Twitter

+

And 19 additional FDA Twitter accounts to follow for up-to-date information

https://twitter.com/FDA_Patient_Net

Resources

www.fda.gov/forpatients

http://go.usa.gov/xKzwb

PatientNetwork@fda.hhs.gov

Thank you!

heidi.marchand@fda.hhs.gov

FDA Orphan Medical Product Designation Program

GAYATRI RAO, M.D., J.D.

An Overview: Office of Orphan Products Development

Gayatri R. Rao, M.D., J.D.
Director, Office of Orphan Products Development
October 30, 2017

What is an “Orphan Product”?

- Product that is used to treat, diagnose, or prevent a **“rare disease or condition”** and includes:
  - Drugs – e.g., Radicava (edaravone) for amyotrophic lateral sclerosis (ALS)
  - Biologics – e.g., Spinraza (nusinersen), for spinal muscular atrophy (SMA)
  - Medical Devices – e.g., Argus II Retinal Prosthesis System “bionic eye” to treat eyes diseases such as macular degeneration and retinitis pigmentosa
  - Medical Foods – e.g., Low phenylalanine diet for PKU

What is a “Rare Disease”?

- Defined by law and is different for drugs/biologics and devices
  - Drugs/Biologics: Disease with a prevalence of <200,000 in US (generally)
  - Devices: Disease with an incidence of <8,000/year in US

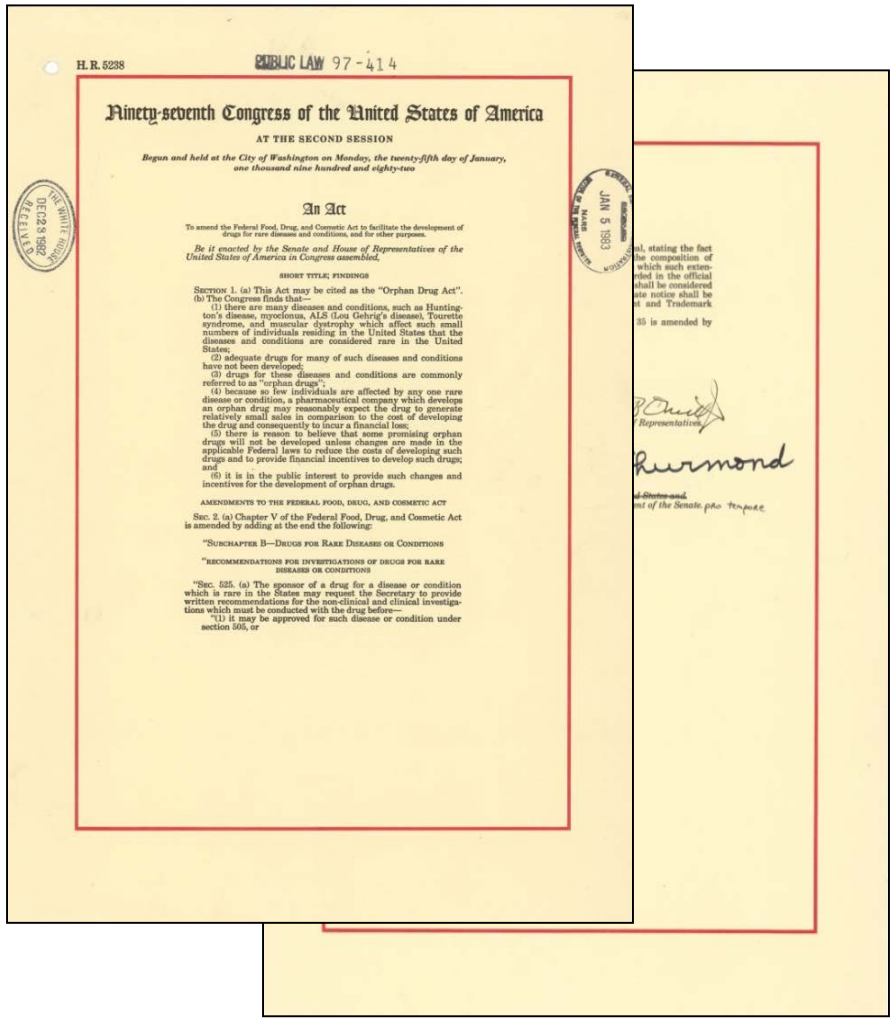
- Definition varies globally; for drugs/biologics:
  - EU: < 5 per 10,000
  - Japan: < 50,000 (4 per 10,000)

- Examples include Cystic Fibrosis, Duchene’s Muscular Dystrophy, ALS

Challenges to Rare Disease Product Development

- Difficulty diagnosing patients
- Small (often *very* small), widely-dispersed patient population
- Natural history of the disease not well understood
- Identifying appropriate biomarkers & surrogate endpoints
- Multiple, different, global regulatory requirements

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

Created incentives for orphan drug development, including:

1. Orphan Drug Designation Program
2. Orphan Products Grants 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 (~$2M)

3. Eligible to receive **7-years of marketing exclusivity** ("orphan exclusivity")
   - FDA will not approve another "same drug" for that rare disease for 7 years

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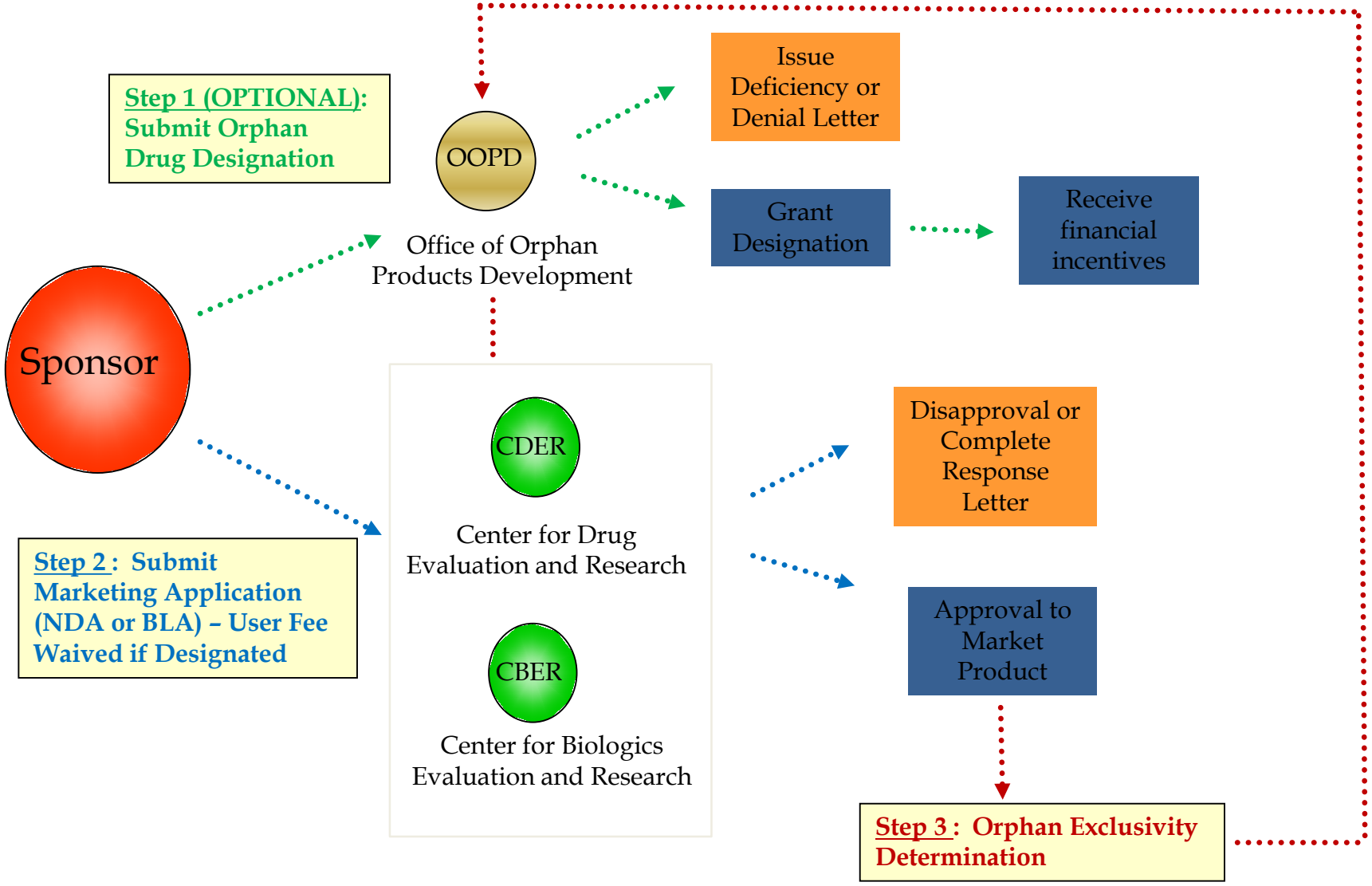
Process


Step 1 (OPTIONAL): Submit Orphan Drug Designation
OOPD
Issue Deficiency or Denial Letter
Grant Designation
Receive financial incentives
Office of Orphan Products Development
Sponsor
CDER
Center for Drug Evaluation and Research
Disapproval or Complete Response Letter
Approval to Market Product
Step 2 : Submit Marketing Application (NDA or BLA) – User Fee Waived if Designated
CBER
Center for Biologics Evaluation and Research
Step 3 : Orphan Exclusivity Determination

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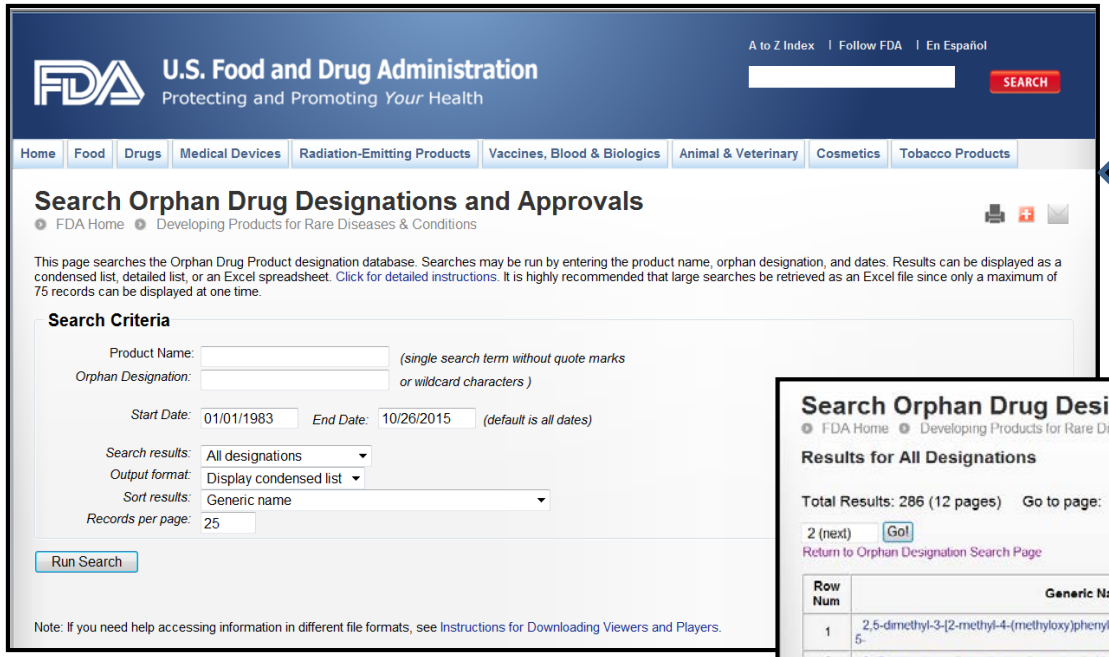
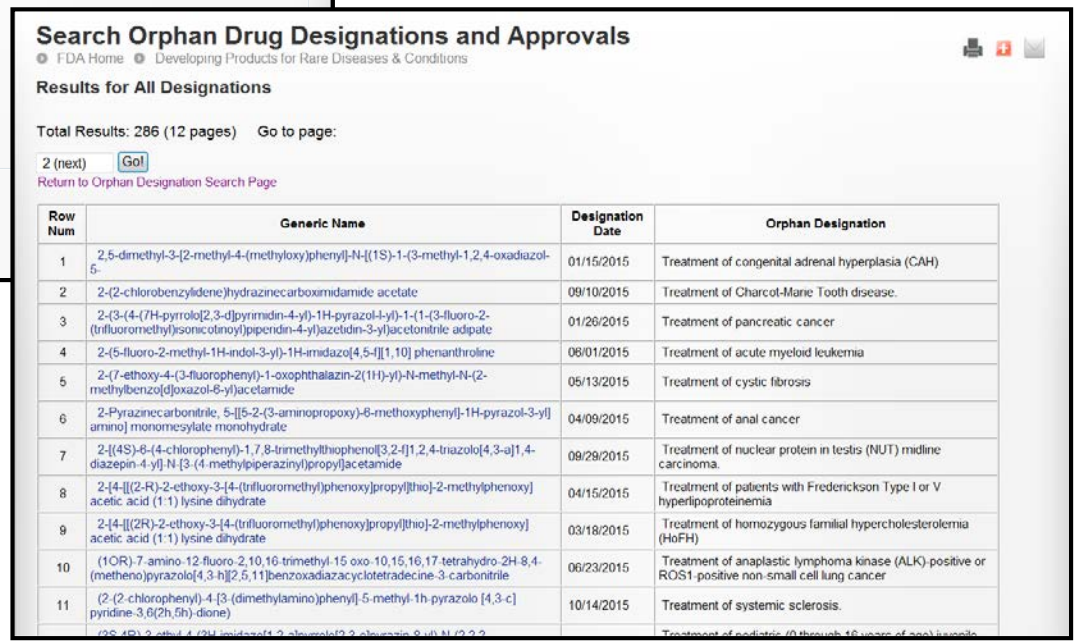
Public Database



To search for orphan drug designations and approvals:

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



Search Orphan Drug Designations and Approvals

FDA Home Developing Products for Rare Diseases & Conditions

Results for All Designations

Total Results: 286 (12 pages) Go to page:

2 (next) Go!

Return to Orphan Designation Search Page

Row Num	Generic Name	Designation Date	Orphan Designation
1	2,5-dimethyl-3-[2-methyl-4-(methyloxy)phenyl]-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-	01/15/2015	Treatment of congenital adrenal hyperplasia (CAH)
2	2-(2-chlorobenzylidene)hydrazinecarboximidamide acetate	09/10/2015	Treatment of Charcot-Marie Tooth disease.
3	2-(3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(1-(3-fluoro-2-(trifluoromethyl)isonicotinoyl)piperidin-4-yl)azetidin-3-yl)acetonitrile adipate	01/26/2015	Treatment of pancreatic cancer
4	2-(5-fluoro-2-methyl-1H-indol-3-yl)-1H-imidazo[4,5-f][1,10] phenanthroline	08/01/2015	Treatment of acute myeloid leukemia
5	2-(7-ethoxy-4-(3-fluorophenyl)-1-oxophthalazin-2(1H)-yl)-N-methyl-N-(2-methylbenzo[d]oxazol-6-yl)acetamide	05/13/2015	Treatment of cystic fibrosis
6	2-Pyrazinecarbonitrile, 5-[[5-2-(3-aminopropoxy)-6-methoxyphenyl]-1H-pyrazol-3-yl] amino] monomesylate monohydrate	04/09/2015	Treatment of anal cancer
7	2-[(4S)-6-(4-chlorophenyl)-1,7,8-trimethylthiopheno[3,2-f][1,2,4-triazolo[4,3-a]1,4-diazepin-4-yl]-N-[3-(4-methylpiperazinyl)propyl]acetamide	09/29/2015	Treatment of nuclear protein in testis (NUT) midline carcinoma.
8	2-[4-[[(2-R)-2-ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl]thio]-2-methylphenoxy] acetic acid (1:1) lysine dihydrate	04/15/2015	Treatment of patients with Frederickson Type I or V hyperlipoproteinemia
9	2-[4-[[(2R)-2-ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl]thio]-2-methylphenoxy] acetic acid (1:1) lysine dihydrate	03/18/2015	Treatment of homozygous familial hypercholesterolemia (HoFH)
10	(1OR)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile	06/23/2015	Treatment of anaplastic lymphoma kinase (ALK)-positive or ROS1-positive non-small cell lung cancer
11	(2-(2-chlorophenyl)-4-[3-(dimethylamino)phenyl]-5-methyl-1h-pyrazolo [4,3-c] pyridine-3,6(2h,5h)-dione)	10/14/2015	Treatment of systemic sclerosis.

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OOPD Core Programs

Mission: To promote the development of drugs, devices, biologics, and medical foods for patients with rare diseases and special populations

DESIGNATION PROGRAMS	
1	**Orphan Drug Designation & Exclusivity**
2	**Rare Pediatric Disease (RPD) Designation** • *New definition- disease or condition must be rare and its serious or life-threatening manifestations must occur in individuals 18 years and younger* • *Co-administer with Office of Pediatric Therapeutics as of May 15, 2017* • *Part of the RPD Priority Review Voucher Program*
3	**Humanitarian Use Device Designation (HUD)** • *Part of the HUD/HDE pathway* • *Disease or condition is not more than 8,000 individuals in the US per year*

GRANT PROGRAMS	
1	**$15M Orphan Products Clinical Trials Grant Program** • *Funding and monitoring 85 rare disease clinical trials*
2	**$6M Pediatric Device Consortia Grant Program** • *Appropriations increased from $3M to $6M in FY2017* • *Funding and monitoring 7 different consortia*
3	**$2M Orphan Products Natural History Grant Program** • *NIH providing additional $3.5M to fund total of 6 studies*

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…

" 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)

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OOPD Contact Information

For more information on Orphan Drug Designation and other OOPD programs go to:

www.fda.gov/orphan

Still have questions?

Email us at orphan@fda.hhs.gov

Call us at 301-796-8660

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CDER Divisions Working with Rare Diseases

JONATHAN GOLDSMITH, M.D.

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research:

Drug Development in the Rare Disease Space

Jonathan C. Goldsmith, MD, FACP

Associate Director, Rare Diseases Program

OND/CDER/FDA

CDER Rare Disease Public Workshop

30 October, 2017

Disclosures

- No conflicts of interest
- Nothing to report
- Opinions expressed are personal and may not reflect those of the FDA

Center for Drug Evaluation and Research

Office of the Center Director

Office of Regulatory Affairs	Office of Medical Policy
Office of Communications	Office of Management
Office of Strategic Programs	Office of Compliance

- **Office of Translational Sciences**
- **Office of Surveillance and Epidemiology**
- **Office of New Drugs**
  - **Immediate Office of the Director**
    - **Rare Diseases Program**
- **Office of Generic Drugs**
- **Office of Pharmaceutical Quality**

Office of New Drugs (OND)

- Office of Drug Evaluation I
  - Division of Cardiovascular and Renal Products (DCaRP)
  - **Division of Neurology Products (DNP)**
  - Division of Psychiatry Products (DPP)
- Office of Drug Evaluation II
  - Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
  - Division of Metabolism and Endocrinology Products (DMEP)
  - Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
- Office of Drug Evaluation III
  - Division of Dermatology and Dental Products
  - **Division of Gastroenterology and Inborn Errors Products**
  - Division of Bone, Reproductive and Urologic Products (DBRUP)
- Office of Drug Evaluation IV
  - Division of Medical Imaging Products
  - Division of Nonprescription Drug Products (DNDP)
  - Division of Pediatric and Maternal Health (DPMH)
- Office of Antimicrobial Products
  - Division of Anti-Infective Products (DAIP)
  - Division of Transplant and Ophthalmology Products (DTOP)
  - Division of Antiviral Products (DAVP)
- Office of Hematology and Oncology Drug Products
  - **Division of Oncology Products 1 (DOP 1)**
  - **Division of Oncology Products 2 (DOP 2)**
  - **Division of Hematology Products (DHP)**
  - Division of Hematology Oncology Toxicology (DHOT)

Challenges for Rare Disease Drug Development

- **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
- **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

For approval FDA/CDER must determine that there is:

- ✓ Substantial evidence of **effectiveness** for treatment of the proposed indication
- ✓ Demonstration that the benefits of the drug outweigh its **risks** for the patient population for which the drug is indicated (21CFR 314.50)
- ✓ **Manufacturing** that ensures product identity, strength, quality (purity)
- ✓ Evidence-based drug **labeling** that adequately guides providers and patients to use the drug safely and effectively

Although the usual approval standard is two adequate and well controlled trials-Flexibility is built into regulations

Special standards for orphan drugs are not needed because the regulations (21 CFR 314) provide for **flexibility** and **judgment** in applying the standards

How does CDER apply flexibility?

Flexible approaches can include:

- Approval supported by **fewer** than 2 adequate and well-controlled **studies**
- Use of the **accelerated approval pathway**
- Use of **novel trial end points**
- Use of **non-concurrent controls**

- CDER reviewers play a major role in helping sponsors **"get it right the first time"**

There are two approval pathways

traditional (regular or "full") **approval**

and

accelerated approval

the statutory standards are the *same* for both

⇩

demonstration of substantial evidence based on adequate and well-controlled clinical study(ies)

Concurrent controls and randomization are the goals when ethically and practicably feasible

- **Randomize early** in development to avoid potentially misleading, uninterpretable findings in open-label trials

- Explore ways to **limit time on placebo** for serious diseases with no approved therapy (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)

The 21st Century Cures Act (P.L.#114-255) Patient Focus

- This new law recognizes the unique position of patients to provide essential insights about what it is like to live with and fight their disease

- This has been FDA's perspective as well, and it is why FDA has continued to advance the science of patient input through patient-focused drug development programs

- "Cures" will enhance these ongoing efforts to better incorporate the patient's voice

Role of a Scientific Board for a Stakeholder Organization

Respected experts in the stakeholder organization disease

Roles and Responsibilities:

*Ensure that the stakeholder organization can interact effectively with granting agencies, researchers, regulators and commercial drug developers

*Provide balanced expertise on potential drug development initiatives from industry and academia

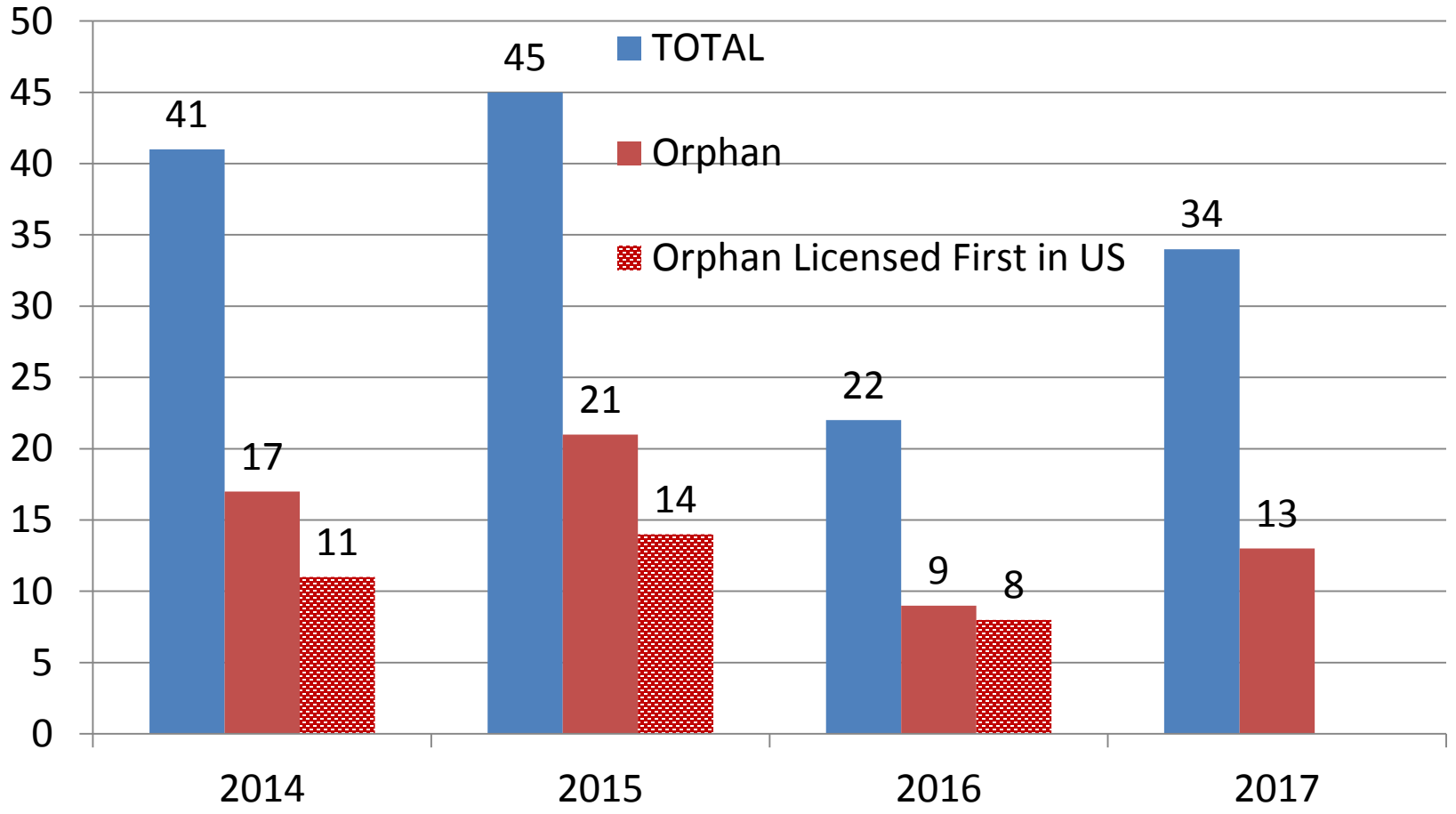
*Provide oversight and scientific evaluation of potential research projects to be funded by or contributed to by the stakeholder organization

*Present disease specific scientific/medical updates to the stakeholder Board of Directors

Externally-Led PFDD Meetings: Personal Perspectives

- Meetings have been well organized and executed
- Patient/family perspectives in support of drug development and evaluation were effectively communicated
- Panel members and other contributors provided clear perspectives on clinically meaningful treatment(s) and the current therapeutic landscape
- *Voice of the Patient* reports have been written and distributed

CDER Novel Orphan Drug Approvals CY 2014 -2017*



* as of 07 October 2017

Thank you very much for your attention!
Questions?

Jonathan.Goldsmith@fda.hhs.gov

Rare Diseases Program/OND/CDER/FDA

CDERONDRareDiseaseProgram@fda.hhs.gov

Professional Affairs and Stakeholder Engagement with CDER

JOHN WHYTE, M.D., PH.D

Questions and Answers

BREAK TIME

10:25 – 10:45 A.M.


30TH
OCT
CDER
RARE
DISEASES
Public Workshop
8 AM.
TO
5PM.

TYPES OF PATIENT ENGAGEMENT WITH CDER AT FDA

Moderator: *Francis Kalush, Ph.D.*

Overview of CDER Patient Engagement and Interactions:

Douglas Throckmorton, M.D

Externally-led Patient-Focused Drug Developed Meetings:

Meghana Chalasani

CureSMA Early Engagement and PFDD Meeting with FDA:

Rosangel Cruz, M.A.

Experience with Patient Engagement in Neurology: *Billy Dunn, M.D.*

Moderator:

FRANCIS KALUSH, PH.D.

Overview of CDER Patient Engagement with CDER at FDA

DOUGLAS THROCKMORTON, M.D.

Externally-led Patient-Focused Drug Development Meetings

MEGHANA CHALSANI

Externally-led Patient-Focused Drug Development Meetings

Meghana Chalasani
Office of Strategic Programs
FDA's Center for Drug Evaluation and Research (CDER)

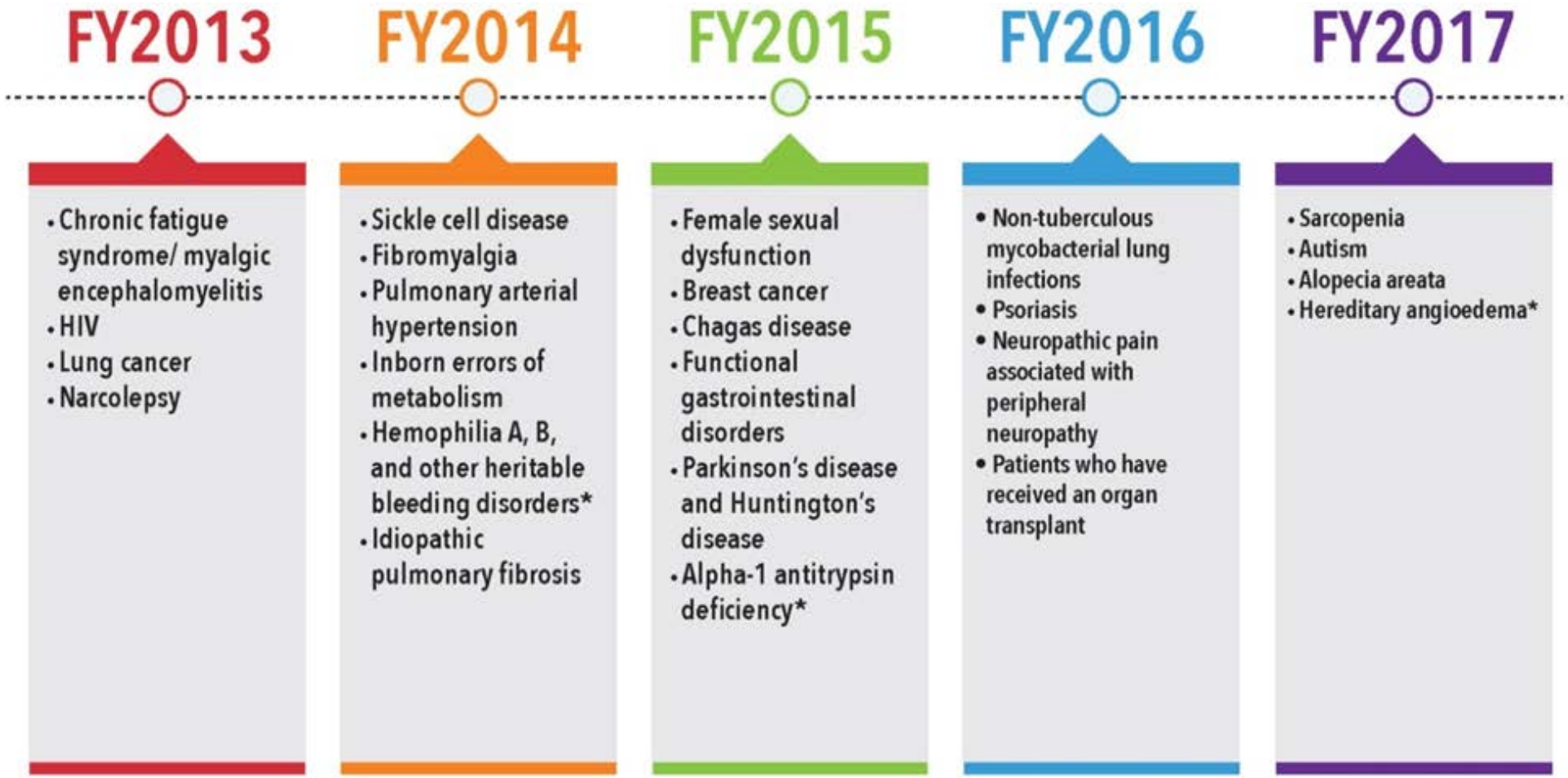
Rare Diseases Public Workshop
October 30, 2017

The views and opinions expressed in this presentation are those of the individual presenter and should not be attributed to or considered binding on the U.S. Food and Drug Administration (FDA).

Patient's Perspectives Inform FDA's Benefit-Risk Framework

Benefit-Risk Summary and Assessment		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	**Sets the context for the weighing of benefits and risks:** • How serious is this indicated condition, and why? • How well is the patient population's medical need being met by currently available therapies?	
Current Treatment Options		
Benefit	**Characterize and assess the evidence of benefit:** • How meaningful is the benefit, and for whom? • How compelling is the expected benefit in the post-market setting?	
Risk	**Characterize and assess the safety concerns:** • How serious are the safety signals identified in the submitted data? • What potential risks could emerge in the post-market setting?	
Risk Management	**Assess what risk management (e.g., labeling, REMS) may be necessary to address the identified safety concerns**	

Creating Opportunities for Dialogue



* Meetings conducted by FDA's Center for Biologics Evaluation and Research

We Ask Questions About…

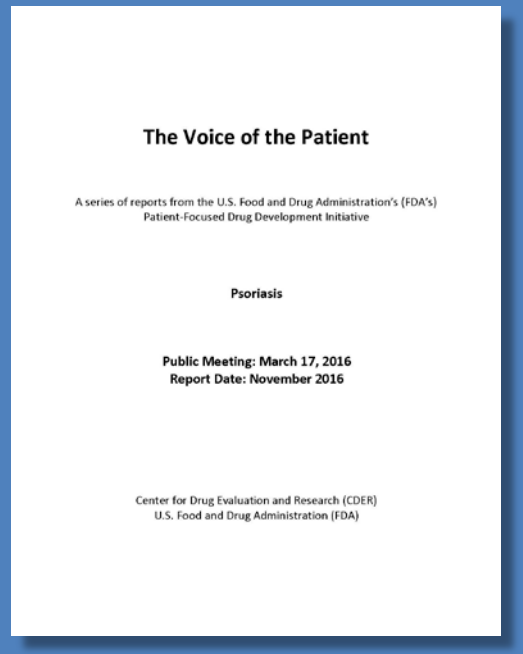
Symptoms and daily impacts that matter most to patients

- Of the symptoms that you experience, which 1-3 symptoms have the most significant impact on your life?
- Are there activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?
- How has your condition and its symptoms changed over time?

Patient perspectives on current treatment approaches

- How well does your current treatment regimen treat the most significant symptoms of your disease?
- What are the most significant downsides to your current treatments, and how do they affect your daily life?
- Assuming there is no complete cure, what specific things would you look for in an ideal treatment for your condition?

Each meeting results in a **Voice of the Patient** report that faithfully captures patient input from the various information streams



The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative

Psoriasis

Public Meeting: March 17, 2016
Report Date: November 2016

Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

This input can support FDA staff, e.g.:

- In conducting benefit-risk assessments for products under review, by informing the therapeutic context
- Advising drug sponsors on their development programs

It might also support drug development more broadly:

- Help identify areas of unmet need in the patient population
- Help identify or develop tools that assess benefit of potential therapies
- Help raise awareness and channel engagement within the patient community

Externally-led PFDD: The Opportunity

- Meetings conducted by external stakeholders provide an opportunity to expand the benefits of PFDD
- An externally-led PFDD meeting and any resulting products (e.g., surveys or reports) will not be considered FDA-sponsored or FDA-endorsed
- The success of an externally-led PFDD meeting requires a joint, aligned effort by multiple patient groups associated with the disease area, and other interested stakeholders

Externally-led PFDD: Planning a Meeting

KEY PARTICIPANTS:

Patients, patient representatives, patient advocates

TARGET AUDIENCE (LISTENING MODE):

Regulatory/other federal agencies, medical product developers, researchers, healthcare professionals

DO NOT HAVE TO BE STANDALONE MEETINGS:

Consider incorporating PFDD-style sessions in annual conferences, scientific workshops, etc.

FDA-led meetings can serve as a model:

- Target disease areas where there is an identified need for patient input on topics related to drug development
- Main discussion topics: (1) Symptoms and daily impacts that matter most to patients and (2) current approaches to treatment
- Facilitator-led large group discussion, interactive webcast, discussion aids (e.g., polling tools)
- Meeting deliverables: Web recording, transcript, summary report

Externally-led PFDD: Key Considerations

Please submit a letter of intent (LOI) to CDER's Office of Strategic Programs. Our team is here to serve as a helpful resource to you.

While we truly understand the effort it takes to plan a PFDD meeting, but it can be done without being resource intensive!

The key to an insightful, robust, and informative PFDD meeting is active community outreach to ensure a representative group of patient perspectives in the room.

We must be respectful of the time of patients and their caregivers.

Some PFDD Learnings to Date

- Patients with chronic serious disease are **experts on what it's like to live with their condition**
- They are able to **identify and articulate specific disease impacts** (symptoms, loss of function) in concrete terms
- They can identify and articulate **what is important to them regarding treatment benefit**
- Their **"chief complaints" may not be factored** explicitly into drug development plans
- They want their experience **described using words that they consider best** to describe how it feels
- Patients **want to be as active as possible** in the work to develop and evaluate new treatments

PFDD Next Steps

Advance science of patient input

- **Engage wider community to discuss methodologically sound approaches** that:
  - Bridge from initial PFDD meetings to more systematic collection of patients' input
  - Generate meaningful input on patients' experiences and perspectives to inform drug development and B-R assessment
  - Are "fit for purpose" in drug development and regulatory context

Provide guidance

- To: patient communities, researchers, and drug developers
- On: **pragmatic and methodologically sound strategies, pathways, and methods** to gather and use patient input, or patient experience data, that can be submitted to FDA for use across drug development programs.

PFDD Guidance Series

- Guidance 1 and Workshop
- Guidance 2 and Workshop
- Guidance 3 and Workshop
- Guidance 4 and Workshop

Describes approaches to **collecting comprehensive and representative patient and caregiver input** on burden of disease and current therapy

Address topics including:

- standardized nomenclature and terminologies (glossary)
- methods to collect meaningful patient input throughout the drug development process
- methodological considerations for data collection, reporting, management, and analysis

December 18th Public Workshop: Collecting Comprehensive & Representative Input

- Discussion on methodological approaches that a person seeking to collect patient experience data for submission to FDA to inform regulatory decision-making may use

- FDA is seeking information and comments from a broad range of stakeholders, including patients, patient advocates, academic and medical researchers, expert practitioners, drug developers and other interested persons.

- Register to attend in person or via webcast: www.pfdd.eventbrite.com

PFDD Guidance Series

Guidance 1 and Workshop

Guidance 2 and Workshop

Guidance 3 and Workshop

Guidance 4 and Workshop

Describes processes and methodological approaches to **develop holistic set of impacts** that are most important to patients

PFDD Guidance Series

- Guidance 1 and Workshop
- Guidance 2 and Workshop
- Guidance 3 and Workshop
- Guidance 4 and Workshop

Describes approaches to **identifying and developing measures for an identified set of impacts** (e.g., burden of disease and treatment), which may facilitate collection of meaningful patient input in clinical trials

PFDD Guidance Series

Guidance 1 and Workshop

Guidance 2 and Workshop

Guidance 3 and Workshop

Guidance 4 and Workshop

Incorporating measures (COAs) into endpoints considered significantly robust for regulatory decision making

For More Information

- FDA's PFDD Meetings
  - Previously conducted FDA-led meetings, including all of meeting materials, such as agendas and discussion questions, as well as the Voice of the Patient summary reports: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm

- Externally-led PFDD Meetings
  - For more information and guidelines for letter of intent (LOI):
  - http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm

- 21st Century Cures (Patient-Focused Drug Development):
  - For the complete work plan for issuance of PFDD guidances, please visit: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf

- Questions?
  - Email patientfocused@fda.hhs.gov
  - FDA CDER's Office of Strategic Programs is leading FDA's PFDD effort

Acknowledgement

Office of Strategic Programs

Theresa Mullin
Pujita Vaidya
Sara Eggers
Graham Thompson
Shannon Woodward

Office of New Drugs

CDER Senior Leadership

CureSMA: Early Engagement and PFDD Meeting with FDA

ROSANGEL CRUZ, M.A.

Cure SMA Early Engagement with FDA & Externally-Led PFDD Meeting

Make today a breakthrough.

Cure SMA

We fund groundbreaking research for treatment and a cure for SMA and provide families the support they need for today.

Impact

- 115,000 supporters throughout the country
- 12,000 members affected by SMA
- 350 newly diagnosed contacts annually
- $60 Million in research funding
- 28th Annual conference, 1500 attended

99

Reasons Cure SMA Approached FDA

- **Relationship Building –** ***Is your organization known to FDA?***
  - Center for Biologics Evaluation and Research, CBER
  - Center for Drugs Evaluation and Research, CDER
  - Review Divisions, OSP, PACE, Office of Rare Diseases, etc.
- **Providing patient perspective,** including SMA's **disease severity** and its **impact on patients' and families' daily lives**
  - Discussed the SMA's community creation of the Voice of SMA booklet
- Engaging in discussions on **outcome measures**, **biomarkers**, **clinical trial design**
- **Educating regulators on clinical meaningfulness** (important for drug approval) and **risk tolerance in our community.**

What is Important to Your Community?!

Opportunities that Led to Positive Interactions with FDA

Informing Regulators On Severity of SMA: Impact on Families/Patients' Lives and Meaningful Change

Disease burden/impact

- SMA has a **broad and devastating impact** (direct & indirect) on the lives of ***all*** those affected and their families

Meaningful change in SMA:

Small change = BIG difference

Additive, incremental change critical to maximal efficacy

- Therapy that prevents decline or gives small improvements has huge value
- Additive or Incremental change could lead to greater overall function
- Both improved respiratory function and fatigue have significant impact
- Importance cited for daily living activities

Meaningful Change

"But if we could just keep what we have, that would be enormous, because then there's still so much functionality there. There's not a breathing machine at night yet. There's not all of the rods in the back. There's not all this stuff that I know could be coming. If I can just hold on to where we are, that would—man, that would be big." (1409-FG5-01 Caregiver Type 3)

What Have We Learned via these Interactions?

- **FDA is as eager to learn about your patient community as you are to share your community with them!**

"Most of our medical education comes from patients. This [meeting] gives us as regulators the opportunity and the privilege to continue our education by listening to you."

-Wilson Bryan, MD

Director of the Office of Tissues and Advanced Therapies in the FDA's Center for Biologics Evaluation and Research

How can you best prepare to ensure a successful engagement with FDA?

- **Be specific about what you are going to talk about**
  - Have a specific topic/agenda prepared
- **Educate yourself about the process**
  - Submitting a Letter of Intent (LOI) to conduct a PFDD - specific information required on LOI?
  - Preparing to conduct an Externally-Led PFDD meeting – ***do your homework!***
- **Don't be afraid to ask/learn from others who have come before you**
  - MDF
  - Amyloidosis
- **You may want to hire help to assist in facilitating interactions with various units at FDA and key division leaders**
  - Regulatory Consultant, James Valentine
  - Consulting Group, DrinkerBiddle

Externally-Led Patient Focused Drug Development (PFDD) Meeting

April 18, 2017

Setting the Stage - In the words of Dr. Wilson Bryan…

"What we hear today will help us to think about clinical trial design, what outcome measures to use in clinical trials, what really matters to patients, and how we as regulators should think about the balance of risks and benefits for patients with SMA…"

- Wilson Bryan, MD, Director of the Office of Tissues and Advanced Therapies in the FDA's Center for Biologics Evaluation and Research.

SMA PFDD – A Labor Of Love!

Well-Attended with Representation from All Key SMA Stakeholders

- **422** individuals registered to attend, with representation from 40 states and 27 countries
  - In person (204) / Via webcast (218)

- **Of those registered to attend in person**:
  - 98 individuals with SMA, parents, and caregivers
    - 10 had someone close to them with SMA
  - 31 representatives from 10 Patient Advocacy organizations
  - 16 FDA leadership staff (CDER, CBER, OHCA, others)
  - 27 Industry members
  - 6 academic clinicians

An Outstanding Group of Panelists was Chosen to Represent the Voices of SMA - All Ages, Stages and Types of SMA

SMA Type II/III: On the Burden of SMA II/III – Fatigue, Muscle Weakness, Progressive Loss of Functional Abilities

6 are patients or parents with type II (5-29)
6 are patients or parents with type III (5-41)

On an Ideal Treatment…

"We want to make sure we understand the impact of the disease and what patients prioritize in the treatment of their disease"

- Dr. Billy Dunn MD, Director, Division of Neurology Products, CDER, FDA

An Ideal Therapy – What matters most to patients with SMA

Type Is

- Ability to speak, communicate how child feels
- Management of secretions
- Respiratory Complications – “being less dependent on machines”

Type II/III

- Small changes / HUGE impact
- Fatigue
- Upper body strength/ diaphragmatic weakness
- Respiratory Complications (type IIs)
- Stopping disease progression, retaining mobility and function (Stabilizing disease)

All Types

- Muscle strength – stronger arms, legs, spine
- Endurance

Yet … What We Really Took Away from this…

- Hope
- Resilience
- Persistence
- Optimism
- Bravery
- Creativity
- Strength
- Love

"[I have heard of…]*Your commitment and love for your children; your courage and determination as adults, older children and teens; and how you maintain hope and unity."* – Dr. Jonathan Goldsmith

FDA's Concluding Remarks

"Your voice, which we heard today loud and clear, and in great detail, helps FDA as we perform our public health mission and as we evaluate and approve new drug applications"

- Jonathan Goldsmith, MD,

Associate Director for Rare Diseases in the Office of New Drugs in the FDA's Center for Drug Evaluation and Research

PFDD Meetings - Influence the Community and Outcomes

- **Enhanced interactions with FDA**
- **Open channels for continued communication with FDA**
  - Voice of the Patient Report
  - Benefit Risk Survey
  - Follow Up workshop
- **Opportunities to engage and support other non-profit, rare diseases organization in sharing “Best Practices”**
- **A more cohesive sense of community amongst all key SMA Stakeholders**
  - Families, Caregivers, and Affected individuals , FDA, Industry, Academicians/Researchers, Other patient-centered organizations

Lessons Learned from Our PFDD

- For externally-led PFDDs, advocacy group must lead on content, speakers, and logistics
- Keep FDA's Office Of Strategic Programs (Dr. Mullin) in the loop, but have realistic expectations on their involvement with planning
- Prepare panelists well

Lessons Learned from Our PFDD, *Continued*

- **Think carefully about your polling questions**
  - Make sure they probe and reinforce the key themes being identified by the panelists
  - Make sure they are phrased correctly and ask what you think they do to ensure data will be useful in the end
- **Pick your moderator very carefully**
  - Make sure he/she understands the big picture and directs audience discussion and questions accordingly
- **Make sure all AV logistics are running before start of meeting**
  - Live polling question, Live streaming video, Transcription service to help write up VOP, presentation slides

Experience with Patient Engagement in Neurology

BILLY DUNN, M.D.

Questions and Answers

LUNCH

12 – 1 P.M.


30TH
OCT
CDER
RARE
DISEASES
Public Workshop
8 AM.
TO
5PM.

CASE STUDIES:
THE IMPORTANCE OF HISTORICAL CONTROLS PATIENT DATA AND REGULATORY FLEXIBILITY WHEN ENGAGING WITH CDER

Moderator: *Francis Kalush, Ph.D.*

Case Study 1 – TSAlliance: Steve Roberds, Ph.D.

Case Study 2- Amyloidosis Research Consortium: Isabelle Lousada

External Controls Patient Data and CDER Flexibility for Rare Disease Drug Approval: Dragos Roman, M.D.

Importance of Controlled Trials and Natural History Studies – Bridging the Gap Between Impressions and Data: Henrietta Hyatt-Knorr, M.A.

Moderator:

FRANCIS KALUSH, PH.D.

Case Study 1 – TSA Alliance

STEVE ROBERDS, PH.D.

Externally-Led Patient-Focused Drug Development Meeting for TSC

Steven L. Roberds, PhD, Chief Scientific Officer

Tuberous Sclerosis Alliance

About Tuberous Sclerosis Complex (TSC)

- Tuberous sclerosis complex (or TSC) is a genetic disorder that causes tumors to form in vital organs, primarily the brain, eyes, heart, kidney, liver, lungs and skin.
- Neurological manifestations are often the most devastating.
- TSC is a leading genetic cause of autism and epilepsy.
- TSC affects ~1 in 6,000 live births.
- An estimated 50,000 Americans have TSC, and more than 1 million worldwide.




Tuberous Sclerosis Alliance

Tuberous Sclerosis Alliance

The TS Alliance, founded in 1974, is committed to finding a cure for tuberous sclerosis complex while improving the lives of those affected:

- by developing programs, support services and resource information;
- by stimulating and sponsoring research; and
- by creating and implementing public and professional education programs designed to heighten awareness of the disease.

www.tsalliance.org

Tuberous Sclerosis Alliance

The Need for FDA Engagement

- Existing FDA-approved treatments have helped many patients but are not sufficient
- TSC affects every individual differently, even identical twins
- Risks of TSC are very high; therefore, some patients or parents may have a very high tolerance for risks of new therapies
- The possibility of preventing some manifestations of TSC is here:
  - Infants are often identified prenatally based upon presence of cardiac rhabdomyomas
  - Need to treat seemingly “healthy” people before the damage of TSC is done

Tuberous Sclerosis Alliance

Designing the Patient-Focused Drug Development Meeting

Two high-priority areas of unmet need and ongoing therapy development:

- Preventing and/or controlling epilepsy, especially in infancy
- Reversing or preventing life-threatening manifestations in adults: tumor growth and cyst formation in kidneys and lungs

Two review divisions: neurology and oncology

Two very different types of clinical endpoints

One meeting – two sessions

Tuberous Sclerosis Alliance

Speaking to the Audience

Addressing FDA's Risk-Benefit Framework

MORNING SESSION – INFANTS AND CHILDREN WITH TSC

- Panel #1: Living with TSC
- Panel #2: Current and future approaches to treating TSC

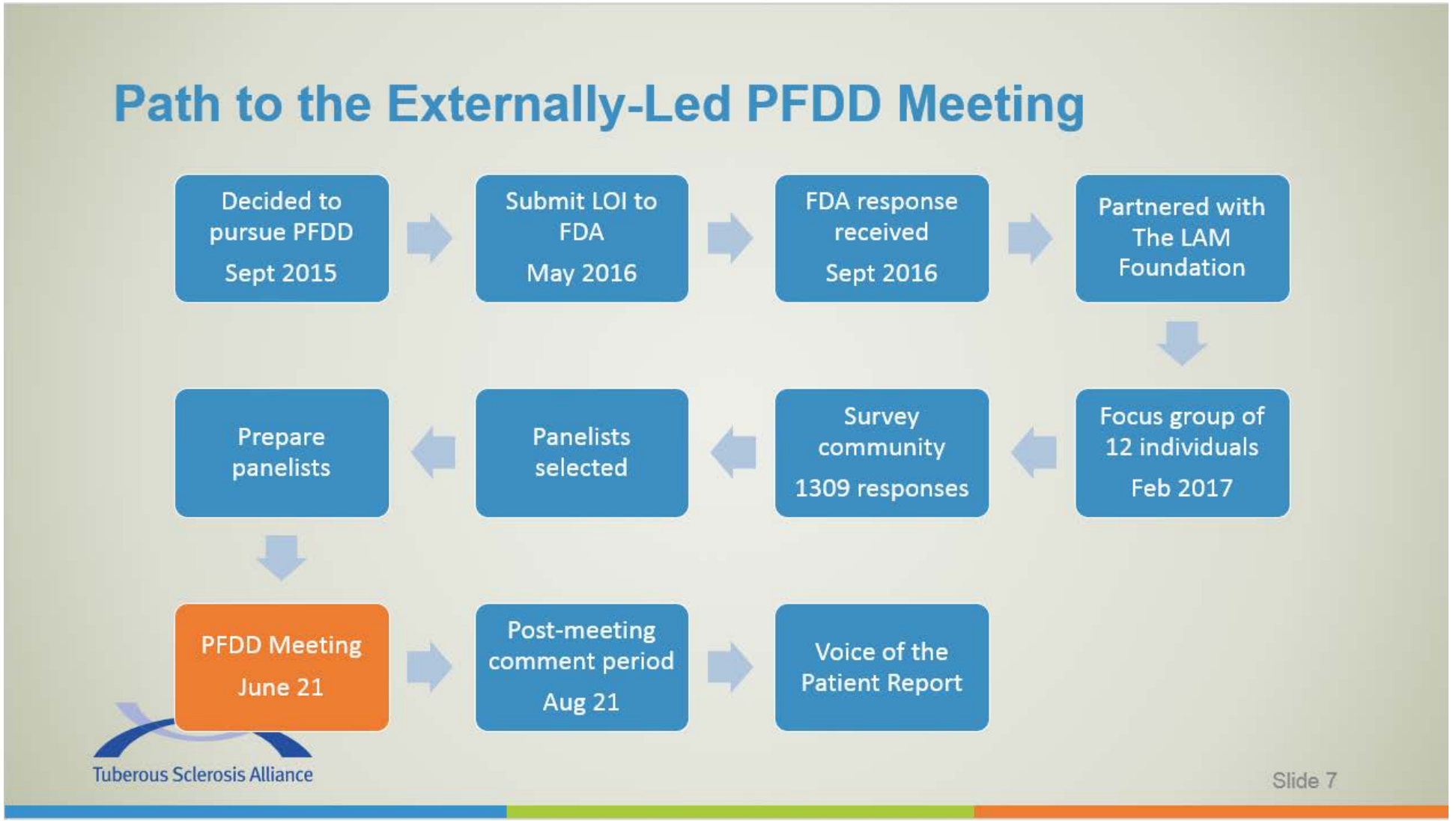
AFTERNOON SESSION – ADULTS WITH TSC AND/OR LAM

- Panel #1: Living with TSC and/or LAM
- Panel #2: Current and future approaches to treating TSC and/or LAM

Each panel's testimony followed by:

- Audience and remote polling
- Moderated audience discussion

Tuberous Sclerosis Alliance


Path to the Externally-Led PFDD Meeting
Decided to pursue PFDD
Sept 2015
Submit LOI to FDA
May 2016
FDA response received
Sept 2016
Partnered with The LAM Foundation
Focus group of 12 individuals
Feb 2017
Survey community
1309 responses
Panelists selected
Prepare panelists
PFDD Meeting
June 21
Post-meeting comment period
Aug 21
Voice of the Patient Report
Tuberous Sclerosis Alliance
Slide 7

How We Engaged the Community

- Focus group of 12 representative individuals to define key issues
- International survey for quantitative input
  - 1309 responses, 66.5% from US
  - Questions in three languages, responses from 57 countries
- 16 panelists representing a variety of TSC and LAM patients
- Webcast with 666 live views
- Live polling questions
- Live commenting on social media
- 30-day post-meeting open comment period

Tuberous Sclerosis Alliance

Reflecting on Our Experience

- Excellent in-person and online turnout
  - Patients and caregivers
  - FDA staff
  - Industry
- Survey data complemented the impact of personal testimony
- Partnering with The LAM Foundation increased engagement and participation

- Advice from FDA and other organizations' experiences strengthened our preparation and ability to communicate our message

Tuberous Sclerosis Alliance

Case Study 2 – Amyloidosis Research Consortium

ISABELLE LOUSADA

amyloidosis research consortium

FDA

Approaching CDER at FDA: Patient Focused Drug Development Meetings

Isabelle Lousada

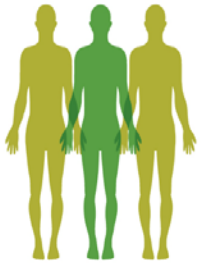
Amyloidosis

FDA U.S. FOOD & DRUG ADMINISTRATION

amyloidosis research consortium

8,220

patients are diagnosed in the US and Europe each year with AL Amyloidosis



1,600,000

African-Americans are estimated to carry the TTR V122I genetic mutation and are at risk of developing ATTR Cardiac Amyloidosis

74%

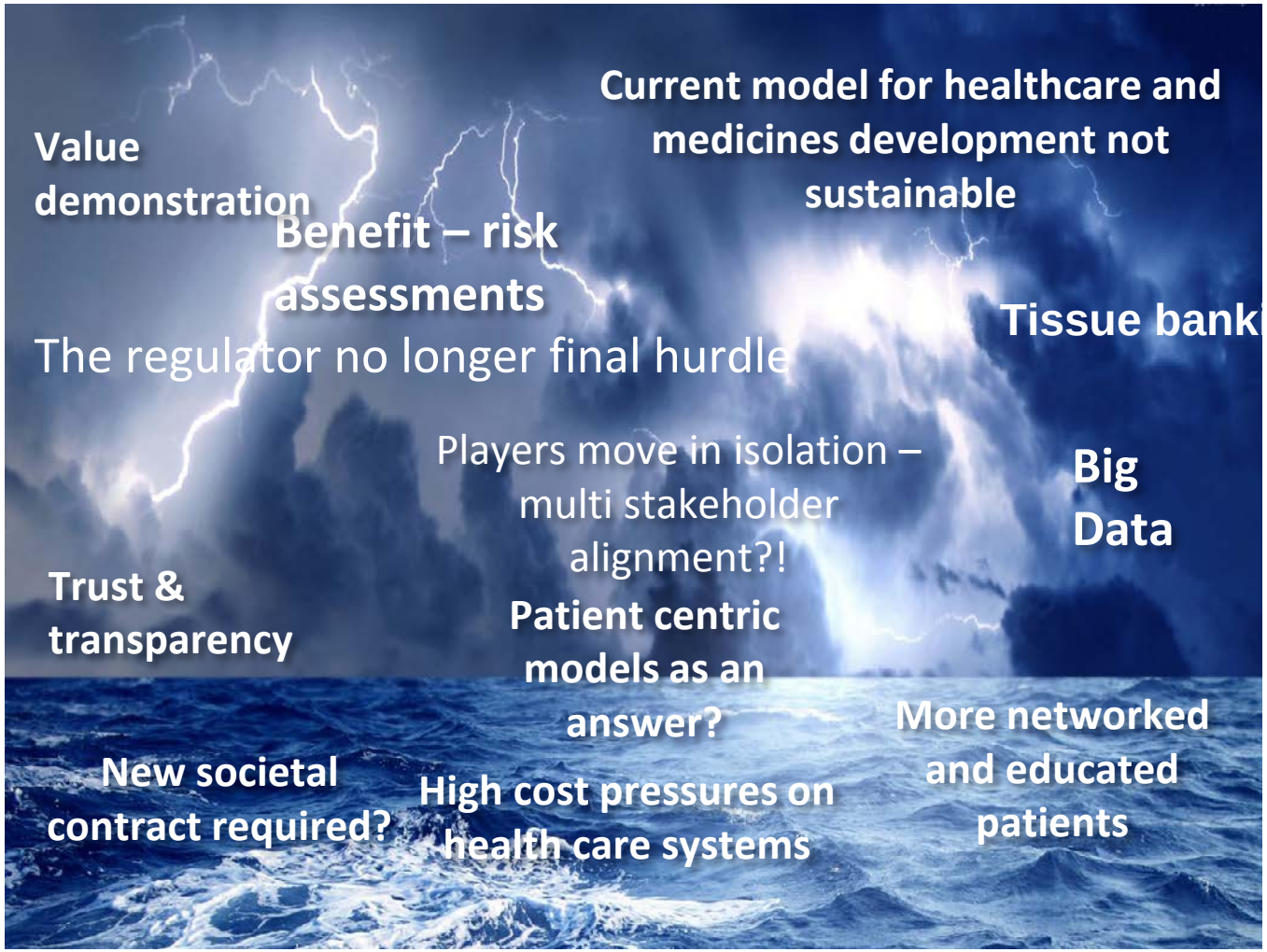
of AL patients have cardiac involvement

4+ is the average number of doctors a patient sees before being diagnosed

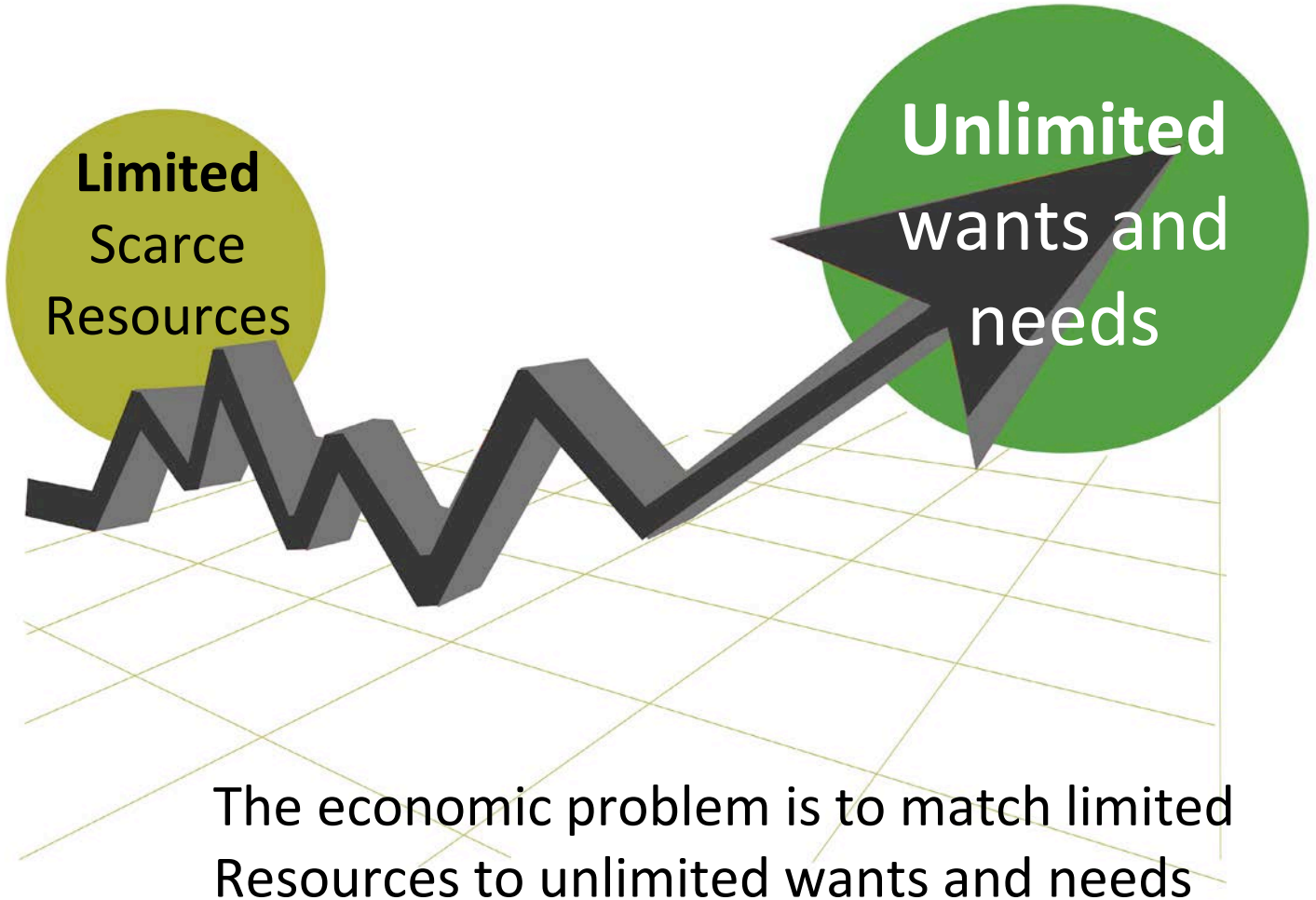
40%

of patients die, because they were diagnosed too late to potentially benefit from treatment

Perfect Storm



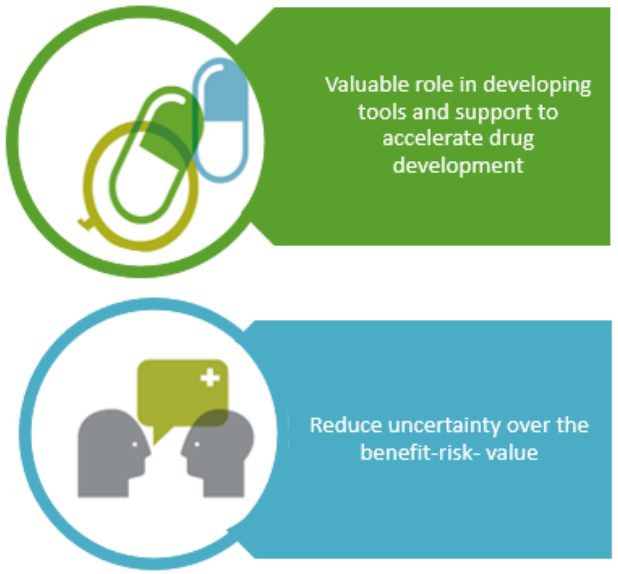
Resources

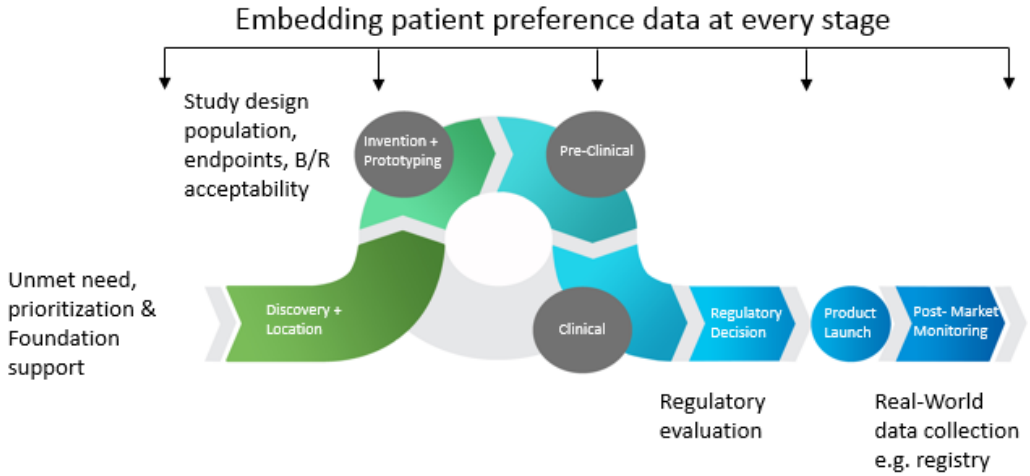


The economic problem is to match limited Resources to unlimited wants and needs

Role of Patient Led Foundations Across Drug Development

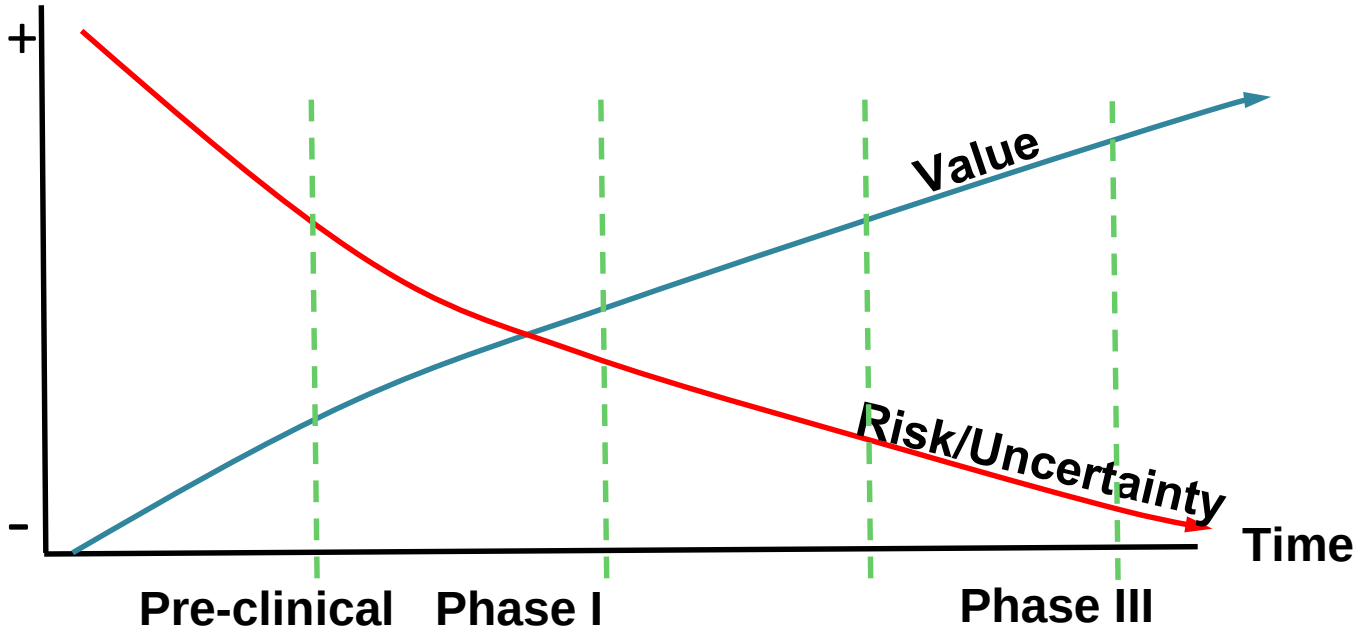
amyloidosis research consortium





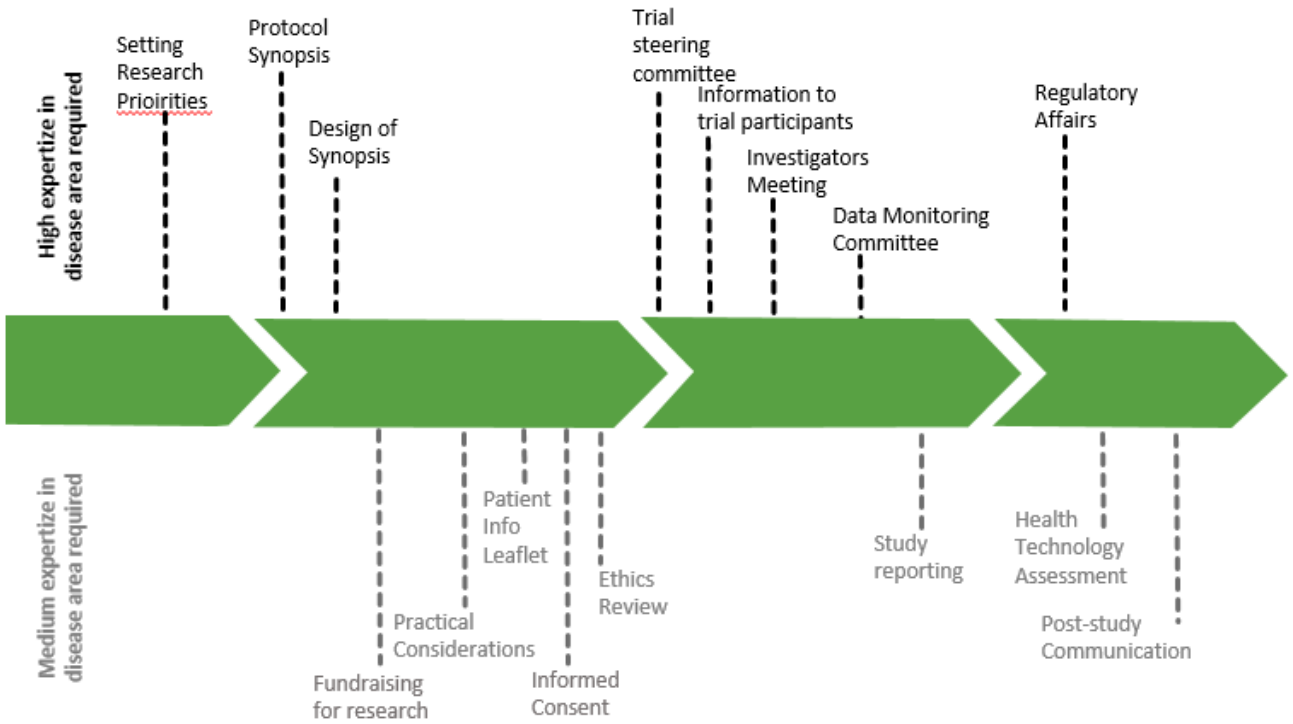
Patients are experts in their disease, and properly engaged can play a vital role in all stages of drug development

De-Risking, Improving Value



Better Research for Better Outcomes

Patient Involvement R&D life cycle



Source: Geissler, Ryll, Leto, Uhlenhopp EPALCO/EUPATI (2015, unpublished)

Building Programs to Support Drug Development

- Drug Development Round Table
- Guidance for Industry on Drug Development
- Biomarker Development
- Patient Focused Drug Development Meeting
- Patient Voice Publication

Externally-Led Patient Focused Drug Development Meeting

ARC's Meeting

- 18th September 2015
- 15th November 2015
- 240 Attendees. Including industry, experts, FDA, and NIH
  - 125 pts and caregivers
- 340 registered for the live webinar
- 38 patients submitted stories

Format of meeting was somewhat different than typical PFDD meetings:

- Presenting data alongside patient voice
- Follow on Survey for patients

External Controls Patient Data and CDER Flexibility for Rare Disease Drug Approval

DRAGOS ROMAN, M.D.

Case Studies in Drug Approval for Rare Diseased – Lessons Learned

CDER Rare Disease Public Workshop
October 30, 2017

Dragos Roman, MD

Deputy Director

Division of Gastroenterology and Inborn Errors Products

OND/CDER/FDA

Disclosure Statement

- The views expressed in this presentation are mine, and do not represent an official FDA position.

- I have no financial interests to disclose.

Outline

- Regulatory standards of drug approval in rare diseases
- Three case studies:
  - Uridine acetate for orotic aciduria
  - Asfotase alfa for hypophosphatasia
  - Cerliponase alfa for neuronal ceroid lipofuscinosis type II
- Lessons learned

Outline

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- Lessons learned

Regulatory Milestones

- 1938: Food, Drug, and Cosmetic Act (FD&C Act) mandated a pre-market review of the **safety** of all new drugs
- 1962: the Kefauver-Harris Amendment to the FD&C Act - requirement that all new drug applications demonstrate **"substantial evidence"** of effectiveness
- 1983: Orphan Drug Act (financial incentives for orphan diseases: <200,000 patients in the US)

Definition of “Substantial Evidence”

- Section 505(d) of the FD&C Act: “Evidence consisting of **adequate and well-controlled investigations**…
- Traditionally **two adequate and well-controlled studies** when each meets its primary endpoint by its prespecified primary analysis with a p-value of less than 0.05
- FDA Modernization Act (FDAMA; 1997) substantial evidence of effectiveness can be based on “**one adequate and well-controlled study and confirmatory evidence**.”

Disease Prevalence

- High prevalence diseases:
  - Diabetes prevalence: 29.1 million (2012)
  - Hypertension: 75 million (2016)
  - NASH: 10-16 million (2017)

- Low prevalence (rare diseases):
  - Hereditary orotic aciduria prevalence: 1:1,000,000
  - Hypophosphatasia: ≈1:100,000
  - Neuronal ceroid lipofuscinosis type 2 ≈1: 300,000

"Flexibility" and Regulatory Requirements

- **21 CFR 314.105 - Approval of an application […]:**
  - "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling…"
  - "… 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 312.80 - Drugs intended to treat life-threatening and severely-debilitating illnesses**
  - FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness.

Outline

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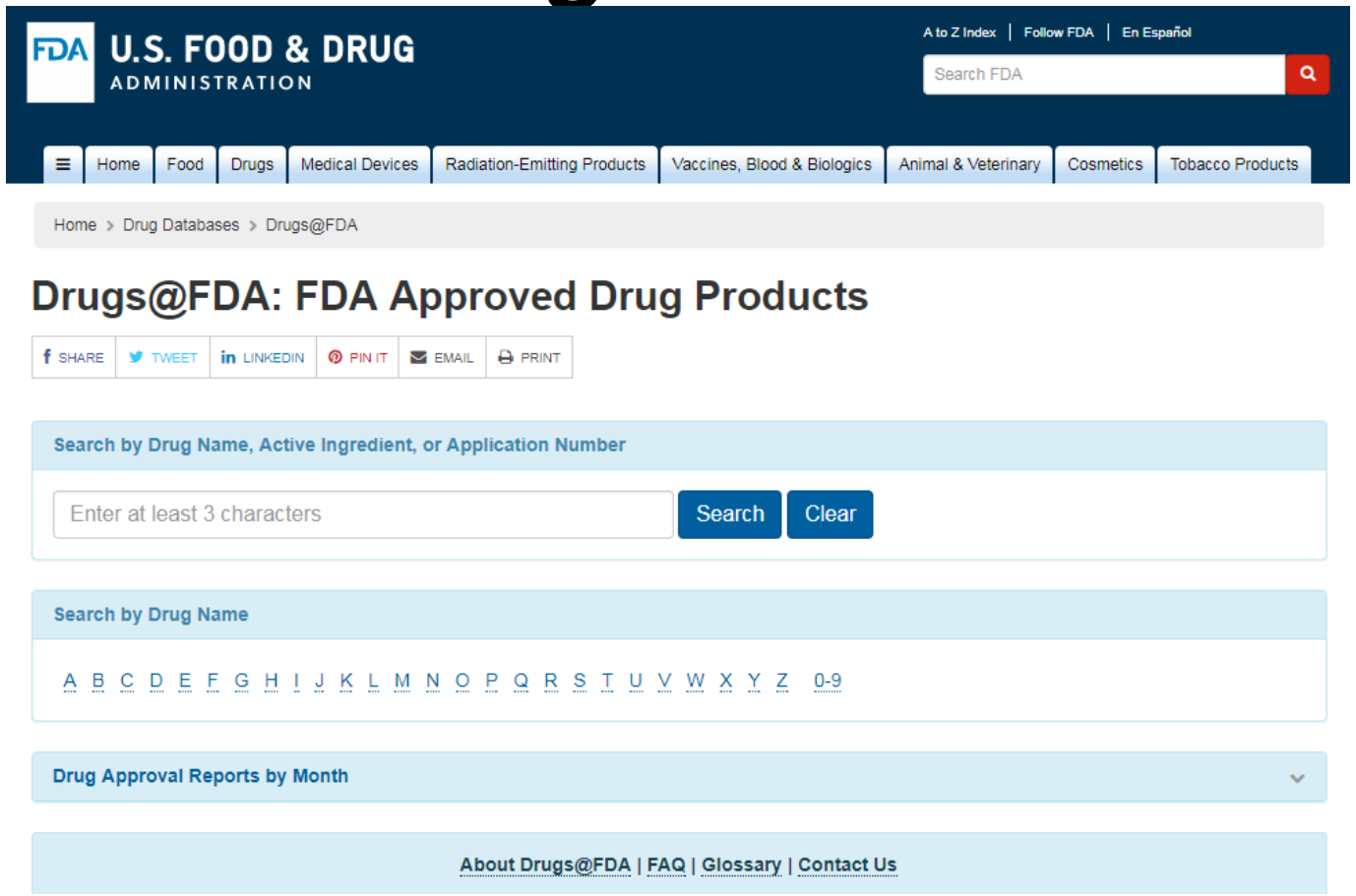
Drugs at FDA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Drug Approval Reports by Month
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Hereditary Orotic Aciduria (HOA)

- enzyme defect: uridine monophosphate synthase
- since original disease description (1959) about 20 patients with HOA have been reported in the medical literature (only 15 or so having been documented in sufficient detail)
- heterogeneous manifestations:
  - hematological (megaloblastic anemia, neutropenia)
  - failure to thrive, developmental delay
  - crystalluria and obstructive uropathy
- no approved drugs until 2015 (uridine used investigationally for decades)

Uridine Triacetate for HOA

- uridine triacetate: pro-drug of uridine - approved in 2015 (Xuriden)
- uridine triacetate was granted:
  - Orphan Drug designation
  - Breakthrough Therapy designation
    - multiple multidisciplinary meetings with input from senior FDA reviewers and managers
  - Rare Pediatric Disease Priority Review designation
  - NDA was reviewed as a Priority Review (shortened review time)

Uridine Triacetate for HOA

- NDA based on a dataset of 4 patients **AND** published literature information
- all major aspects of the HOA clinical program have been discussed with the applicant
- 505(b)(2) application:
  - published literature can be used in support of a New Drug Application (NDA)

Uridine Triacetate for HOA

- Existing literature data provided:
  - understanding of the physiological requirements for *de novo* pyrimidine synthesis in adults
  - estimate of exogenous uridine doses necessary for replacement treatment in patients with HOA
  - confirmation of an effective range of doses (doses of 50-300 mg/kg/day) in treating anemia (the most common disease manifestation in HOA) in multiple independent reports
  - a minimally effective dose (50 mg/kg/day)
  - timecourse for PD markers (reticulocyte count, urinary orotic acid)
  - persistence of treatment for months/years as long as doses are adjusted
  - data mostly for anemia but also for other manifestations of the disease (hematological or not)

Uridine Triacetate for HOA

- NDA leveraged the existing literature data and provided:
  - a starting dose of uridine triacetate (60 mg/kg/day) and a dose range of effective doses (60-120 mg/kg/day) informed by an understanding of
    - the mass ratio between uridine and uridine triacetate - allowed calculation of Xuriden doses which provide similar molar concentrations as specific uridine doses
    - differences in bioavailability between uridine and uridine triacetate (4 times more bioavailable than uridine on a weight basis)
  - confirmation that Xuriden maintains similar pharmacodynamic (biochemical and hematological) effects in a small group of patients (4) with HOA already treated successfully with uridine

Uridine Triacetate for HOA – Lessons Learned

- A successful clinical program requires early discussions and steady collaboration between drug developers and regulators
- Always leverage any existing data!
- Plan very thoughtfully how to maximize the value of patient information/data
- Incentives facilitate drug development in rare diseases and bring treatments to the market (Rare Pediatric Disease Priority Review Voucher)

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- Lessons learned

Hypophosphatasia (HPP)

- rare metabolic bone disease (prevalence: 1/100,000 for severe forms of HPP)
- due to inactivating mutations in tissue-nonspecific alkaline phosphatase (TNSALP)
- TNSALP is essential for bone mineralization:
  - releases inorganic phosphate from inorganic pyrophosphate (PPi)
  - inorganic phosphate a precursor of calcium phosphate
  - hydroxyapatite crystals in the bone matrix giving strength and rigidity to the bones
- no approved drug prior to 2015

Hypophosphatasia – Clinical Manifestations

- defective bone mineralization
- rickets and osteomalacia
- deformities and fractures of the long bones
- abnormalities of the thoracic cage resulting in respiratory dysfunction and insufficiency
- non-skeletal manifestations include pyridoxine-responsive seizures
- hypercalcemia, hypercalciuria (including nephrocalcinosis)
- myopathy (contributing to delayed or abnormal gait)
- dental manifestations
- clinical variability: perinatal/infantile, juvenile, and adult forms

Asfotase Alfa

- biologic: glycoprotein composed of two identical polypeptides, each polypeptide chain is a fusion of
  - the catalytic domain of human tissue non-specific alkaline phosphatase,
  - the Fc domain of the human immunoglobulin G1
  - a bone targeting domain (a deca-aspartate peptide).

Asfotase Alfa for Hypophosphatasia

- asfotase alfa (Strensiq) was approved in 2015 (Strensiq)
- asfotase alfa was granted:
  - Orphan Drug designation
  - Fast Track Designation (“rolling review”)
  - Breakthrough Therapy designation
  - Priority Review

Asfotase Alfa – Clinical Program

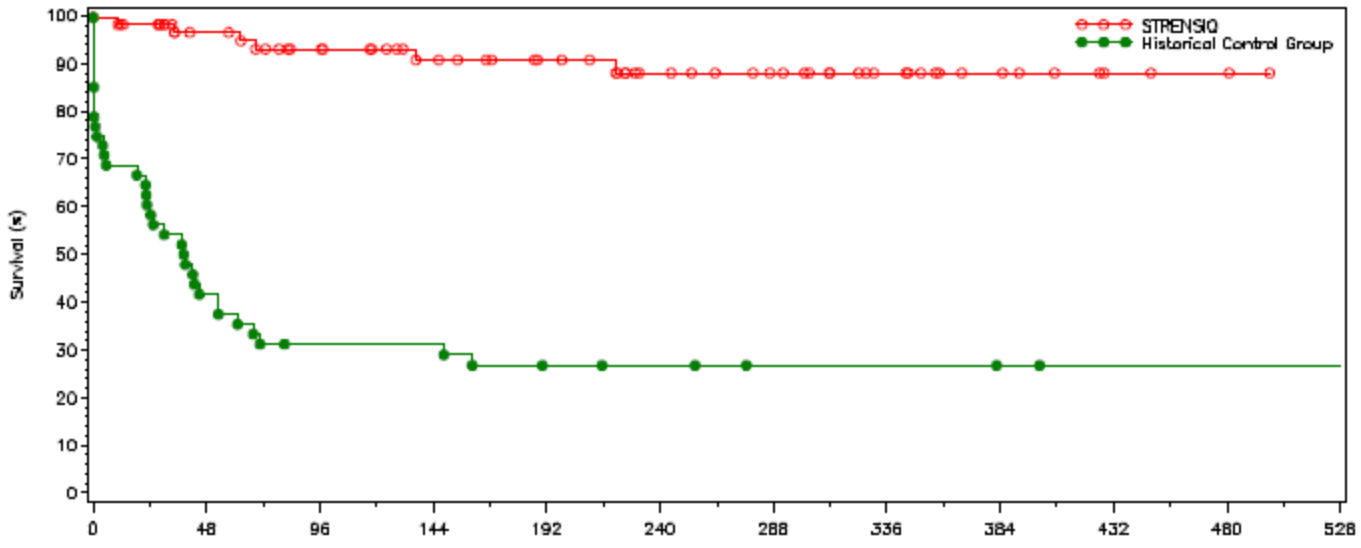
- Perinatal/infantile form
  - a prospective, open-label, single-arm trial in 11 patients (24-weeks with extension)
  - a prospective, open-label, single-arm study in 59 patients (up to 96 weeks)
- A natural history clinical study
- Juvenile form
  - prospective, open-label, single-arm, clinical trial in 8 patients (24-week plus extension)

Asfotase Alfa – Clinical Program

- major aspects of the asfotase alfa clinical program have been discussed with the applicant
- for the perinatal/infantile form the severe lethal course was well documented
- no placebo group was used: the clinical trial data were compared to the data from the a natural history cohort
- agreed endpoint: overall survival and ventilator-free survival (“hard endpoint”)

Efficacy Results

Figure 1: Overall Survival in STRENSIQ-Treated versus Historical Control Patients with Perinatal/ Infantile-Onset HPP



x–axis truncated at Week 528; there were 6 historical control patients censored after truncation with censored times ranging from 538 to 1030 weeks

Asfotase Alfa – Lessons Learned

- when “hard endpoints” are used and the natural history of the disease is well characterized, a placebo arm may not always be necessary
- close collaboration between drug developers and regulators is essential

Outline

- Regulatory standards of drug approval in rare diseases
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- Lessons learned

Neuronal Ceroid Lipofuscinosis Type 2 (CLN2)

- Progressive neurodegenerative lysosomal storage disease
- Single gene defect: tripeptidyl peptidase-1 (TPP1)
- Following lysosomal uptake TPP1 activates at acidic pH and cleaves tripeptides from the N-terminus of proteins accumulating in the lysosomes
- Prevalence: estimated at 1:300,000
- No approved therapy until 2017

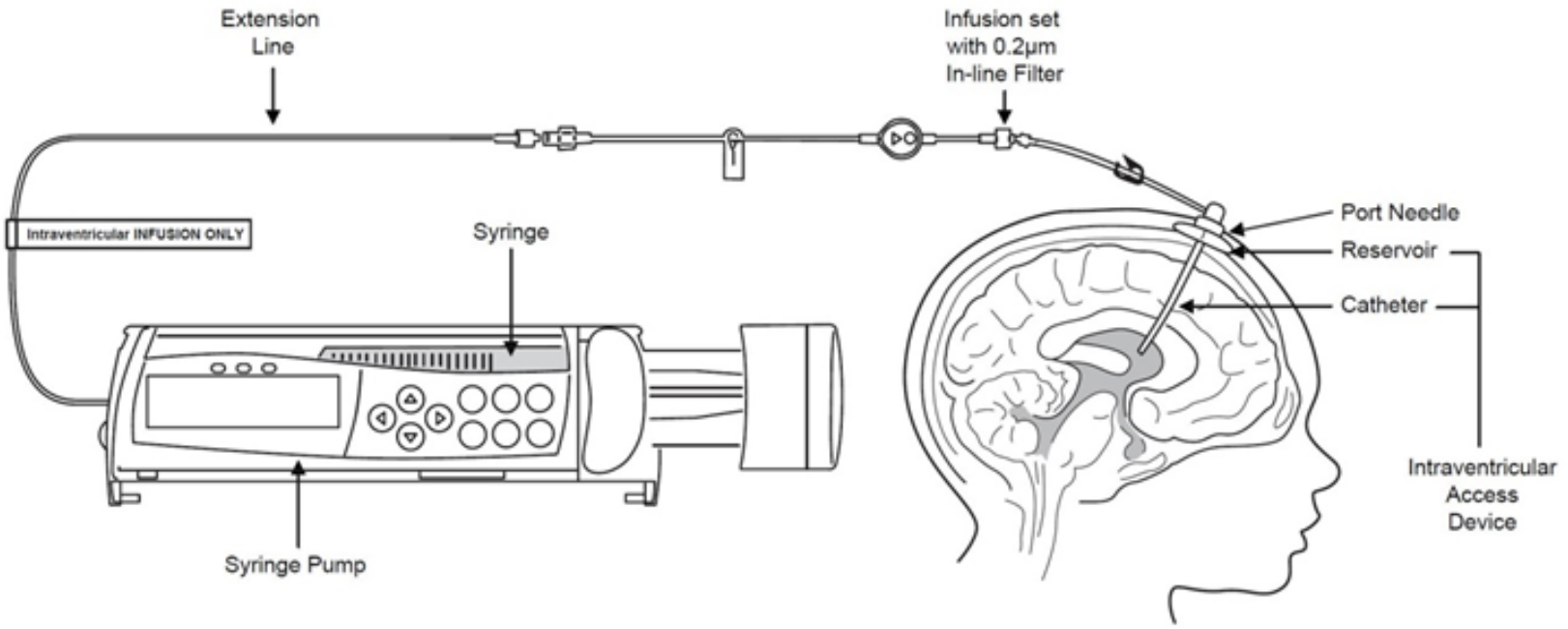
Neuronal Ceroid Lipofuscinosis Type 2 – Clinical Manifestations

- Marked by inexorable neurodegeneration
  - Typically seizures between 2-4 years of age with relatively predictable neurological deterioration
  - Myoclonus
  - Impaired speech and swallowing
  - Developmental regression
  - Loss of vision
  - Most are blind and wheelchair bound by age 6 yrs
  - Death typically at 10-16 yrs

Cerliponase Alfa – Clinical Program

- Single-arm, open-label, 48 week study with an extension
  - population: (n=24) ≥ 3 yo
  - primary endpoint: CLN2 scores (observer reported outcome)
- Natural history registry
  - population: (n=69)
  - mostly retrospective, a limited prospective component
  - variable amounts of data collected among patients
  - analyzable population (n=42)
  - assessed CLN2 scores with a slightly different questionnaire

Cerliponase Alfa Administration

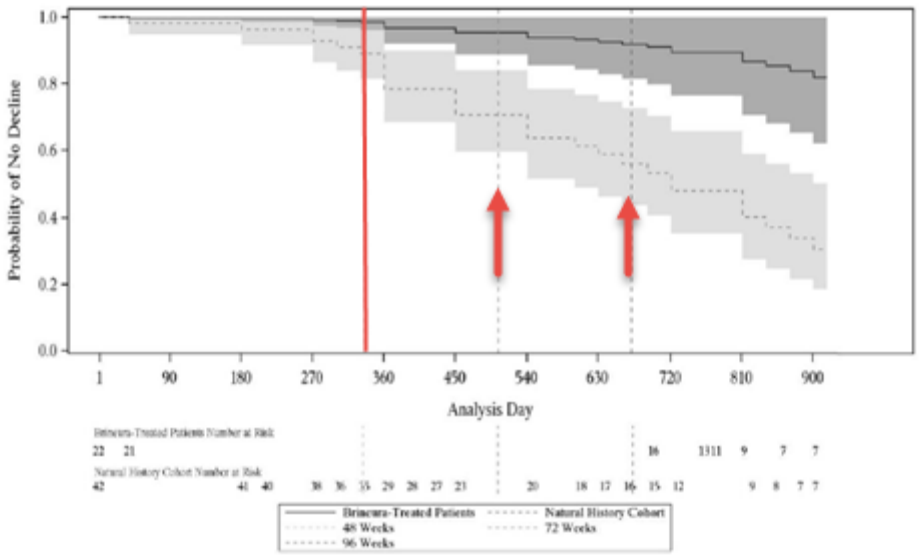


Cerliponase Alfa - Clinical Program

- Challenges:
  - Populations differences (genetics, age, timing of data collection)
  - Data in the natural study were mostly retrospective (much earlier in some patients – possible different standard of care)
  - Modified rating scales in the intervention study vs. the natural history study (particularly related to the language domain)
- Solutions:
  - Found the best matched groups (genetics, disease severity)
  - Extend the observation time
  - Complex statistical analyses to confirm the efficacy claim

Cerliponase Alfa

Figure 7. Estimated Time to Unreversed (Sustained) 2-Category Decline or Unreversed Score of Zero in Motor Domain for Symptomatic Pediatric Patients in the Brineura Single-Arm Clinical Study with Extension and for Patients in a Natural History Cohort (Based on the Cox Proportional Hazards Model Adjusting for Covariates)



Shading represents 95% confidence intervals.

Cerliponase Alfa – Lessons Learned

- When endpoints other than “hard endpoints” are used there are significant challenges to comparisons to a natural history study
  - seek best match in the patient populations
  - use the same instrument (e.g. questionnaire, rating scale, assay, etc.) to collect critical data
  - if matching is not optimal ensure enough time of observation to eliminate residual uncertainty about the validity of the comparison

Drug Development in Rare Diseases – Final Thoughts

- early discussion and involvement of regulators
- think globally: phase 1, phase 2, and phase 3 programs are a continuum in generating data and cannot be artificially split
- consider innovative designs (but talk with us before implementing them!)
- always necessary to collect good data (every patient data point counts!)
  - standardize data collection – will help facilitate meaningful comparisons
  - "totality of data" does not mean ANY data, but WELL PLANNED collection of INFORMATIVE data

Drug Development in Rare Diseases – Final Thoughts

- we want to hear patient's voice
- patients' experience can inform drug development in many ways:
  - helps understanding of the disease burden
  - helps identification of specific symptoms or disease manifestations that are relevant to patients (how the patient feels or functions)
  - helps the selection of assessments and endpoints in clinical trials
  - helps to identify benefits that may not be obvious to outside observers or readily measurable

Importance of Controlled Trials and Natural History Studies – Bridging the Gap Between Impressions and Data

HENRIETTA HYATT-KNORR, M.A.

Importance of Natural History Studies and Clinical Trials: Bridging the Gap Between Impressions and Data

How ORDR Intends to Facilitate the Production of Good Data

By Henrietta D. Hyatt-Knorr, MA

Office of Rare Diseases Research/NCATS

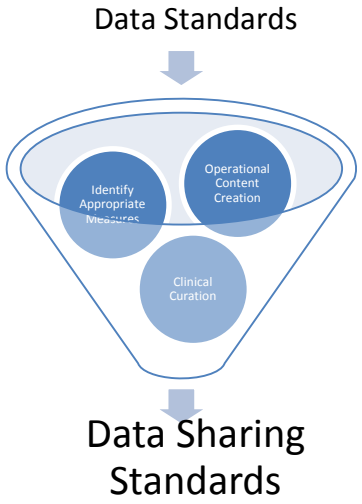
Where to begin…

What is a Natural History Study: Following subjects who have or may develop a specific disease.

- Begin with the end in mind …
- Knowledge of the disease's natural history is important when planning to develop a treatment
- Many of the 7,000 or so rare diseases are poorly understood
- The lower the prevalence, the more likely that a disease is not well understood
- Usually, the ultimate hope is a first treatment for a rare disease
- Requires careful planning
- Often high phenotypic diversity

Three Phases

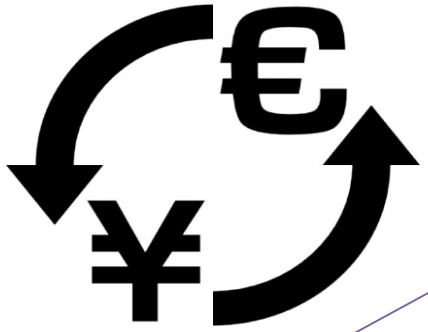
- Planning Phase - Data Standards
  - “FAIR” Principle
    - Findable
    - Accessible
    - Interoperable
    - Reusable
- Data Input Phase - Content Standards
  - Operationalize Content Creation
  - Identification Appropriate Measures
  - Clinical Content Curation
- Sharing Phase - Data Sharing Standards
  - Clinical Research Outcomes Data Sharing/Hosting



PLANNING PHASE

Data Standards – Accessible and Interoperable

FAIR → Accessible
Currency Exchange → Yens to Euros



Interoperable → Data Standards ICD9/10

Lingua Franca A language that is adopted as a common language among speakers whose native languages are different. **Male = 1, Male = M, Male = Male**

DATA INPUT PHASE

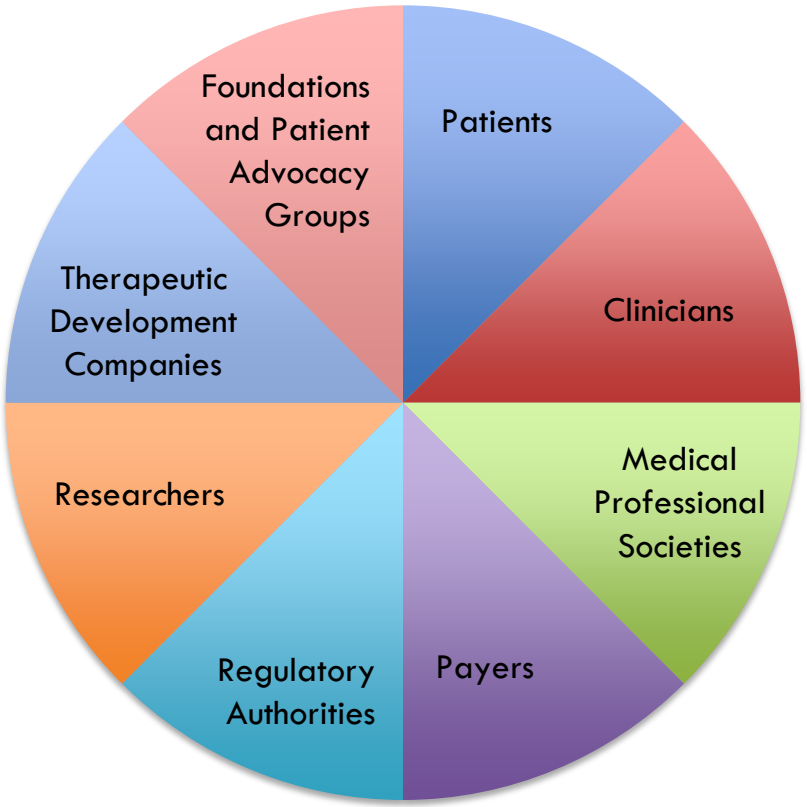
Why Data Collection and Management Matter

Data management—the integrated system for collecting, cleaning, storing, monitoring, reviewing, and reporting on data—determines the utility of the data for meeting the goals of the study.

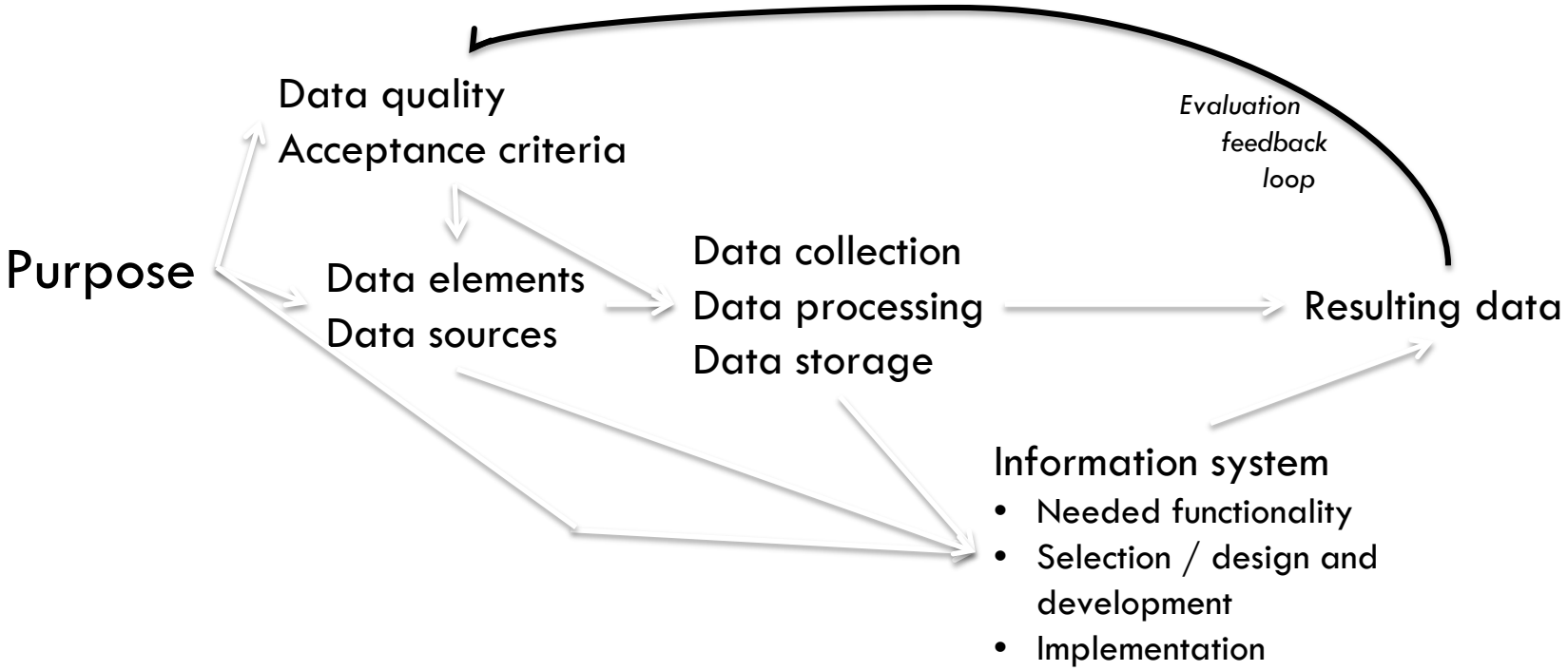
Quality assurance, on the other hand, aims to assure that the data were, in fact, collected in accordance with these procedures and that the data stored in the database meet the requisite standards of quality, which are generally defined based on the intended purposes.

- AHRQ 2014

Multiple Stakeholders



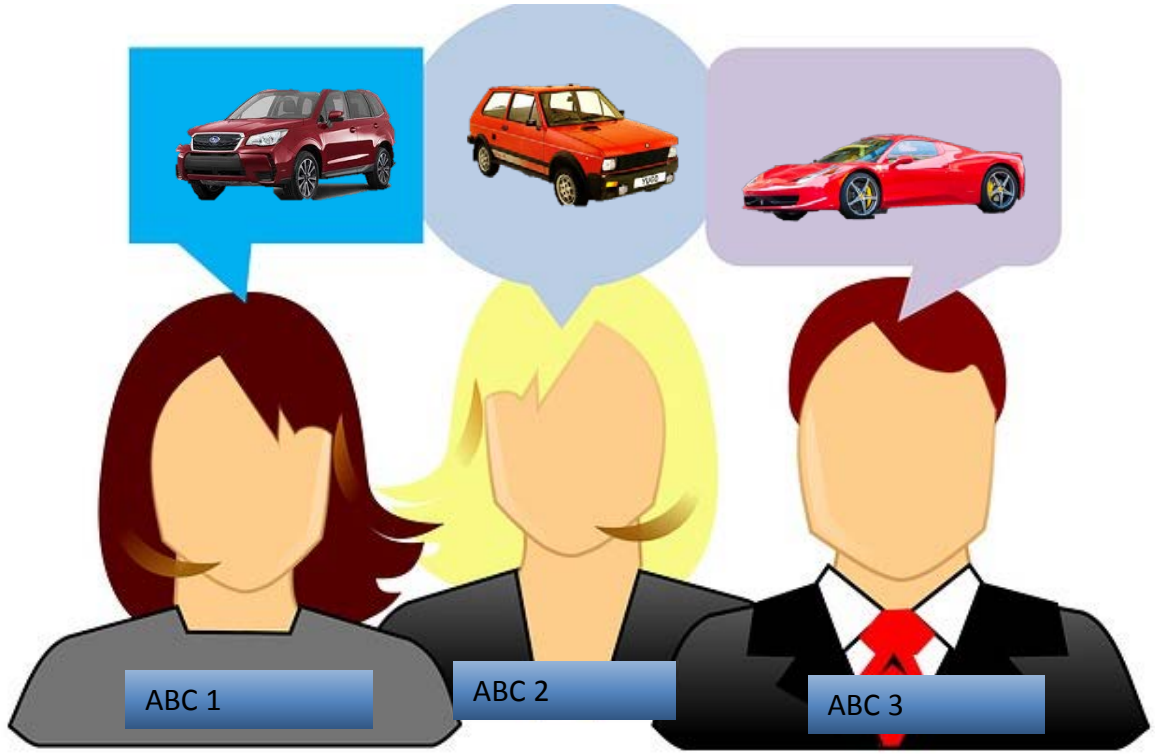
Data collection and management Components



Data collection and Management Components

Topic
Purpose
Data quality acceptance criteria
Data element selection
Data element definition
Data source selection
Data standards selection
Data observation/measurement methods
Data collection workflow analysis & design
Data recording methods
Data processing methods
Identification of information system needs
Information system testing
Information system implementation
Data quality assessment and assurance
Traceability

Across Stakeholders



DATA SHARING

Key messages

- Exchanging or sharing data without sufficient metadata is irresponsible and can be dangerous.
- Too many choices (“standards”) and lack of collaboration to harmonize (models, terminologies, metadata standards, CDEs) creates confusion and exacerbates the problem; redundancy and duplication of efforts are barriers to data sharing.
- Data and metadata must be available in a format that is useful ‘downstream’ for appropriate aggregation, analysis and interpretation.
- Research data is PRECIOUS, especially for rare diseases; ‘big data’ solutions are not appropriate.

End User Considerations

- How do I request access to the data ?
- Who makes the decision about who gets access to the data. What are the decision criteria? *DAC : data access committee.*
- How long does it take to get a decision?
- How long do I get to keep the data and what is the process for renewing my access?

End User Considerations

- What restrictions are placed on use of the data?
- What type of infrastructure do I need to process the data? Where am I allowed to store the data and what types of security measures do I need to put in place?
- How technically challenging is it to work with the data? Decryption, data organization, ability to integrate with other data sets.
- What quality assurance measures have been applied to the data? How much do I trust the data?

BREAK TIME

2:15 – 2:30 P.M.


30TH
OCT
CDER
RARE
DISEASES
Public Workshop
8 AM.
TO
5PM.

SO, YOU WANT TO MEET WITH CDER? DEVELOPING AN EFFECTIVE ENGAGEMENT STRATEGY

Moderator: *Kendall Davis, M.P.H.*

CDER Expert Perspective – Best Practices:

Laurie Muldowney, M.D.

Patient Advocate Perspective – Best Practices:

James Valentine, J.D., M.P.H.

CDER Expert Perspective: Best Practices

LAURIE MULDOWNEY, M.D.

U.S. FOOD & DRUG ADMINISTRATION

Developing an Effective Engagement Strategy

Laurie Muldowney, M.D.
Associate Director for Medical Policy
Office of Translational Sciences

Rare Disease Advocacy Workshop: October 30, 2017

Outline

- The Patient Voice
  - *How is patient input used?*
- Patient Focused Drug Development
- Engagement with CDER
  - *Types of Engagement*
  - *When to engage*
- How to prepare

Outline

- **The Patient Voice**
  - ***How is patient input used?***
- Patient Focused Drug Development
- Engagement with CDER
  - *Types of Engagement*
  - *When to engage*
- How to prepare

- **Identify what matters/what is important to patients**
- **Aid in development of clinical trials that are meaningful and realistic**
- **Raise Awareness**

Outline

- The Patient Voice
  - *How is patient input used?*
- **Patient Focused Drug Development**
- Engagement with CDER
  - *Types of Engagement*
  - *When to engage*
- How to prepare

FDA Patient-Focused Drug Development (PFDD)

- PFDD introduced in 2012 (PDUFA V)
  - Develop a more systematic way of gathering patient perspective on their condition and available treatment options to inform B-R assessment
  - Conduct public meetings focused on specific disease areas

Key Learnings: Patients with chronic serious disease are experts on what it is like to live with their condition. Their "chief complaints" may not be factored into drug development and data collection plans.

Cures Act Title III Subtitle A
Patient-Focused Drug Development (PFDD)

Section 3001: Patient Experience Data

- Following the approval of an NDA/BLA submitted after June 12, 2017, make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such application.

Section 3002: PFDD Guidance -- to address the following

1. Methodological approaches for collection of patient experience data to ensure data are relevant, objective, accurate and **representative of the intended population**, including methods to collect **meaningful patient input throughout drug development** and methodological considerations for data collection, reporting, management, and analysis;
2. Methodological approaches to develop and **identify what is most important to patients** with respect to **burden of disease, burden of treatment**, and the **benefits and risks** in the management of the patient's disease;
3. Approaches to identifying and developing **methods to measure impacts to patients** that will help **facilitate collection of patient experience data in clinical trials**;
4. Methodologies, standards, and technologies to **collect and analyze clinical outcome assessments for purposes of regulatory decision-making**;

Cures Act Title III Subtitle A
Patient-Focused Drug Development (PFDD)

Section 3002: PFDD Guidance – contd.

5. **How** a person seeking **to develop and submit proposed draft guidance** relating to patient experience data **for consideration by FDA** may submit such proposed draft guidance to the Secretary;
6. **Format and content required for submissions** under this section to the Secretary, including with respect to the information described in paragraph (1);
7. **How FDA intends to respond** to submissions of information described in paragraph (1), if applicable, including timeframe; and
8. **How FDA anticipates using** relevant patient experience data and related information **to inform regulatory decision-making**

Outline

- The Patient Voice
  - *How is patient input used?*
- Patient Focused Drug Development
- **Engagement with CDER**
  - ***Types of Engagement***
  - ***When to engage***
- How to prepare

Engagement with CDER

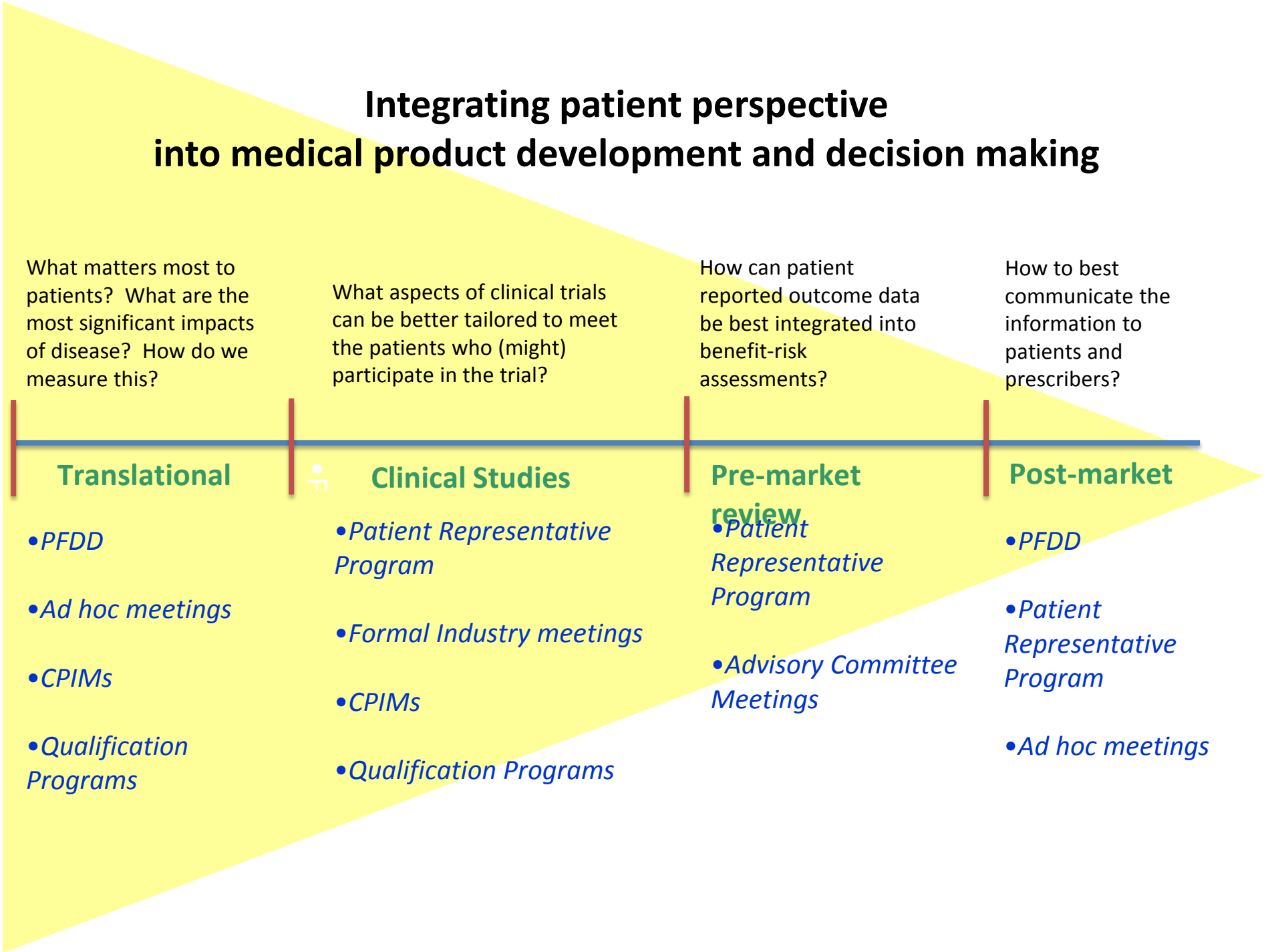
Independent of Specific Drug Development Program

- PFDD meetings, meetings organized by Professional Affairs and Stakeholder Engagement (PASE) staff
  - Focused on better understanding the disease and patient experience.
- Critical Path Innovation Meetings (CPIMs)
  - Communicate and receive general advice on new methodology or technology that may improve efficiency and success in drug development.
- Ad hoc opportunities
  - Typically scheduled with the Review Division
- Qualification programs
  - Biomarkers, clinical outcome assessments, animal models

Drug Development Program Specific

- Formal industry meetings
  - Meetings scheduled with the sponsor by review division
- Patient Representative Program
  - Participate in Advisory Committee meetings, review division meetings, and FDA workshops
- Advisory Committee Meetings
  - Open Public Hearing Portion

Integrating patient perspective into medical product development and decision making



Outline

- The Patient Voice
  - *How is patient input used?*
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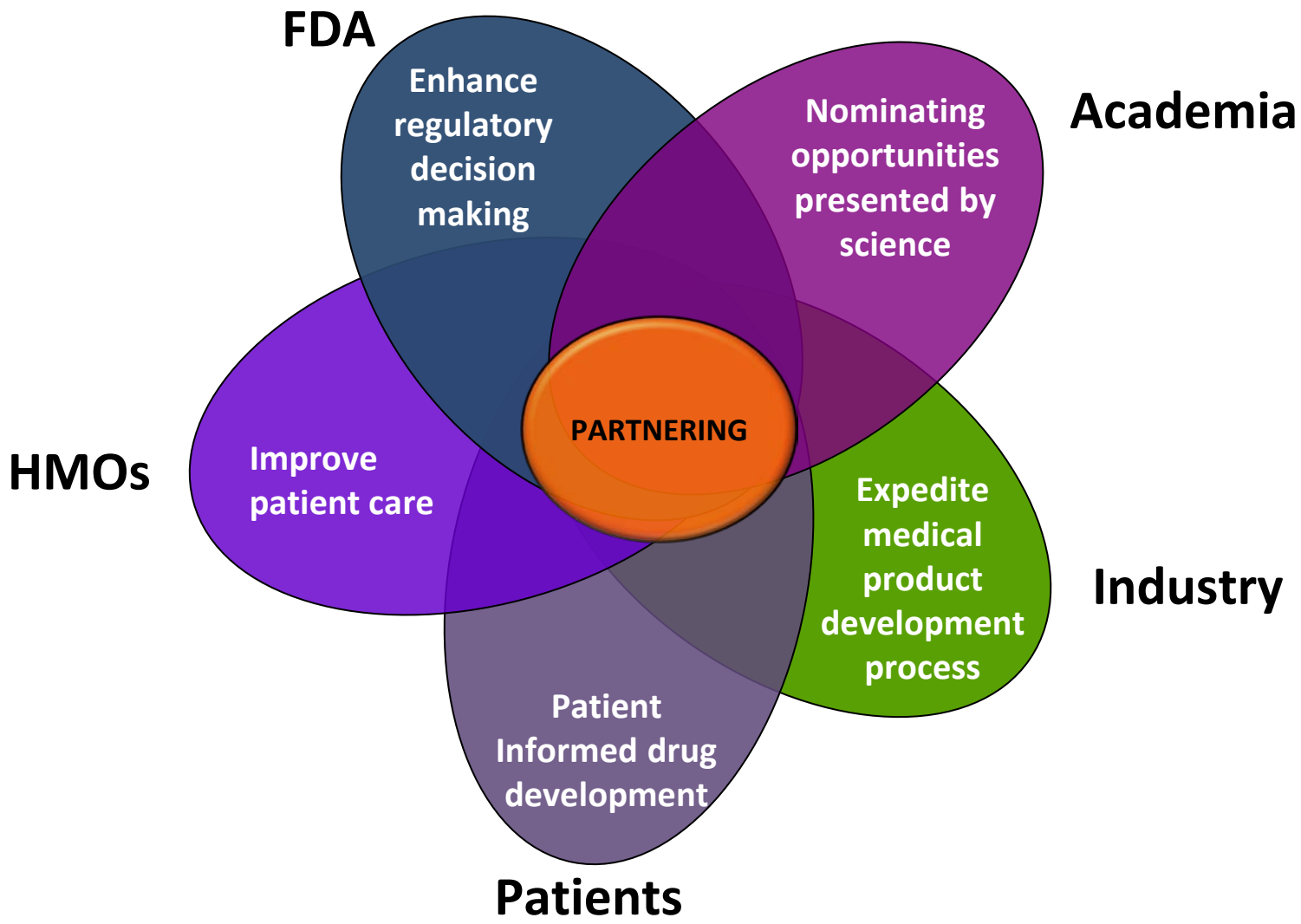
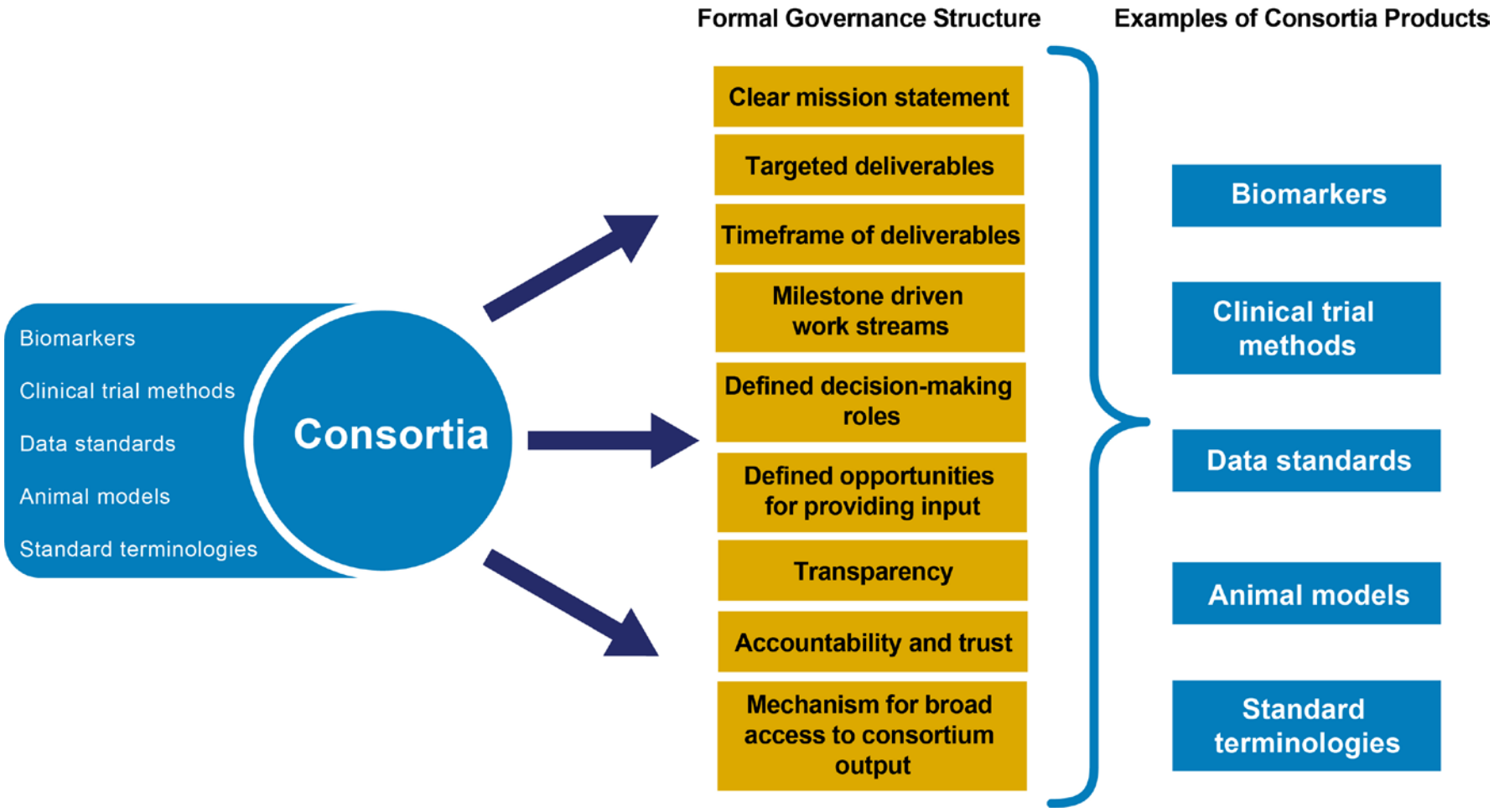
- **How to prepare**

Collaboration is Needed



Adapted from figure 1 supplied courtesy of RM Long, NIH. S Buckman, S-M Huang, S Murphy, Clin Pharmacol & Ther, 81(2): 141-144, Feb 2007

Value of consortia



Reference: Consortium Sandbox: Building and Sharing Resources Mark D. Lim Sci Transl Med 2014;6:242cm6

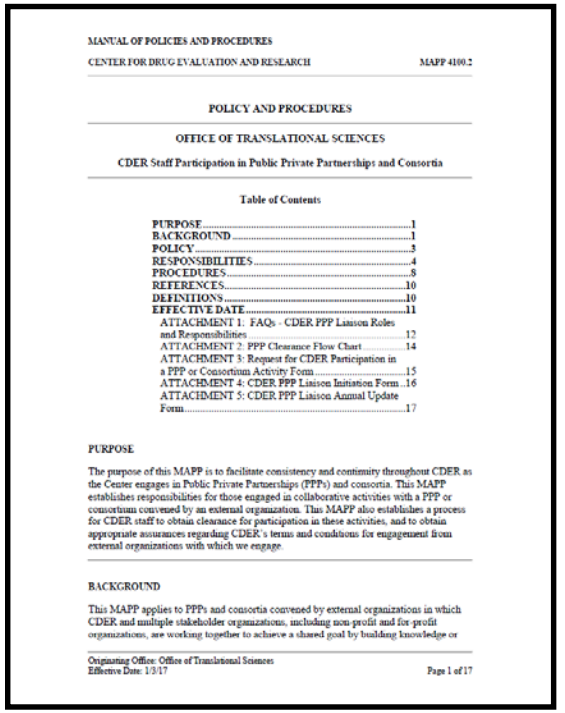
CDER Engagement with Public Private Partnerships (PPPs)

- CDER is involved in several PPPs to promote development of research tools, platforms, clinical databases, and predictive models to advance knowledge of diseases and safety profiles of drugs.

- For CDER staff to engage with consortia, see our Manual of Policies and Procedures available on our website.

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM532571.pdf

MAPP 4100.2
CDER Staff Participation in Public Private Partnerships and Consortia.



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 4100.2

POLICY AND PROCEDURES

OFFICE OF TRANSLATIONAL SCIENCES

CDER Staff Participation in Public Private Partnerships and Consortia

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PURPOSE

The purpose of this MAPP is to facilitate consistency and continuity throughout CDER as the Center engages in Public Private Partnerships (PPPs) and consortia. This MAPP establishes responsibilities for those engaged in collaborative activities with a PPP or consortium convened by an external organization. This MAPP also establishes a process for CDER staff to obtain clearance for participation in these activities, and to obtain appropriate assurances regarding CDER's terms and conditions for engagement from external organizations with which we engage.

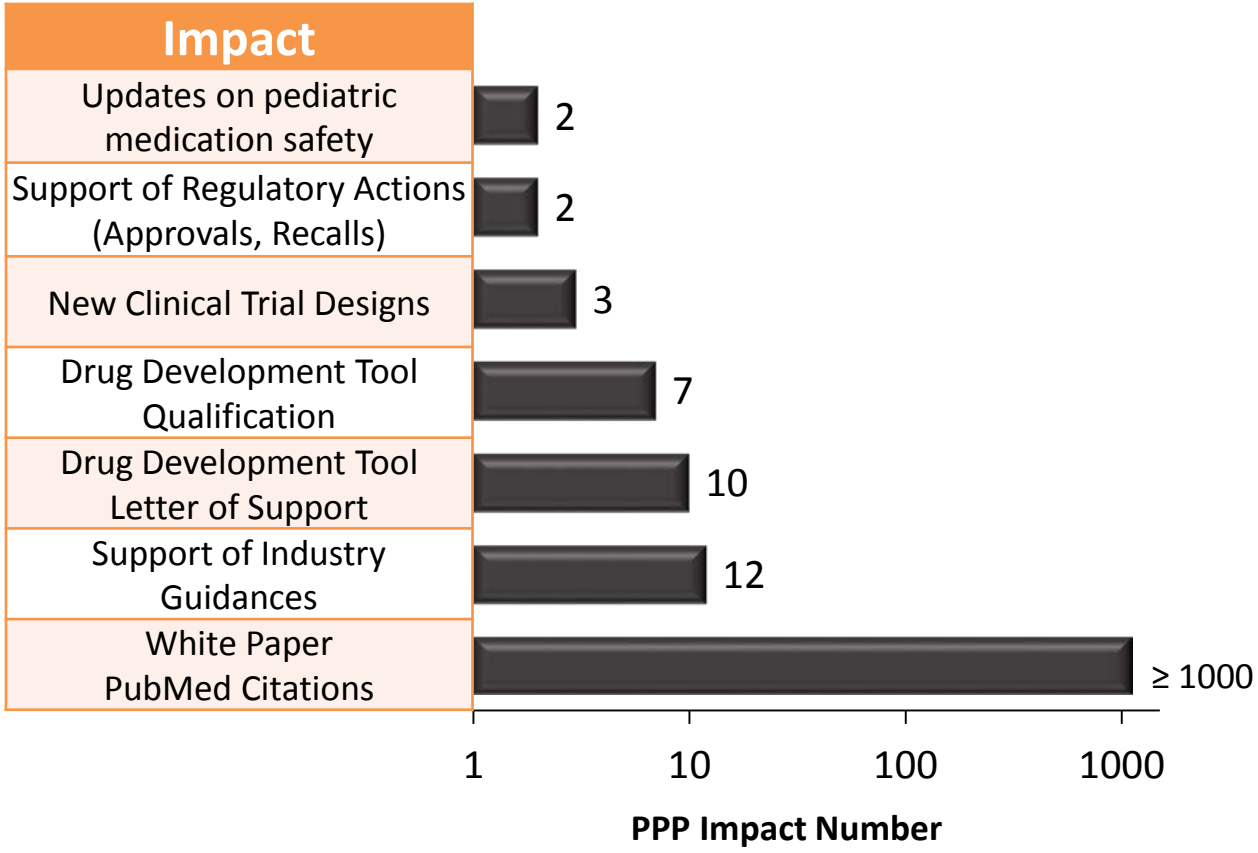
BACKGROUND

This MAPP applies to PPPs and consortia convened by external organizations in which CDER and multiple stakeholder organizations, including non-profit and for-profit organizations, are working together to achieve a shared goal by building knowledge or

Originating Office: Office of Translational Sciences
Effective Date: 1/3/17 Page 1 of 17

Examples of Deliverables from PPPs with CDER Engagement

(2004-July 2016)



Maxfield, K. E., Buckman-Garner, S. and Parekh, A. Clinical And Translational Science. doi:10.1111/cts.12488

Janet Woodcock

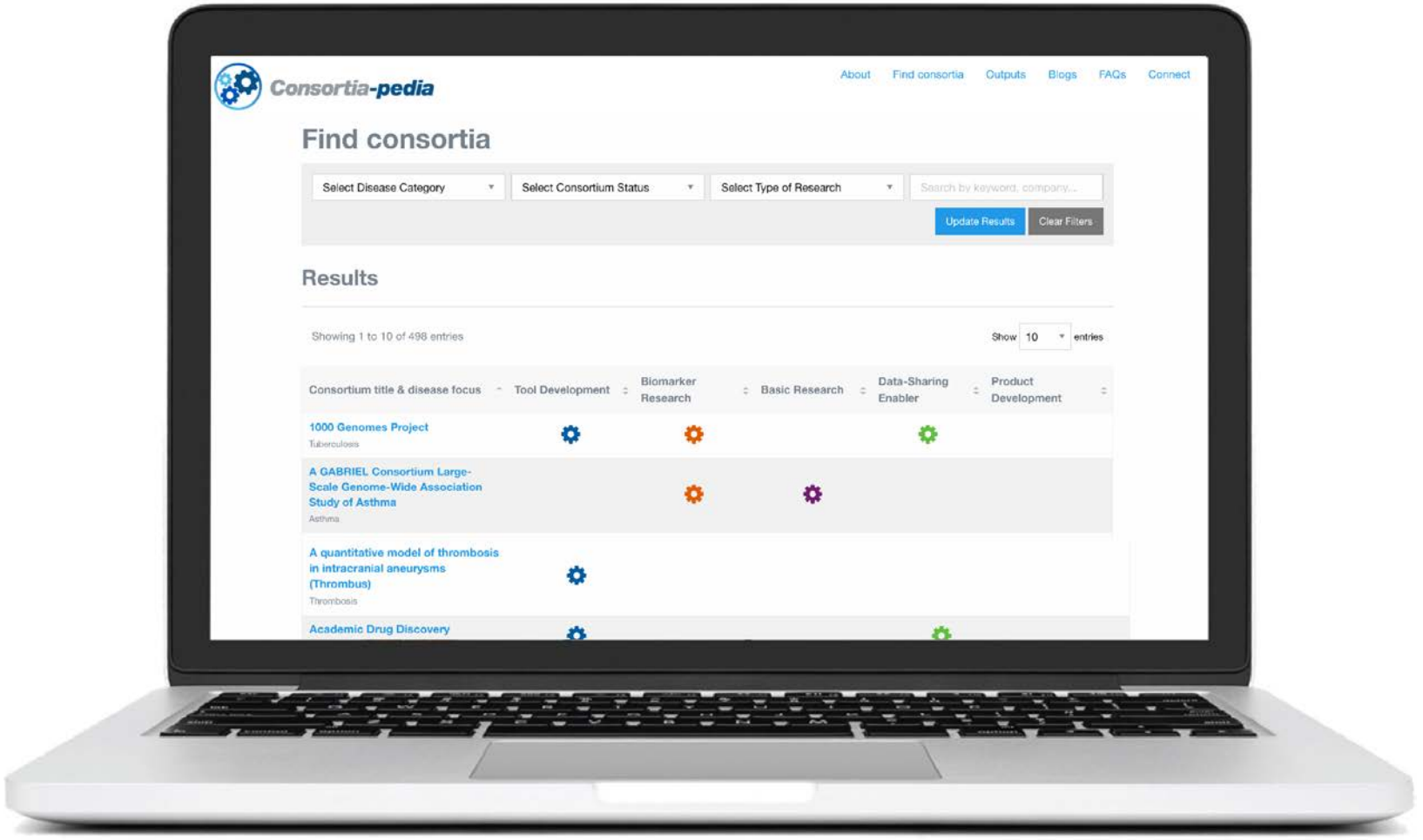
Director, Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

CDER's Janet Woodcock on PPPs –

"Facilitating collaborative partnerships among government, academia, industry, and patients groups is arguably the most important role that CDER plays in supporting advancement of drug development and regulation"

J Woodcock. Nature Review Drug Discoveries. 2014 Nov;13(11):783-4.
http://www.nature.com/nrd/journal/v13/n11/full/nrd4435.html

FIND CONSORTIA



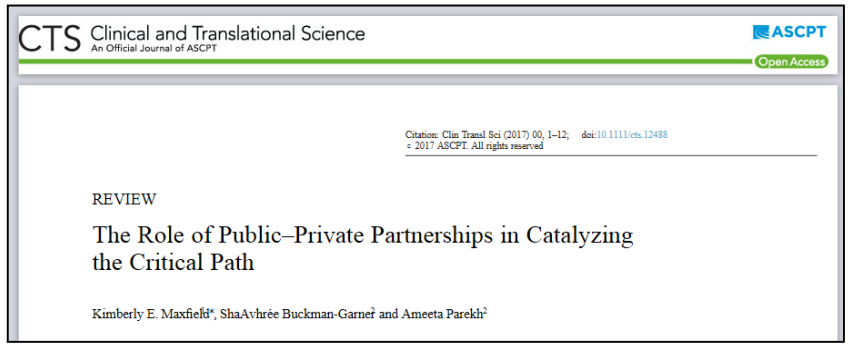
http://consortiapedia.fastercures.org/

Resources:

CDER policy and procedures for PPP engagement:
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM532571.pdf

Find a consortia - Consortiapedia:
http://consortiapedia.fastercures.org/

Additional information on the impact of PPPs:
https://www.ncbi.nlm.nih.gov/pubmed/28776943



Questions?

Thank you and Acknowledgements

- ShaAvhrée Buckman-Garner, MD PhD
- Ameeta Parekh, PhD
- Kimberly Maxfield, PhD
- Pujita Vaidya, MPH
- Michelle Campbell, PhD

Thank you for your time and consideration ~

Thank you!

Laurie Muldowney
Laurie.muldowney@fda.hhs.gov

Patient Advocate Perspective: Best Practices

JAMES VALENTINE, J.D., M.P.H.

Developing an Effective Engagement Strategy – Patient Advocate Perspective

CDER Rare Diseases
Public Workshop
October 30, 2017

James E. Valentine, J.D., M.H.S., Regulatory Counsel

DISCLOSURES

NTM ir
Nontuberculous Mycobacteria
NTM Info & Research, Inc.

Tuberous Sclerosis Alliance

THE LAM FOUNDATION
A BREATH OF HOPE

National Kidney Foundation™

amyloidosis research consortium

Jett

HEREDITARY NEUROPATHY FOUNDATION

Arthritis Foundation®

MYOTONIC DYSTROPHY FOUNDATION

NORD®
National Organization for Rare Disorders

LUPUS RESEARCH ALLIANCE

Mundo Sano

cure SMA
Make today a breakthrough.

EVERYLIFE FOUNDATION
FOR RARE DISEASES

LUPUS and ALLIED DISEASES Association, Inc.

SYSTEMIC JIA FOUNDATION
connecting the dots to find a cure

FARA
Friedreich's Ataxia Research Alliance

Global Genes®
Allies in Rare Disease

LUPUS™
FOUNDATION OF AMERICA

Overview

- Needs Assessment
- Asset Assessment

1

NEEDS ASSESSMENT

Deciding what type of engagement is needed

NEEDS

Match your expertise and assets to phases of R&D in your disease/ condition, as well as your own organization’s priorities

Targeting needs at the right time

Research questions of interest to your community

- Pre-discovery
- Pre-clinical

Data on unmet need & therapeutic burden

- Pre-discovery
- Pre-clinical
- Clinical
- FDA review

Characterizing the disease & relevant mechanisms

- Pre-Discovery

Targeting needs at the right time (cont.)

Inform study eligibility criteria

- Pre-Clinical
- Clinical

Providing translational tools (e.g., animal models, biomarkers)

- Pre-clinical

National history database & patient registry info

- Pre-Discovery
- Pre-Clinical
- Clinical
- FDA review
- Post-approval

Targeting needs at the right time (cont.)

Meaningful clinical endpoints, including PROs

- Pre-Clinical
- Clinical

Need for trial adaptations or modifications

- Clinical

Benefit-risk preferences

- Pre-Clinical
- Clinical
- FDA Review

Safety surviellance

- Post-market

Draft guidance

- Pre-Clinical

Feedback on patient experience & trial results

- Clinical
- FDA Review

Lessons Learned on Needs Assessments

- Strive to understand the FDA regulatory framework
- Listen to your industry partners' insights
- Don't let this hold up engaging, this can be part of your first discussion with FDA
- Always keep your own community's priorities foremost

There are limits to what any one patient organization can accomplish alone

2

ASSETS ASSESSMENT

Leveraging your own expertise and assets of value to FDA

ASSETS

Designing your engagement to leverage your organization’s skills, experience, capabilities, and resources

Charting your own assets

You bring patient perspectives, experiences, and preferences

- Your organization’s broad experience across the community
- Access to patients and their caregivers to query and bring to the table
- Data from meetings, surveys, registries/NH studies, and even online communities/real world information

Charting your own assets (cont.)

You provide important clinical development assets

- Educated advocates
- Understanding of disease mechanisms & natural history
- Financial and organizational support beginning at basic science & discovery
- Translational tools
- Patient preference and benfit-risk assessments
- Patient registries & natural history databases
- Clinical centers of excellence

Charting your own assets (cont.)

You serve as a neutral convener & connecter

- Ability to assemble expertise and tools during each stage of development and review
- Connect FDA with your senior leadership, advisors, and partners beyond the patient perspective (e.g., investigators, KOLs)
- Host workshops & meetings
- Collaborators in public-private partnerships

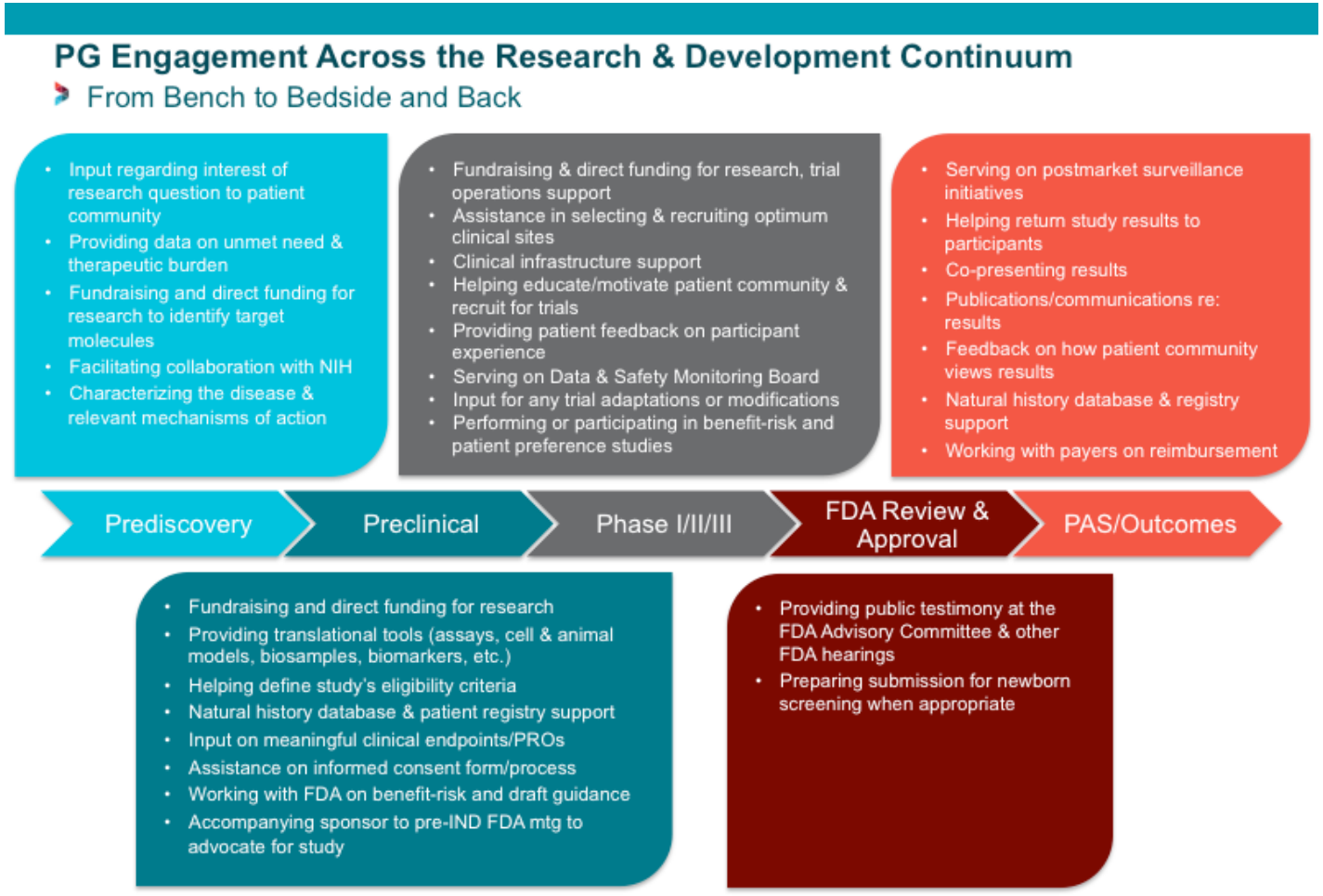
Your biggest asset

- The foundation of trust you have with your patient community, families, and the clinicians who care for them

Lessons Learned on Asset Assessments

- Be creative, maximize all you've done
- Be transparent and provide disclosure of partnerships and sponsorships
- Use this opportunity to plan future assets based off current and future needs
- Get FDA input when planning future activities

Matching Needs & Assets



*Adapted from Parkinson's Disease Foundation materials for CTTI's Patient Groups & Clinical Trials Project

CTTI

7000+

Known rare diseases

30 million

People in U.S. living with rare diseases

>4,000

CDER employees

THANKS!

Any questions?

You can find me at

jvalentine@hpm.com

DISCUSSION PANEL: DETERMINING YOUR NEXT STEPS

Moderator: *Meredith Cagle, M.P.H*

Panelists:

Jonathan Goldsmith, M.D.
Billy Dunn, M.D.
Isabelle Lousada
Steve Roberds, Ph.D.
John Whyte, M.D., M.P.H.
Rosangel Cruz, M.A.
James Valentine, J.D., M.P.H.
Henrietta Hyatt-knorr, M.A.

Closing Remarks

MEREDITH CAGLE, M.P.H.

FRANCIS KALUSH, PH.D.

THANK YOU AND SAFE TRAVELS!

Share your feedback:

PASE-Rare-Diseases@fda.hhs.gov


30TH
OCT
CDER
RARE
DISEASES
Public Workshop
8 AM.
TO
5PM.


FDA
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ADMINISTRATION