FDA Drug Topics: Rare Diseases - Challenges and Progress in Drug Development

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Disclosure

This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred

The materials presented are available in the public domain

Objectives

- Describe the challenges involved in developing a drug for a rare disease.
- Identify key aspects of the FDA regulatory framework that are relevant to rare disease drug development.
- Summarize the efforts of the FDA Center for Drug Evaluation and Research to accelerate rare disease drug development through innovation and engagement.

Outline

- Rare disease overview and challenges in rare disease drug development
- Key aspects of FDA regulatory framework
- CDER rare disease programs and initiatives

Rare Diseases/Orphan Products

Rare Disease: a disease or condition that affects < 200,000 persons in US

Orphan Drug: a drug or biological product for prevention, diagnosis, or treatment of a rare disease

Public Health Impact of Rare Diseases

1 in 10 Americans have a rare disease (~30 million)

- Approximately 7,000 – 10,000 identified rare diseases
- Impact often overlooked due to small numbers of patients per disease

Many rare diseases are serious and progressive, fatal, and few have FDA approved treatment

72% are genetic* - severe impact on patients and their families

*Nguengang Wakap S, Lambert DM, Olry A, *et al*. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020 Feb;28(2):165-173.

Why is drug development for rare diseases a challenge?

We face common challenges in supporting rare disease drug development programs

- **Natural history** is often poorly understood
- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs**
- **Small populations** often restrict study design options
- **Phenotypic and genotypic** diversity within a disorder
- **Development programs often lack solid translational background**
- **Drug development tools** - **outcome measures** and **biomarkers** often **lacking**
- Lack of **precedent**, including **clinically meaningful endpoints**, for drug development in many rare diseases

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The 1983 Orphan Drug Act

Enacted to stimulate product development for rare disease/condition diagnosis, prevention or treatment

- Prior to the enactment of the ODA, between 1973 and 1983 there were fewer than 10 drugs supported by industry approved by the FDA for the treatment of a rare disease
- Now, at least 40% of novel drug approvals are for treatment of rare diseases

Patel S, Miller Needleman K I. FDA's Office of Orphan Products Development: providing incentives to promote the development of products for rare diseases. J Pharmacokinet Pharmacodyn 46, 387–393 (2019). https://doi.org/10.1007/s10928-019-09645-4

What does the Orphan Drug Act NOT do?

The ODA does not alter the statutory standard for drug approval.

The regulatory requirements and process for obtaining marketing approval are the same for drugs granted Orphan Drug Designation as for common disease drugs

Safe and Effective

"Effective" is codified in statute:

- Demonstrates "substantial evidence that the **drug* will have the effect** it purports or is represented to have under proposed labeled conditions of use"

(21CFR314.125, 21CFR314.126)

- A drug's "effect" forms the basis of its translation to **meaningful clinical benefit**

"Safe" can be interpreted as the determination that a drug's **benefits outweigh its risks for drug's intended use**

- Safety is considered in relation to the **condition treated, the efficacy purported, and ability to mitigate risk**

*For simplicity, the term "drug" is used in this presentation to mean both drugs and biologics
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

Demonstrating Substantial Evidence of Effectiveness

- Adequate & well-controlled clinical investigations
  - At least 2 adequate & well-controlled clinical investigations
  - 1 large, multicenter trial that is scientifically and functionally the equivalent of 2

- 1 adequate & well-controlled clinical investigation PLUS confirmatory evidence

FDA Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019 https://www.fda.gov/media/133660/download

Key Features of "Adequate and Well-Controlled Investigations"

Clear statement of study objectives

Design that permits a valid comparison with a control

Adequate assurance that subjects have the condition being studied

Adequate measures to minimize bias of subjects, observers, and data analysts and assure comparability of treatment groups

Well-defined methods for assessing treatment response

Analysis of study results adequate to assess the effects of the drug

21 CFR 314.126

Examples of Confirmatory Evidence

- Adequate and well-controlled clinical trial in closely related approved indication
- Strong mechanistic support
- Data from natural history studies
- Scientific knowledge about the effectiveness of other drugs in same pharmacological class

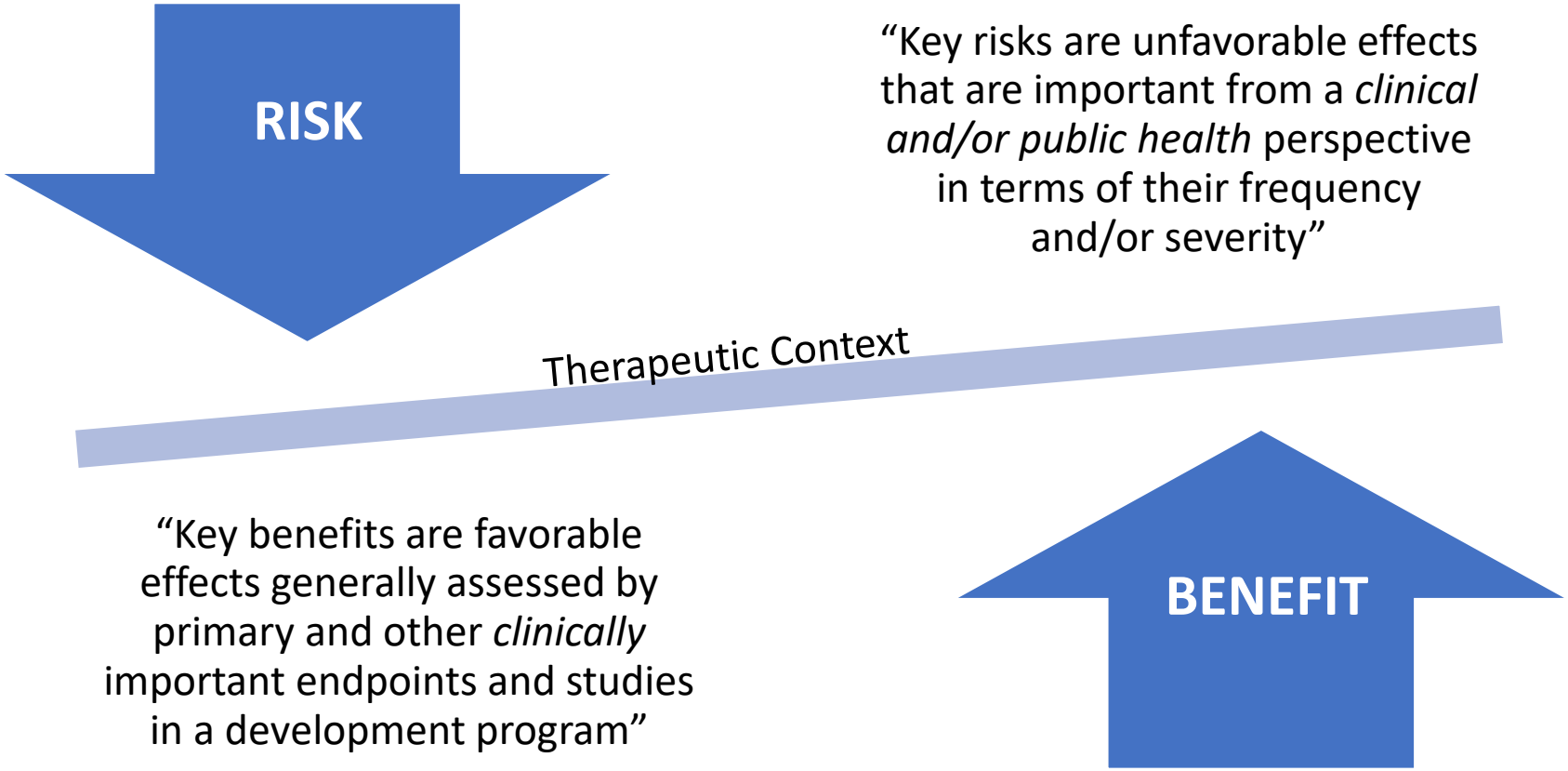
What is benefit-risk assessment in human drug review?

Evaluation of the demonstrated benefits and risks of a medical product, and

Making a **judgment** as to whether the expected benefits outweigh the potential risks associated with its expected use

From FDA's Patient-Focused Drug Development Glossary, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610317.htm

Weighing the key benefits and risks of a drug product



M4E(R2): The CTD — Efficacy Guidance for Industry –July 2017 ICH

Efficacy Endpoints: Measures of Clinical Benefit

Clinical benefit: positive effect on how an individual **feels, functions, or survives**

- Measured through clinical outcome assessments (COAs)
- Must be well-defined, valid and reliable

Biomarkers: do not directly measure clinical benefit

- Used as surrogate endpoints in special circumstances
  - "Validated" surrogates may support full approval
  - Surrogates "reasonably likely" to predict clinical benefit may support accelerated approval

Selection of Efficacy Endpoints in Rare Diseases Creates Unique Challenges

- Small trial populations
- Limited understanding of natural history
- Lack of regulatory precedent
- Clinical endpoints need to capture key signs and symptoms and directly measure how a patient feels, functions, or survives
- Surrogate endpoints challenging in diseases with slow progression

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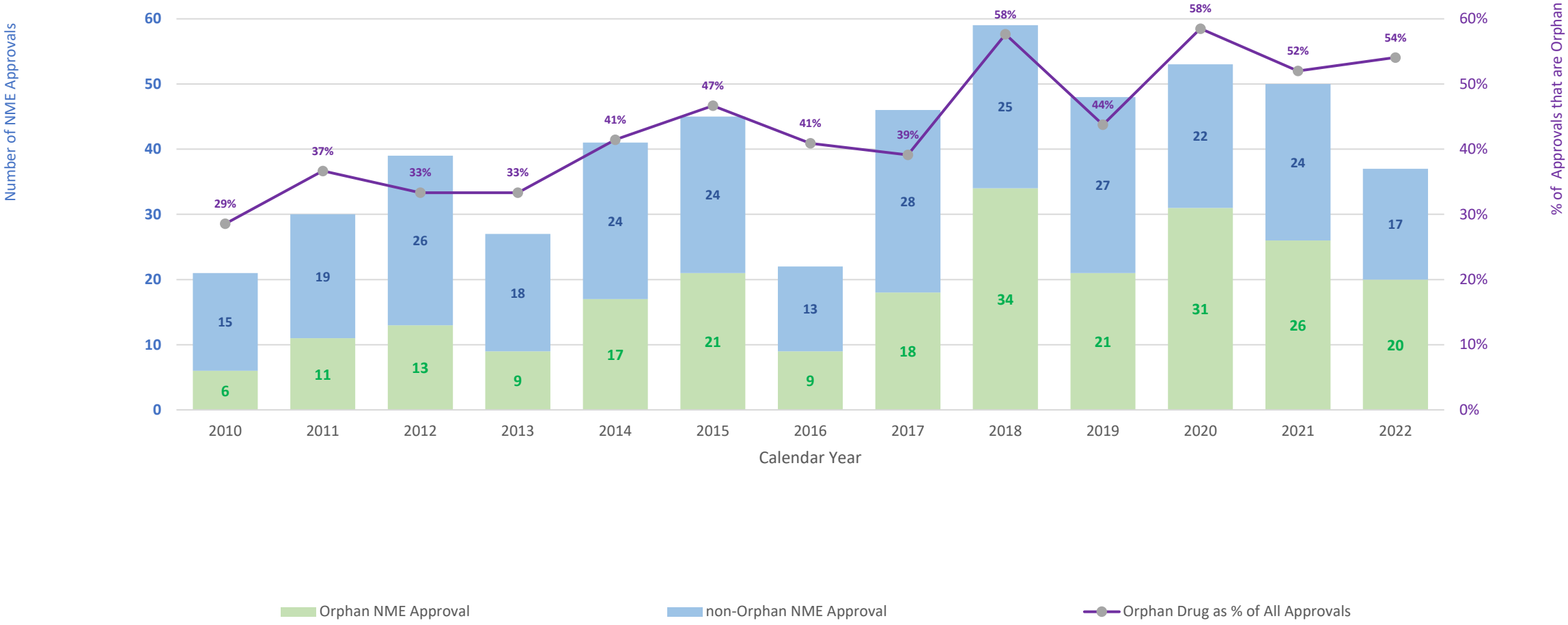
CDER Rare Disease Programs and Initiatives

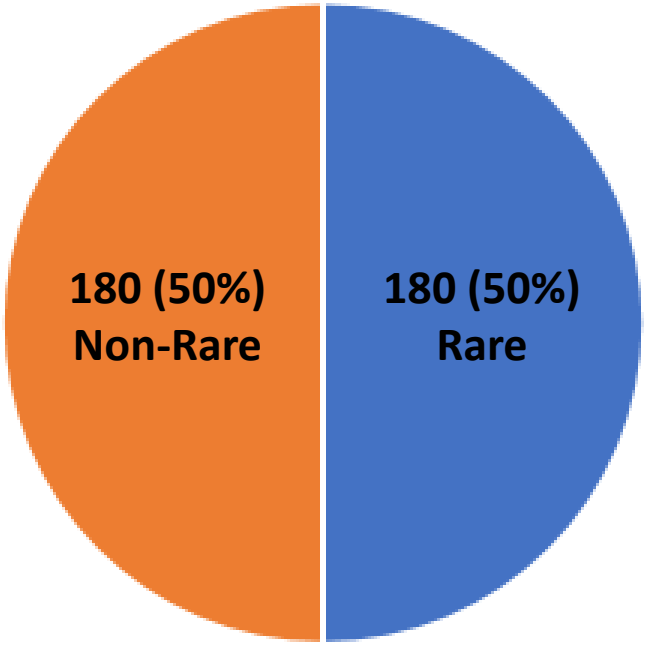
- Update on rare disease drug approvals
- Engaging patients
- Accelerating Rare disease Cures Program (ARC)
- Rare Disease Endpoint Advancement (RDEA)
- Global collaboration and guidances

Proportion of CDER Novel Drug Approvals that are Orphan



Rare Disease Progress

Total CDER Novel Drug Approvals 2015-2022



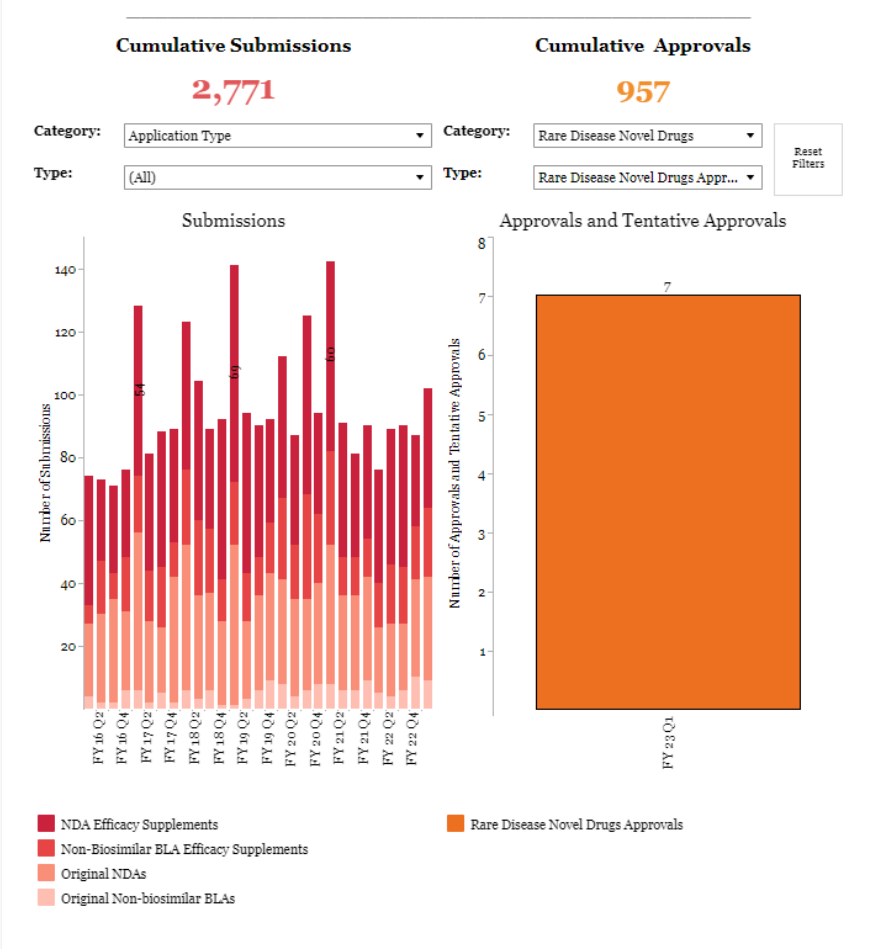
and… FDA has approved over 550 unique drugs and biologics for over 1,100 rare disease indications since the passage of the Orphan Drug Act (1983)

but… ~30 million Americans live with a rare disease

Vast majority do not have approved treatments

https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
https://www.fda.gov/drugs/news-events-human-drugs/cder-continues-advance-rare-disease-drug-development-new-efforts-including-accelerating-rare-disease
https://www.fda.gov/news-events/fda-voices/fda-continues-important-work-advance-medical-products-patients-rare-diseases#:~:text=The%20FDA%20will%20host%20its,medical%20products%20for%20rare%20diseases.

Tracking Rare Disease Approvals



FDA-TRACK: Center for Drug Evaluation and Research: Drugs and Biologics Dashboard

Patient Input

FDA recognizes importance of incorporating patient input/preference in development/regulatory process

Frequent Patient Listening Sessions

- Opportunities to hear experiences/ perspectives of patients and caregivers
- 57 listening sessions on rare diseases since October 2018

CDER Patient-Focused Drug Development (PFDD)

- Establishing the therapeutic context is an important aspect of benefit-risk assessment
  - Patients are uniquely positioned to inform understanding of this context

- PFDD is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation

- PFDD efforts include:
  - FDA-led PFDD Meetings
  - Externally-led PFDD Meetings
  - PFDD Methodological Guidance Series
  - Clinical Outcomes Assessment (COA) Grant Program

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

PFDD Meetings

Designed to engage patients and elicit their perspectives on two topic areas:

(1) the most significant symptoms of their condition and the impact of the condition on daily life;

(2) their current approaches to treatment.

FDA has conducted 30 PFDD meetings

Upcoming FDA-led PFDD Meeting:

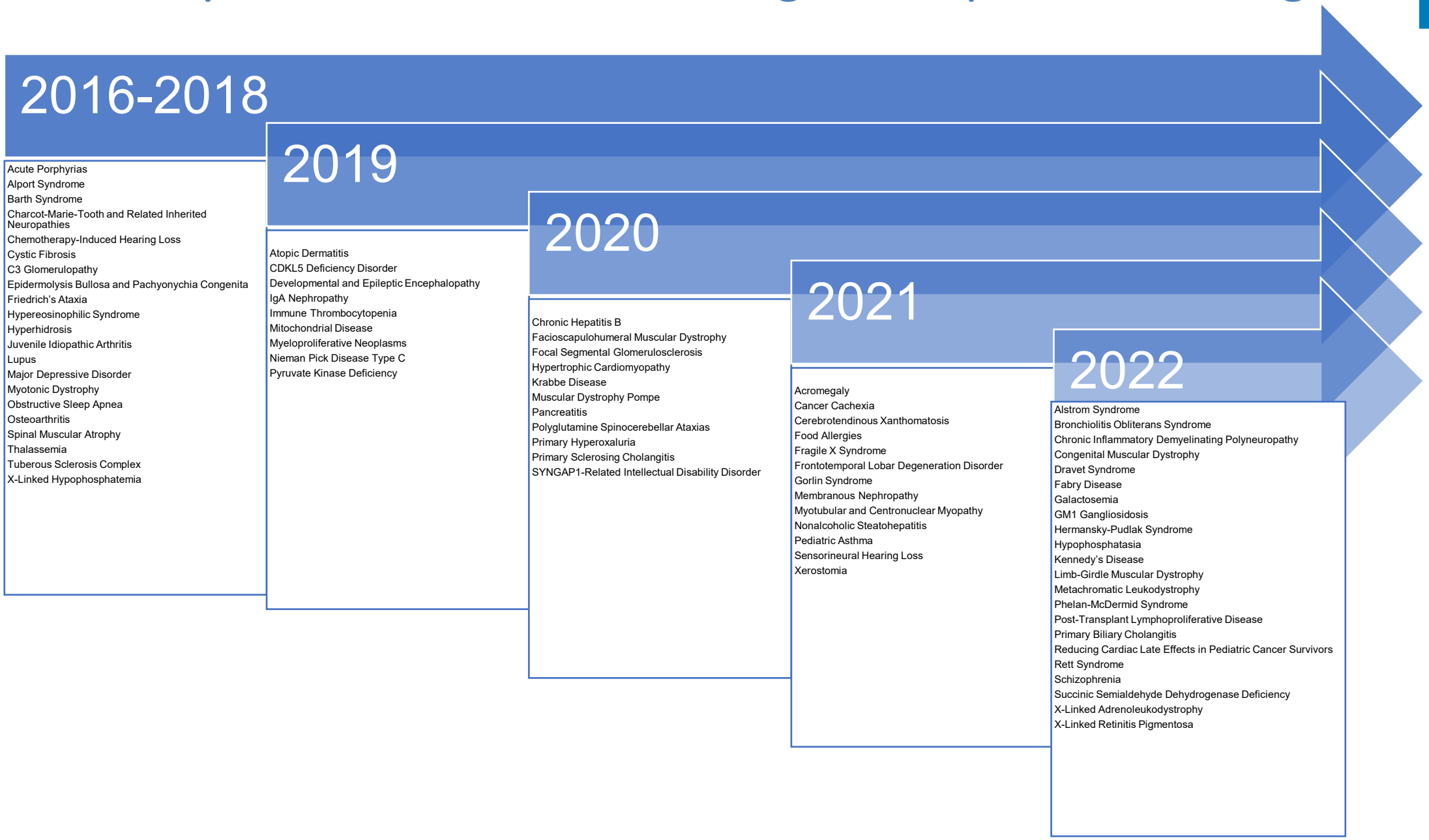
- PFDD Meeting on Long COVID

Externally-Led PFDD Meetings

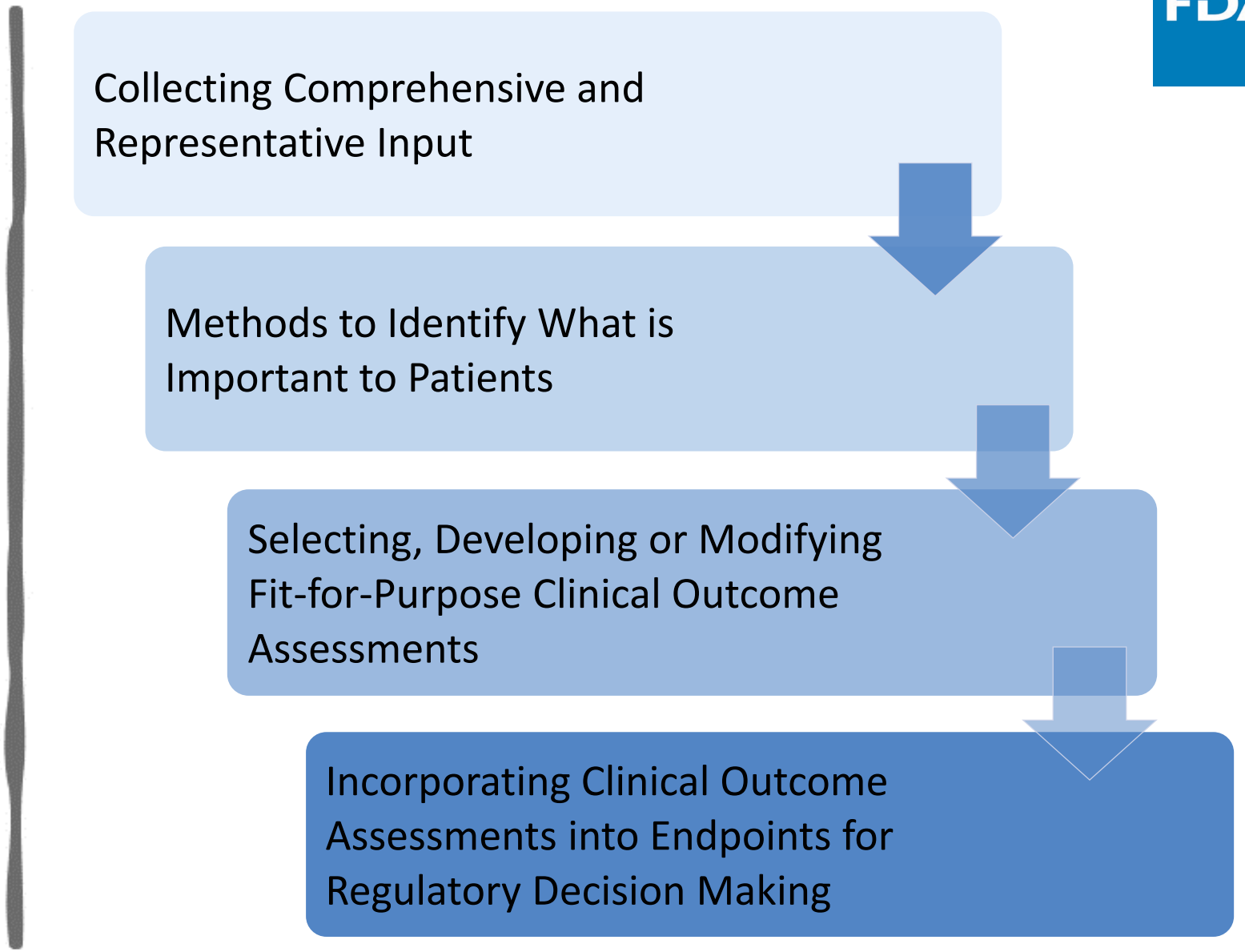
In the past year, patient groups have conducted 22 EL-PFDD meetings

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings
https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings

Externally-Led Patient-Focused Drug Development Meetings



Methodologic Guidance Documents



https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

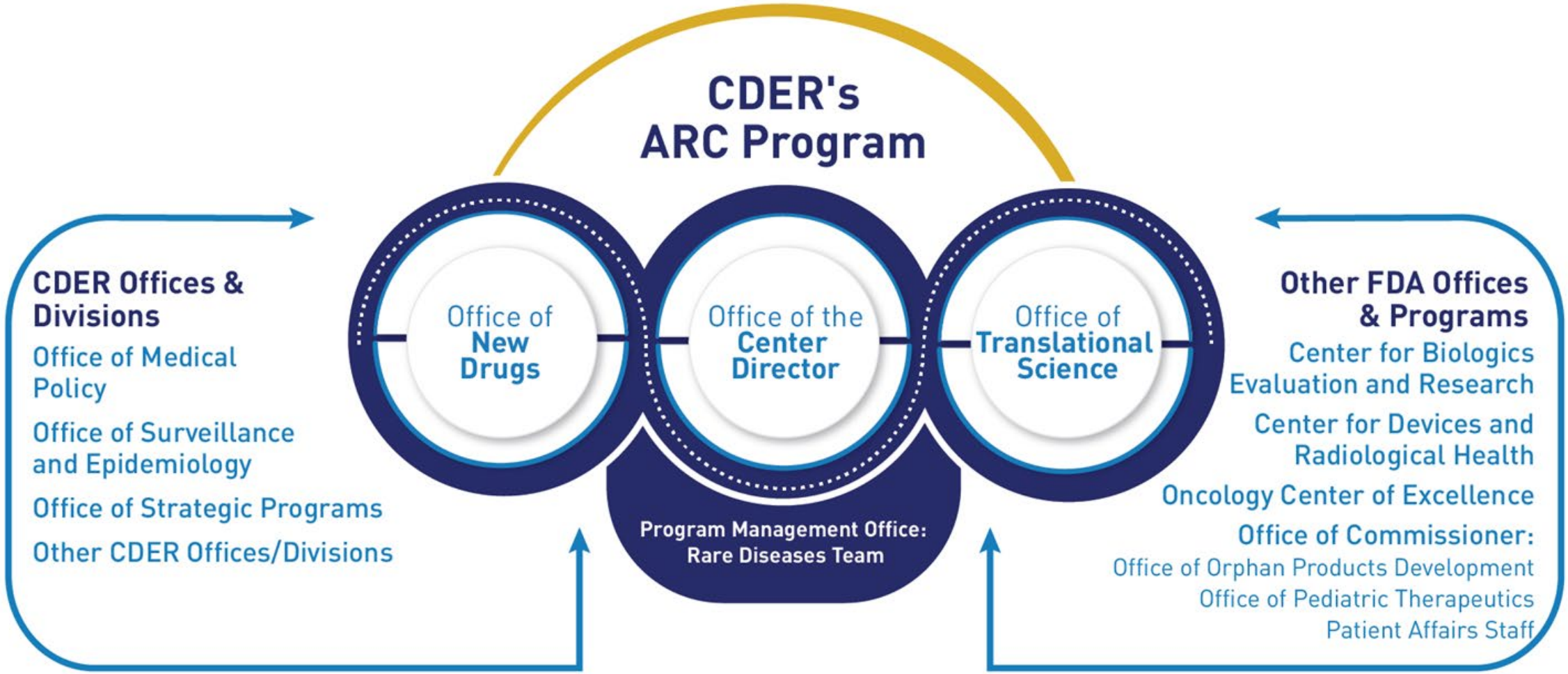
Vision

Speeding and increasing the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.

Mission

CDER's Accelerating Rare disease Cures (ARC) Program drives scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

CDER's Accelerating Rare disease Cures Program



ARC Year 1: Focus on Engagement

Engagement in year 1 will inform CDER of stakeholder priorities and needs in rare disease drug development

FDA/NIH Regulatory Fitness in Rare Disease Clinical Trials conference, May 16-17, 2022

- CDER's Rare Diseases Team and National Center for Advancing Translational Sciences
- Focus on academic investigators and those looking to learn how to bridge the gap between academic investigation and the regulatory aspects of drug development
- FDA Meeting Link

FDA and Duke Margolis Virtual Public Workshop: Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More, May 24-25, 2022

- Focus on translational science and the development of surrogate endpoints

Patients & Patient Organizations

- Patient Focused Drug Development staff to lead enhanced patient engagement through public workshops
- CDER's Patient Focused Drug Development website
- Email: PatientFocused@fda.hhs.gov

FDA CDER & JHU CERSI Virtual Workshop

Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools

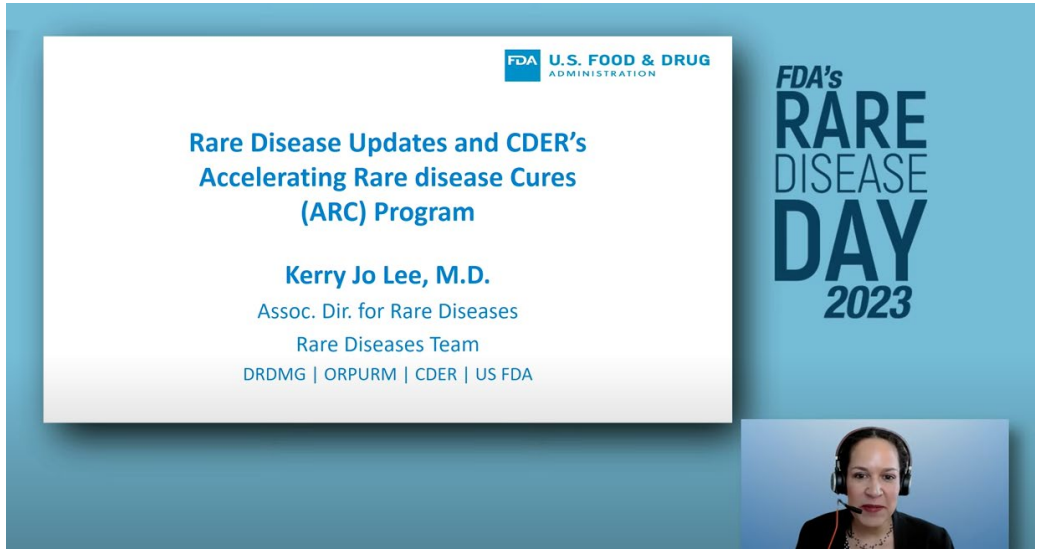
- May 2-3, 2023 from 9 am-12 pm
- Meeting information

FDA CDER=Food and Drug Administration Center for Drug Evaluation and Research
JHU CERSI=Johns Hopkins University Center of Excellence in Regulatory Science and Innovation

ARC Featured at FDA's Rare Disease Day 2023

Intersections with Rare Diseases – a Patient Focused Event

- Virtual public meeting information

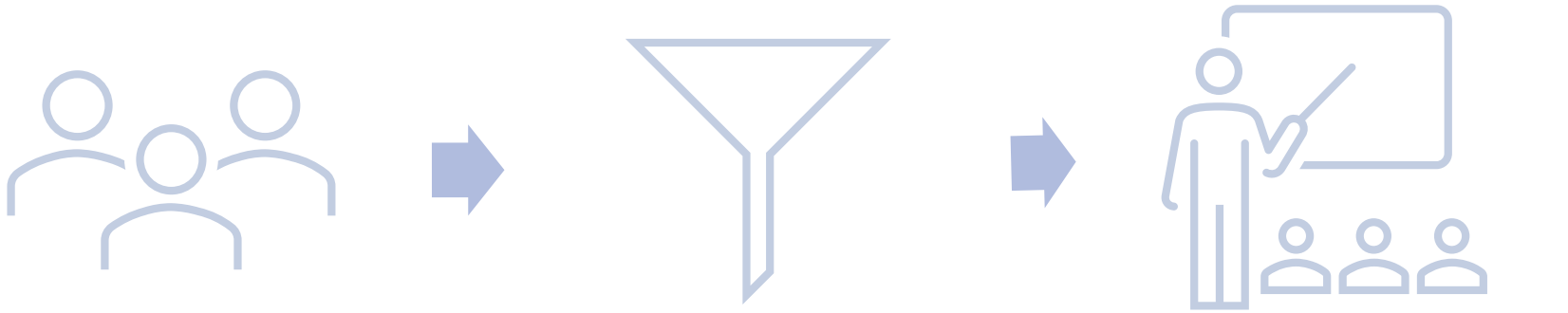


CDER's ARC Quarterly Newsletter

To subscribe: U.S. Food and Drug Administration (govdelivery.com)

LEARNING AND EDUCATION TO ADVANCE AND EMPOWER RARE DISEASE DRUG DEVELOPERS (LEADER 3D)

What is LEADER 3D?



CDER is seeking input from stakeholders who design or conduct rare disease drug development programs

Identify knowledge gaps for stakeholders about the regulatory process of rare disease drug development

Create or expand educational resources for stakeholders

LEADER 3D

Better understand the challenges in bringing rare disease drug products to market.

Identify knowledge gaps and produce educational materials on fundamental topics important to our stakeholders, such as:

- Nonclinical and clinical pharmacology considerations
- Clinical trial design and interpretation
- Regulatory considerations for rare disease drug development

In parallel with the LEADER 3D effort, CDER is working with the National Organization for Rare Disorders to develop an advanced drug development education series for patients and patient groups.

https://www.fda.gov/drugs/news-events-human-drugs/cder-continues-advance-rare-disease-drug-development-new-efforts-including-accelerating-rare-disease

Rare Disease Endpoint Advancement (RDEA) Pilot Program

- A joint program of CDER and the Center for Biologics Evaluation and Research (CBER) under PDUFA VII
- Provides a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process
- Supports novel efficacy endpoint development
- Designed for sponsors with an active investigational new drug (IND) or pre-IND for the rare disease
    - It is also intended for sponsors who do not yet have an active development program but have (or are initiating) a natural history study where they intend to examine the proposed endpoint.

RDEA Pilot Program Overview

Submissions: FDA will select a limited number of qualified proposals for admission into RDEA that increases after the first year of PDUFA VII:

- FY 2023: Sponsors may submit proposals beginning in Q4, and FDA will accept a maximum of 1 proposal
- FY 2024 – FY2027: FDA will accept up to 1 proposal per quarter with a maximum of 3 proposals per year

Transparency:

- FDA will conduct up to 3 public workshops by the end of FY 2027 to discuss various topics related to endpoint development for rare diseases
- To promote innovation and evolving science, novel endpoints developed through RDEA may be presented by FDA, such as in guidance documents, on a public-facing website, or at public workshops, including prior to FDA's approval for the drug studied in the trail

Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development -

Virtual

- June 7 and 8, 2023; 1-5 pm
- Jointly hosted by FDA's Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and the Duke-Margolis Center for Health Policy
- For more information and to register for this workshop, please visit https://healthpolicy.duke.edu/events/rare-disease-endpoint-advancement-pilot-program-workshop-novel-endpoints-rare-disease-drug
- Questions? Email RDEA.Meetings@fda.hhs.gov

Importance of Global Cooperation in Rare Disease Drug Development

Rare diseases are RARE

- Development is often multinational
- Every patient is an important partner

Drug development is often without precedent

- Novel endpoint development and selection
- Trial design considerations
- Natural history can be poorly understood

International Rare Diseases Cluster

Participants:
FDA, EMA, & Health Canada (HC)

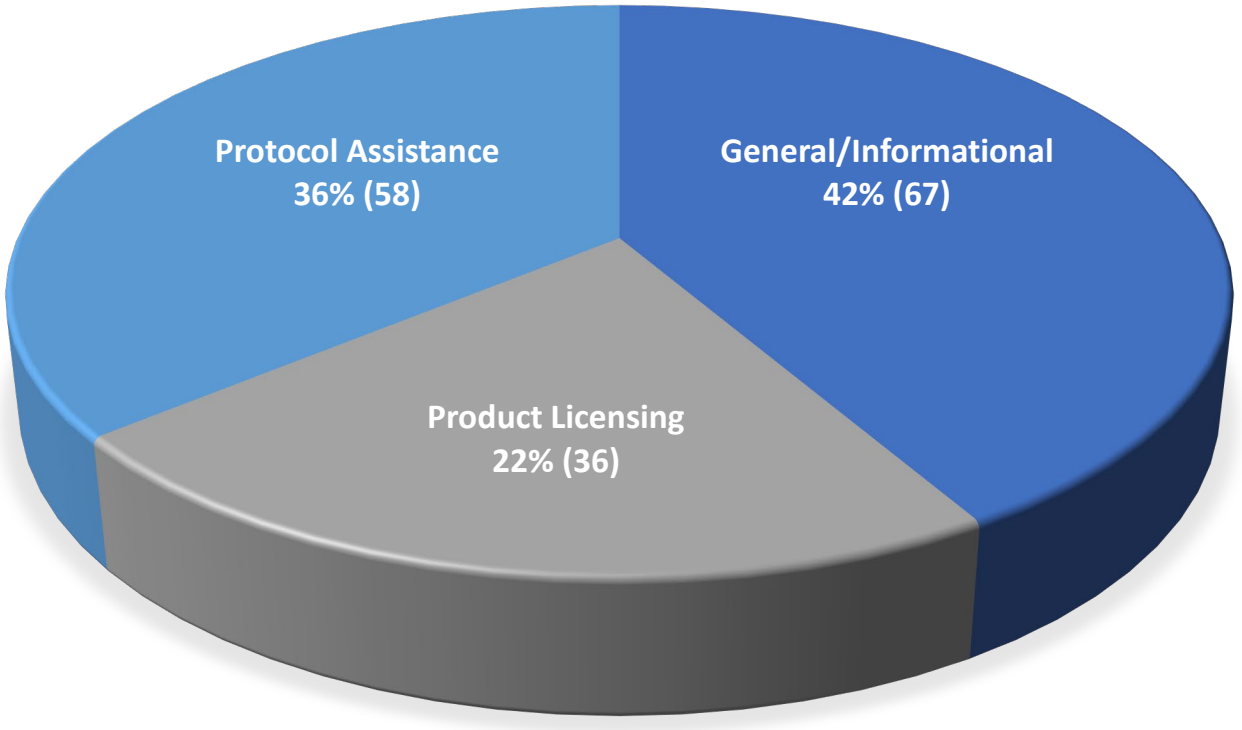
First convened in September 2016

Goal:
To conduct joint meetings that facilitate exchange between regulatory agencies about:

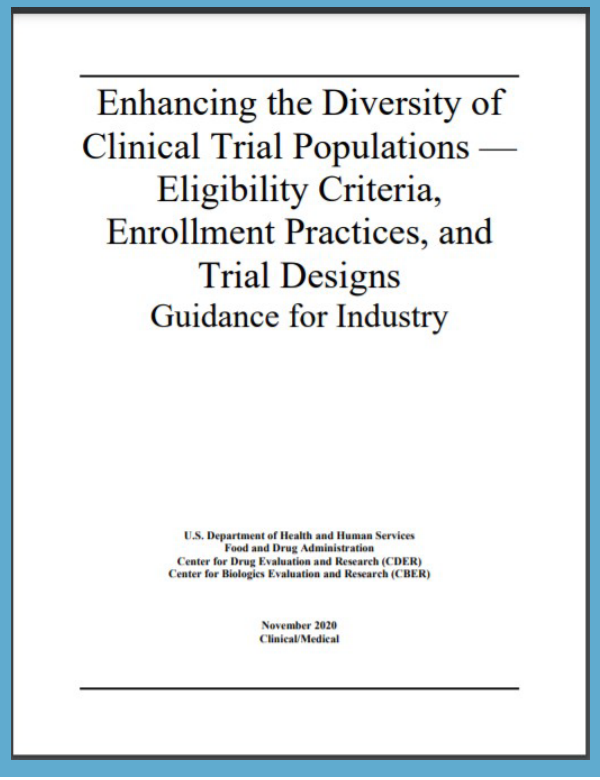
- Scientific advice
- Product licensing/marketing
- Protocol assistance
- Informational topics related to rare disease drug development

Overview of Rare Diseases Cluster Topics

(September 2016 – February 2023)



Relevant Guidances

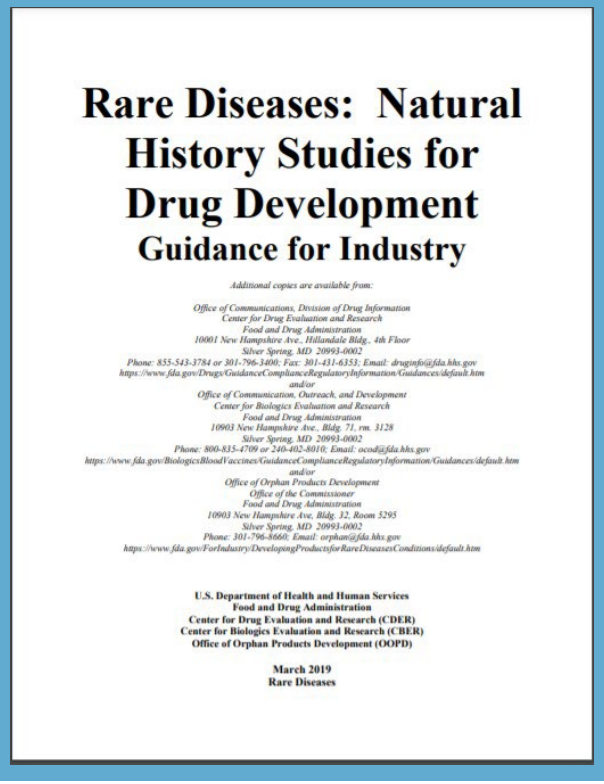


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

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

November 2020
Clinical/Medical

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial



Rare Diseases: Natural History Studies for Drug Development
Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach, and Development
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
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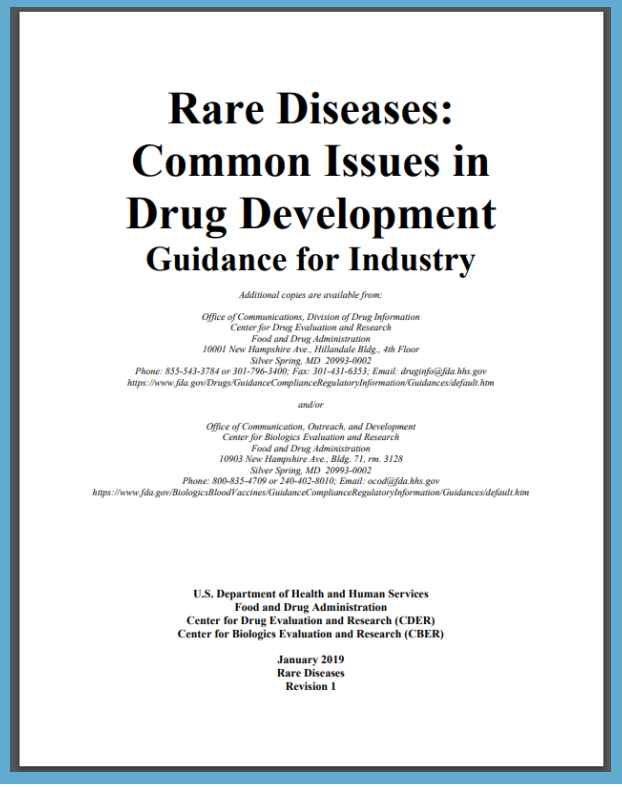
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Orphan Products Development
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave, Bldg. 32, Room 5295
Silver Spring, MD 20993-0002
Phone: 301-796-8660; Email: orphan@fda.hhs.gov
https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

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

March 2019
Rare Diseases

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development



Rare Diseases: Common Issues in Drug Development
Guidance for Industry

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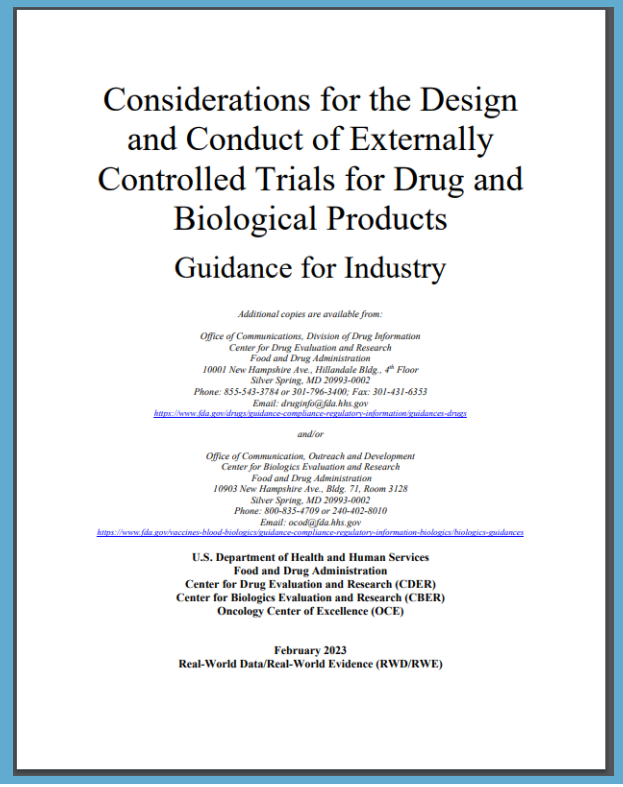
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2019
Rare Diseases
Revision 1

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry



Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
Guidance for Industry

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https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

Summary

- Developing drugs for rare disease presents many challenges
- 50% of the novel drugs approved by FDA since 2015 have been for rare diseases
- CDER has numerous programs, including the ARC Program, to promote engagement and to drive scientific and regulatory innovation in rare disease drug development

Selected References

- Accelerating Rare disease Cures (ARC) Program. Content updated: 3/27/2023. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program
- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration. December 2019. https://www.fda.gov/media/133660/download
- FDA Patient Engagement Opportunities. Content updated: 7/22/2021. https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-engagement-opportunities
- New Drug Therapy Approvals 2022. Content updated: 1/10/2023. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2022#:~:text=these%20expedited%20programs.-,CDER's%20Novel%20Drug%20Approvals%20of%202022,been%20approved%20in%20the%20U.S
- Rare Diseases: Common Issues in Drug Development Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration. January 2019. https://www.fda.gov/media/119757/download

Thank You