Accelerating Rare disease Cures (ARC) Program

RARE DISEASES AT FDA CENTER FOR DRUG EVALUATION AND RESEARCH – CHALLENGES AND PROGRESS IN DRUG DEVELOPMENT

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Rare Diseases Team

DRDMG | ORPURM | CDER | US FDA

April 15, 2024

FDA U.S. FOOD & DRUG ADMINISTRATION

Learning Objectives

- Discuss rare disease and orphan product approval trends
- Discuss challenges and considerations in rare disease drug development
- Share resources that can assist those involved in rare disease drug development
- Share updates on CDER's Accelerating Rare disease Cures (ARC) Program and on CDER's Prescription Drug User Fee Act VII (PDUFA) rare disease commitment: Rare Disease Endpoint Advancement (RDEA) Pilot Program

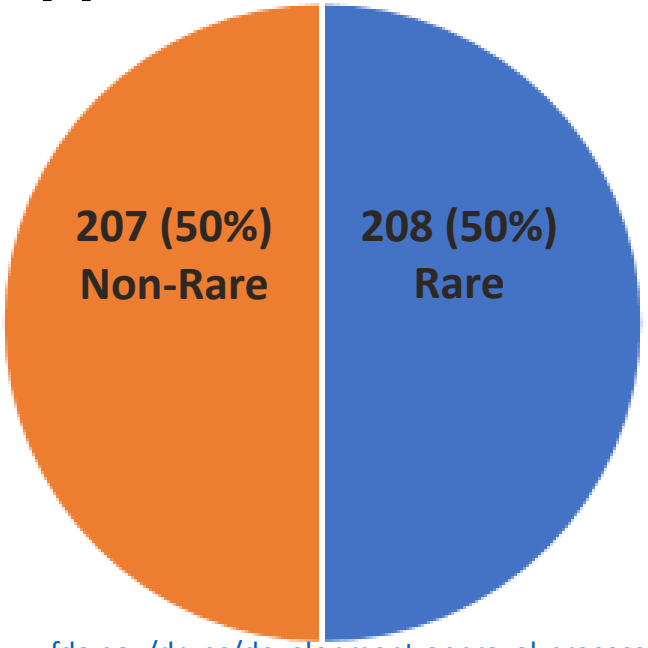
Orphan Drug Act

- Enacted in 1983
- Prior to the Act, “The relatively limited prevalence of a particular disease acted as a barrier for commercial investment.”
- Offers incentives such as:
  - Market exclusivity
  - Tax credits for research and development expenses

https://www.fda.gov/industry/fdas-rare-disease-day/story-behind-orphan-drug-act

Rare Disease Progress

Total CDER Novel Drug Approvals 2015-2022



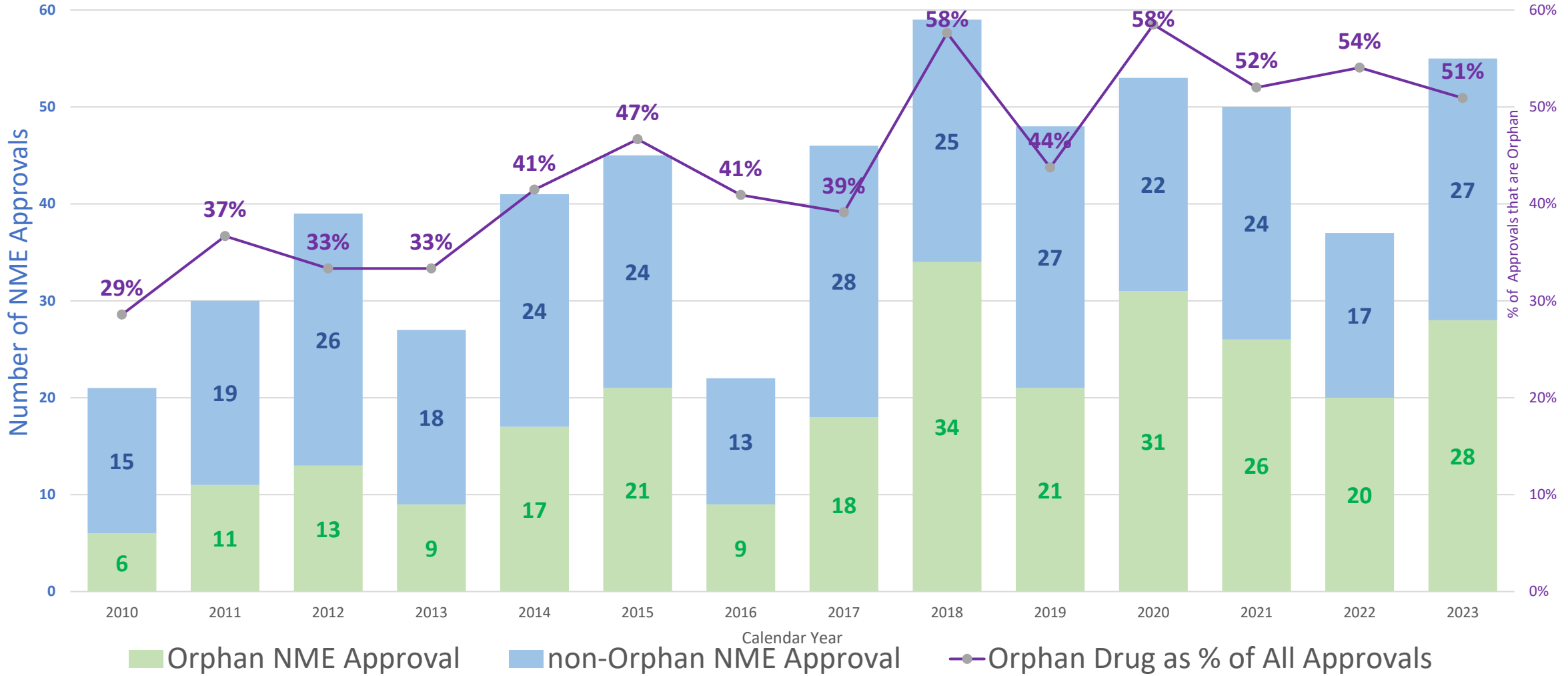
and… FDA has approved over 550 unique drugs and biologics for over 1,100 rare disease indications since the passage of the Orphan Drug Act (1983).

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.

Proportion of CDER Novel Drug Approvals that are Orphan



FDA's Expedited Programs

EXPEDITED PROGRAMS	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Qualifying Criteria	• Drug that treats a **serious condition** • nonclinical or clinical data **demonstrate the potential to address unmet medical need**	• Drug that treats a **serious condition** • **preliminary clinical evidence** indicates that the drug **may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies**	• Drug that treats a **serious condition** • provides a **meaningful advantage over available therapies** • demonstrates an effect on a **surrogate endpoint** that is **reasonably likely to predict clinical benefit** or on a **clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM)** that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical benefit)	• Application (original or efficacy supplement) for a drug that treats a **serious condition** • If approved, would provide a **significant improvement in safety or effectiveness**

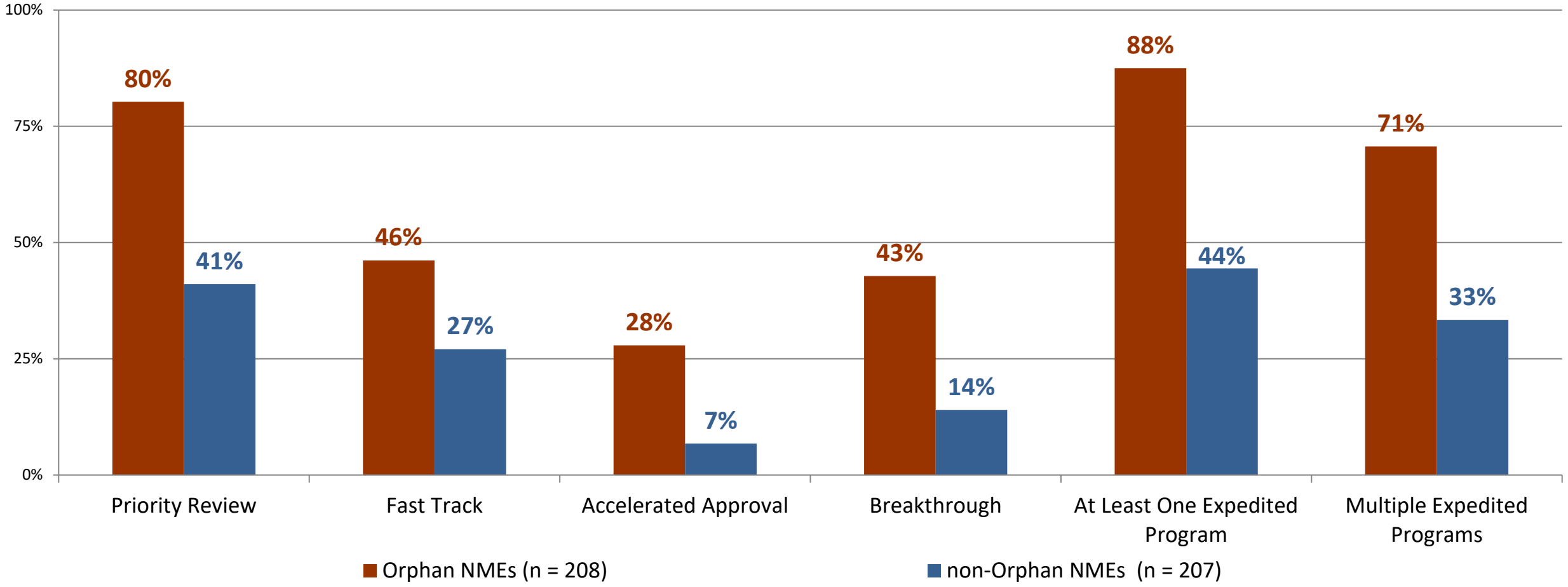
FDA's Expedited Programs (cont.)

EXPEDITED PROGRAMS	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review from filing date)

Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics - 2014
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

CDER Use of Expedited Programs

NME and New Biologic Approvals CY 2015 - 2023



We Face Common Challenges in Rare Disease Drug Development

- **Natural history** is often poorly understood
- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs,** many have **pediatric onset**
- **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

And, Common Considerations in the "Environment" for Rare Disease Drug Development

- Many smaller companies with less regulatory experience
- Active patient stakeholder groups looking to navigate and participate in rare disease drug development
- A dedicated academic community that may have limited knowledge of regulatory requirements or aspects of clinical trial development

= We must engage our stakeholders to enhance their understanding, and gain their alignment and support

CDER'S Accelerating Rare disease Cures Program

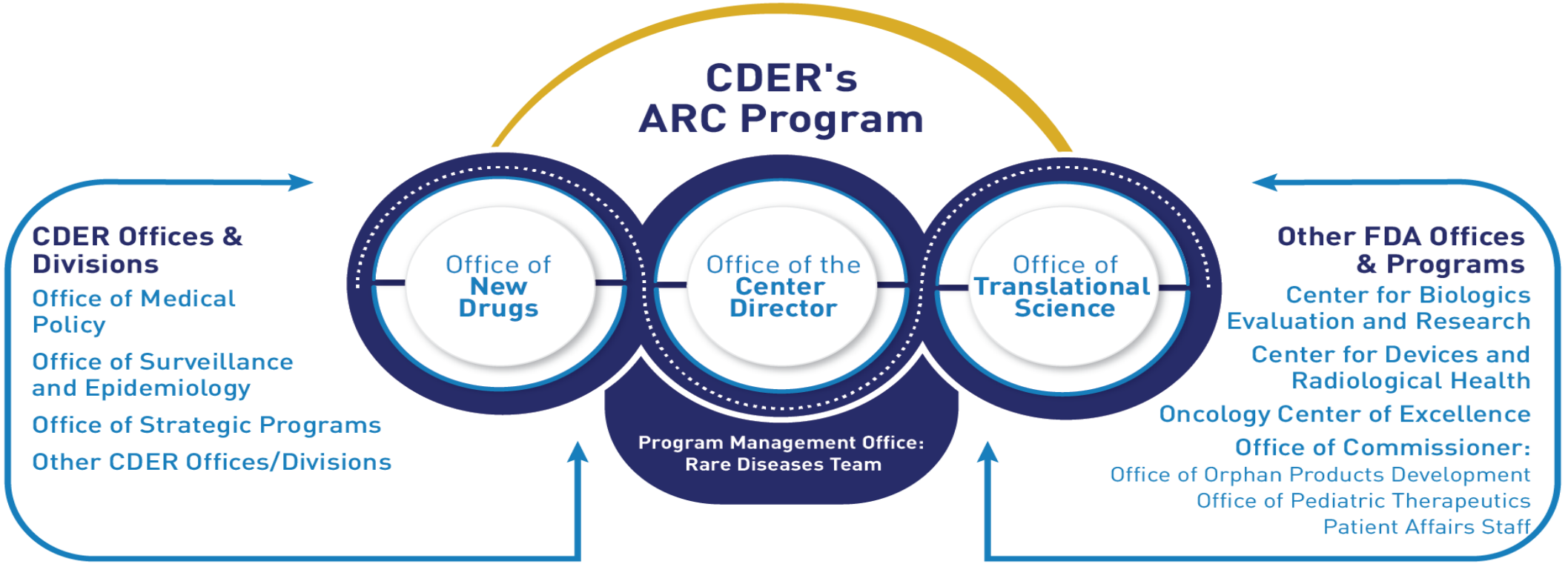
- Vision

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



CDER_ARC_Program@fda.hhs.gov

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-arc-program

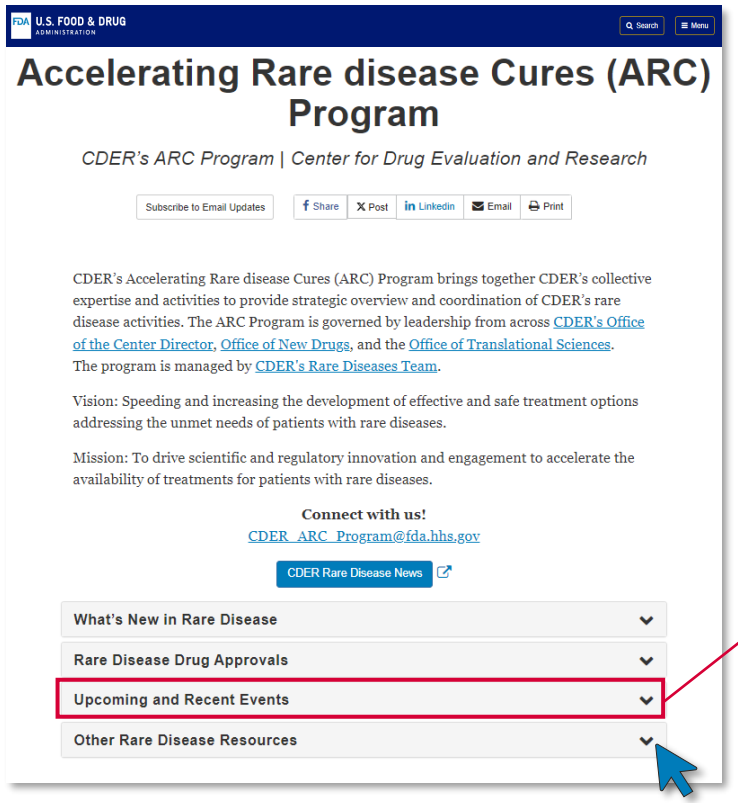
Resources for Rare Disease Drug Developers

ARC Website

- https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program

ARC Website: Conferences and Workshops Tab

ARC Website



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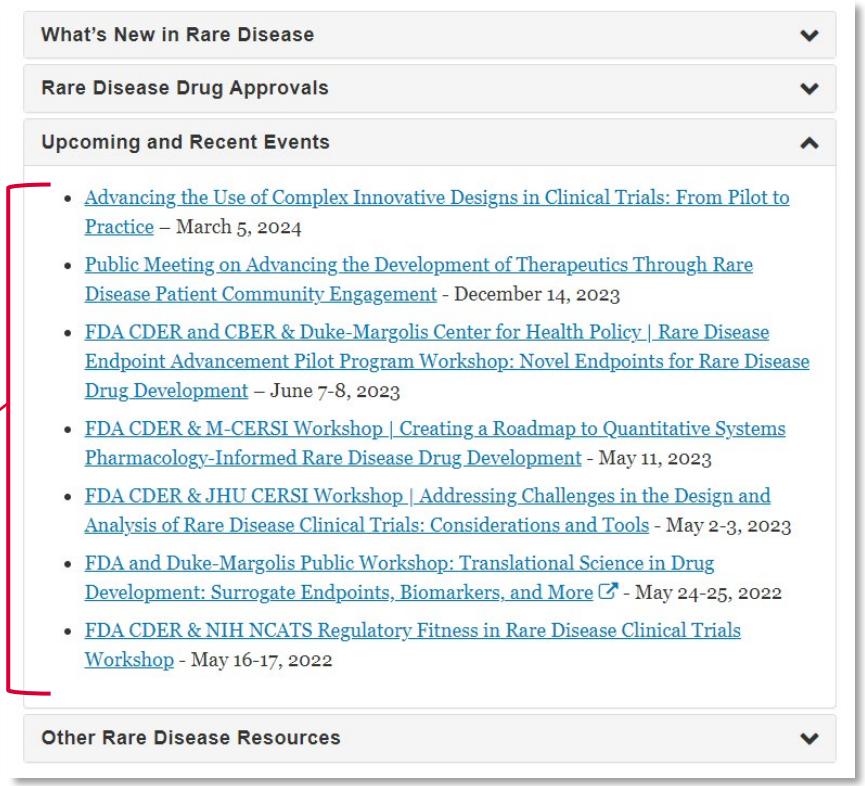


Natural History Studies and Registries in the Development of Rare Disease Treatments

Hybrid Public Workshop

May 13, 2024 | 10am-4pm *(eastern)*

Upcoming Event: May 13th, 2024

Natural History Studies and Registries in the Development of Rare Disease Treatments

Reagan-Udall Foundation for the FDA, in collaboration with FDA's Rare Diseases Team within the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine; Office of New Drugs; Center for Drug Evaluation and Research and the National Institutes of Health's Division of Rare Diseases Research Innovation within the National Center for Advancing Translational Sciences, is hosting a public workshop.

The workshop will bring together rare disease patient advocates, academic researchers, regulated industry, and other key stakeholders to discuss considerations for the use of natural history study and registry data in rare disease drug development programs.

To register for the meeting and find out more information: https://www.fda.gov/drugs/news-events-human-drugs/natural-history-studies-and-registries-development-rare-disease-treatments-05132024

Guidances

Guidance Documents for Rare Disease Drug Development

Share | Post | Linkedin | Email | Print

Guidances | Drugs

Product-Specific Guidances for Generic Drug Development

Guidance Snapshot Pilot

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in agency guidances means that something is suggested or recommended, but not required.

Below are selected guidances that are relevant to rare disease drug development, organized by topic. This list does not include all FDA guidances on or relevant to rare disease drug development but represents our most commonly used guidances. This list may be updated periodically.

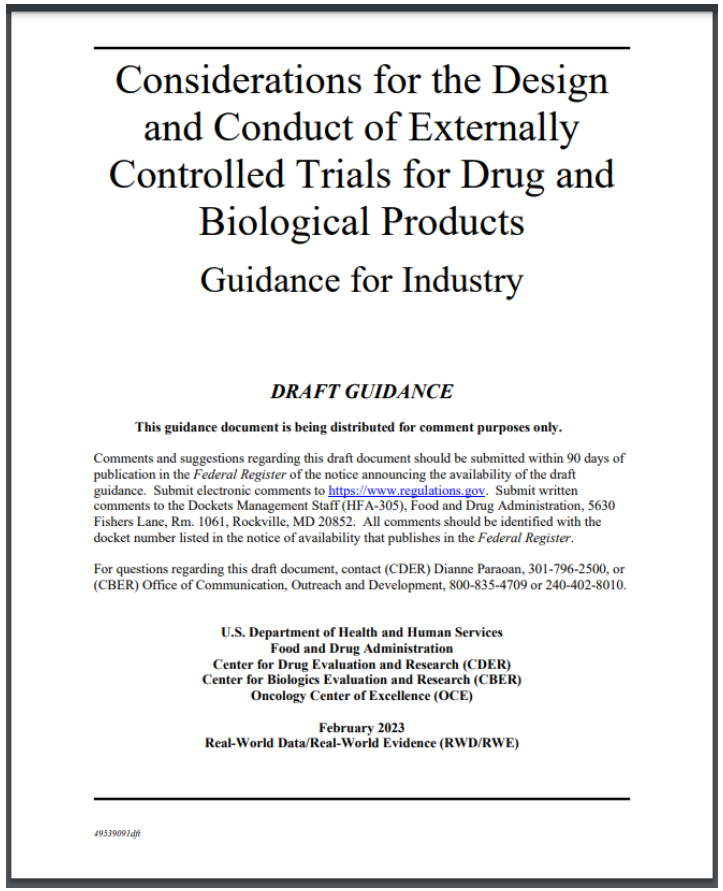
You can search all FDA Guidances by topic, FDA Center, or issue date here.

- Rare Disease
- Benefit-Risk
- Biomarkers
- Clinical Pharmacology
- Clinical Trials
- Complex Innovative Trial Design
- Communication with FDA
- Digital Health
- Effectiveness
- Expanded Access
- Expedited Programs
- Individualized Antisense Oligonucleotide Drugs Products
- Investigational New Drug Applications
- Meetings with FDA
- New Drug Applications (NDAs)
- Neurology
- Non-Clinical
- Orphan Designation
- Patient Focused Drug Development (PFDD)
- Patient Reported Outcomes
- Pediatrics
- Real World Evidence
- Statistical Analysis
- Voucher Program

Content current as of: 09/19/2023

Regulated Product(s) Drugs

Externally Controlled Trials



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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dianne Paraoan, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

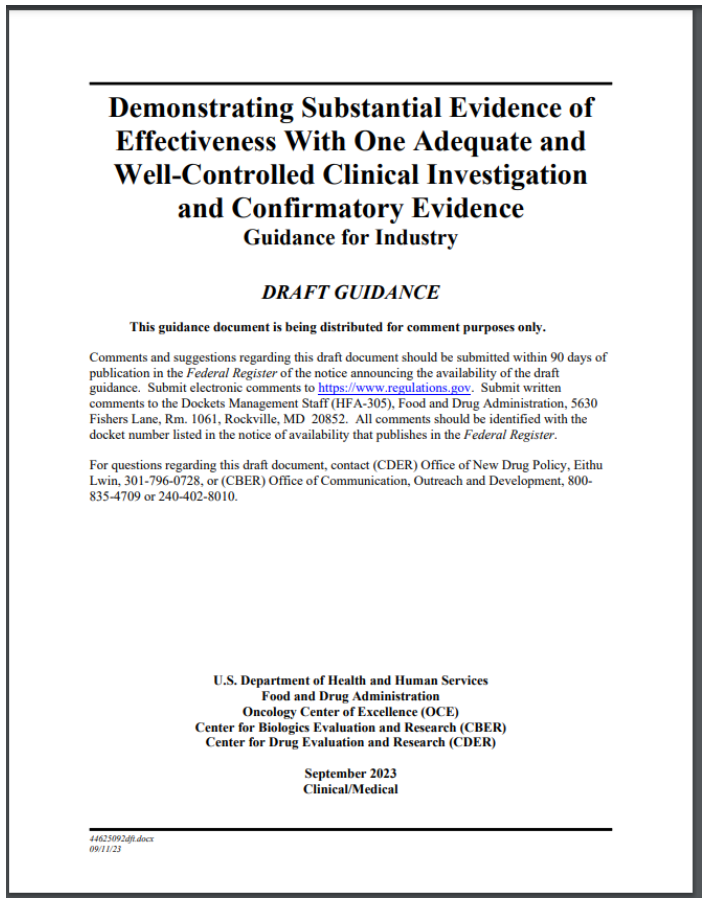
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

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

49539091dft

- Focuses on design, data, and analysis considerations for externally controlled trials.
- Sponsors should consult with FDA early in a drug development program about whether it is reasonable to conduct an externally controlled trial instead of a randomized controlled trial.

Confirmatory Evidence



Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of New Drug Policy, Eithu Lwin, 301-796-0728, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

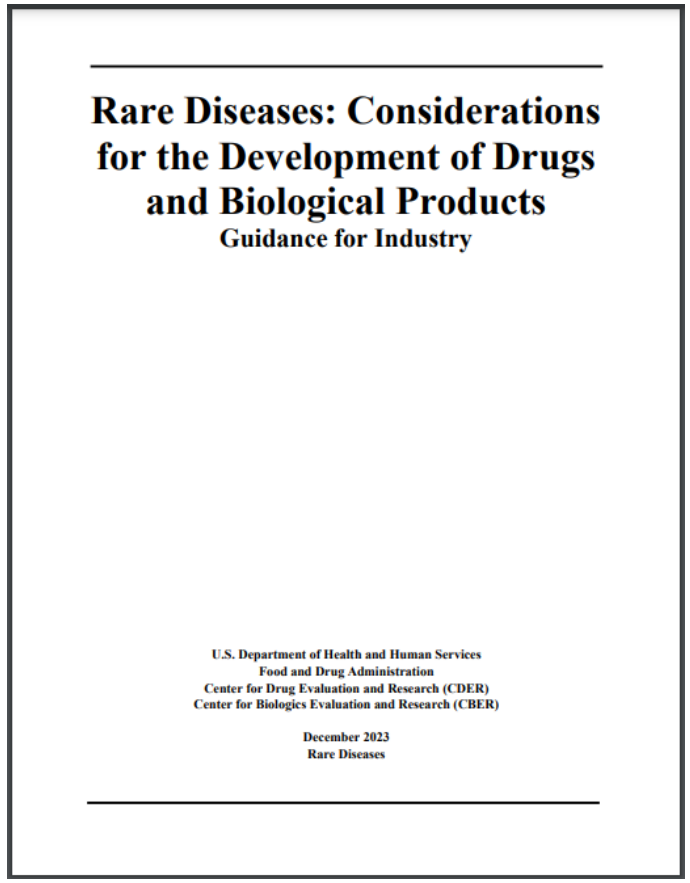
U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

September 2023
Clinical/Medical

44625092dft.docx
09/11/23

- Describes factors to consider when assessing whether a single adequate and well controlled clinical investigation and confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness
- Provides examples of types of data that could be considered confirmatory evidence

Considerations Guidance

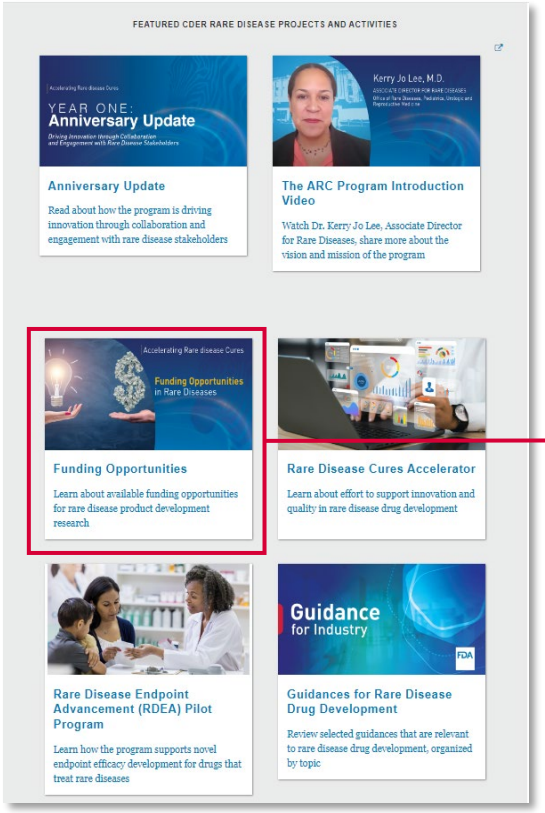

Rare Diseases: Considerations for the Development of Drugs and Biological Products
Guidance for Industry

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)

December 2023
Rare Diseases

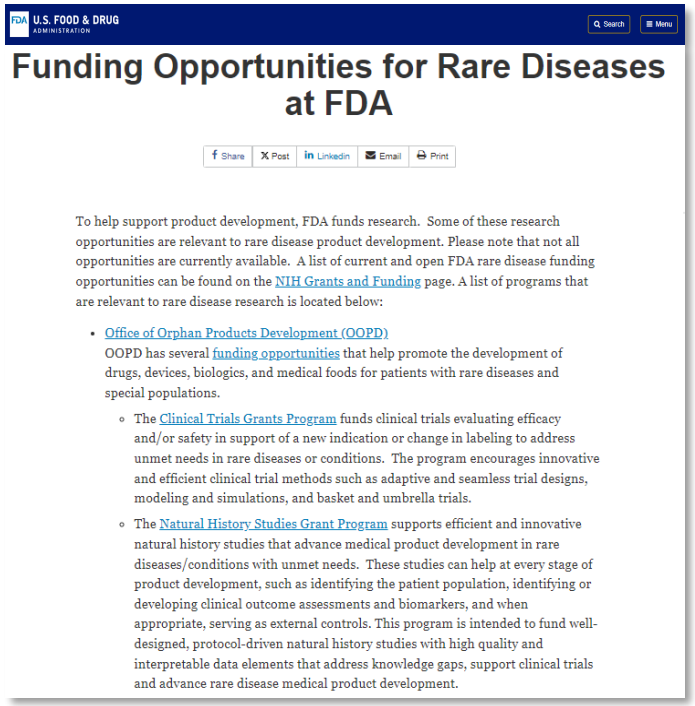
- Addresses considerations in rare disease drug development due to limited medical and scientific knowledge, poorly understood natural history data, and sample size constraints.
- Covers the rare disease perspective for a myriad of important topics, including non-clinical studies and clinical trial considerations, such as the demonstration of effectiveness and safety

ARC Website: Funding Opportunities Placard



Funding Opportunities Placard

Learn About Funding Opportunities

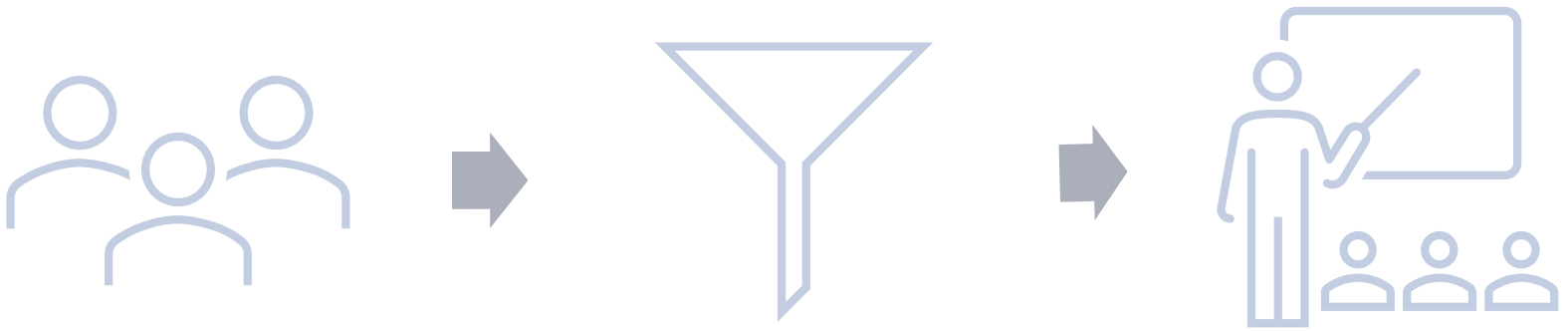


ARC's Quarterly Newsletter

- 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

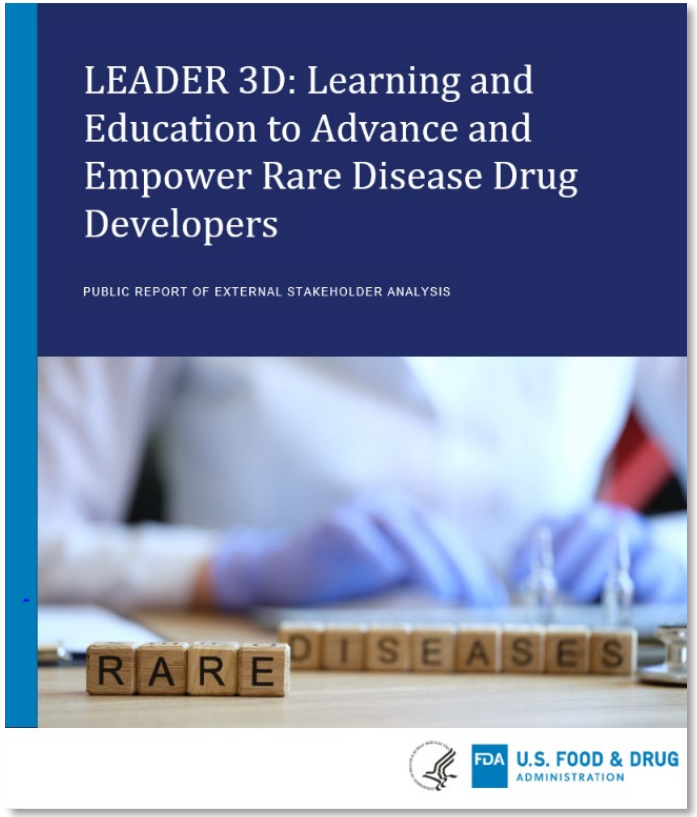
LEADER 3D (CONT.)

- 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 PFDD 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

LEADER 3D: Public Report

- Solicited feedback from those who design or conduct rare disease drug development programs.
- Educational opportunities include:
  - Nonclinical studies
  - Dose-Finding
  - Natural History Studies and Registries
  - Novel Endpoint and Biomarker Development
  - Clinical Trial Design and Analysis
  - Rare Disease Drug Development Regulatory Considerations



Focusing on Endpoints: PDUFA VII RDEA Pilot Program Overview

- **Scope**: The Rare Disease Endpoint Advancement (RDEA) pilot program is a **joint CDER and CBER program** that seeks to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process. An endpoint, or endpoints, will be considered eligible for proposal submission to RDEA if each of the following criteria are met:
  - The associated development program **should be active and address a rare disease**, with an active IND or pre-IND for the rare disease
  - The proposed endpoint is a **novel efficacy endpoin**t intended to establish substantial evidence of effectiveness for a rare disease treatment
- For each RDEA proposal admitted into the pilot program, the agency will conduct an initial meeting and, if requested, up to three follow-up meetings.
- Current application quarter closes on March 31st, 2024

WEBSITE RESOURCES

- ***FAQs***
- ***Proposal Elements***
- ***Meeting Package Elements***
- ***Disclosure Elements***
- ***Endpoint Development Resources***

RDEA=Rare Disease Endpoint Advancement
PDUFA=Prescription Drug User Fee Act
https://www.fda.gov/media/151712/download
https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program

RDEA Pilot Program Overview (cont.)

- **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 trial

RDEA Updates

- Website: https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program
- FAQs
- Proposal Elements
- Meeting Package Elements
- Disclosure Elements
- Endpoint Development Resources

START Pilot Program: Executive Summary

- CDER OND and CBER OTP jointly published an FRN announcing the Support for clinical Trials Advancing Rare disease Therapeutics START Pilot Program, the goal of which is to further accelerate the pace of development of certain CBER- and CDER- novel drug and biological products that are intended to treat a rare disease by giving selected pilot participants the opportunity for enhanced communication with the FDA on issues specific to the development of their product

- This pilot program is designed to:
  - Augment the currently available formal meetings between sponsors and FDA to address a variety of specific programmatic issues for a select number of promising individual development programs. For example, these issues can be related to clinical study design, choice of control group, fine tuning the choice of patient population, selecting appropriate endpoints for accelerated approval, selecting statistical methodology, leveraging nonclinical information, or product characterization
  - Be milestone-driven, with the aim to getting participants' development programs to expeditiously reach pivotal stages of drug development.

START Pilot Program: Executive Summary (cont.)

- Eligible participants include:
  - *CBER and CDER applicants* who have submitted an IND in or converted to Electronic Common Technical Document (eCTD) format, unless the IND is of a type granted a waiver from eCTD format and remains in active status; and
  - *CBER and CDER applicants* who have demonstrated substantial effort to ensure that that Chemistry, Manufacturing, and Controls (CMC) development aligns with clinical development;* and
  - *CBER applicants* for an existing OTP-regulated IND for a cellular or gene therapy under which the product is being developed toward a marketing application. And the product is intended to address an unmet medical need as a treatment for a rare disease or serious condition, which is likely to lead to significant disability or death within the first decade of life; or
  - ***CDER applicants* for a product that is intended to treat rare neurodegenerative conditions (including those of rare genetic metabolic etiology)**

*For example, through documented control of manufacturing and testing procedures to ensure clinical and CMC development timeline are in alignment

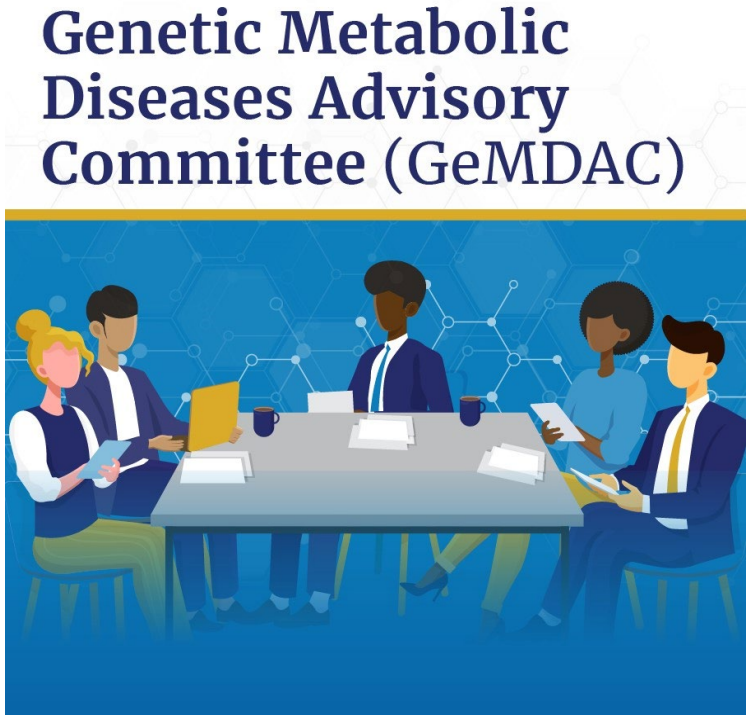
On December 12, FDA CDER announced the new Genetic Metabolic Diseases Advisory Committee (GeMDAC)

- This AC is being established to advise the Agency on products for genetic metabolic diseases under the purview of CDER's Division of Rare Diseases and Medical Genetics (DRDMG).

- To establish the new AC, FDA is publishing four federal register notices:
  - Notice of establishment
  - Voting members request for nominations
  - Consumer representative request for nominations
  - Industry representative request for nominations

- GeMDAC will provide a forum for discussion of complex issues with specialized and diverse technical and scientific experts in the fields of:
  - Metabolic genetics
  - Management of inborn errors of metabolism
  - Small population trial design
  - Translational science
  - Other related specialties (e.g., pediatrics, epidemiology, stats)

- FDA GeMDAC WEBSITE: https://www.fda.gov/advisory-committees/human-drug-advisory-committees/genetic-metabolic-diseases-advisory-committee-gemdac



Case Study

- Velmanase
- Indication: for the treatment of non-central nervous system manifestations of alpha-mannosidosis (AM) in adult and pediatric patients.
- Approved: February 16, 2023

Alpha-mannosidosis

- A rare autosomal recessive lysosomal disorder
- Enzyme deficiency leads to oligosaccharide accumulation in various tissues
- Involves central nervous system (CNS), musculoskeletal, and immune system
- Velmanase catabolizes the oligosaccharides that accumulate in the lysosomes.

We Face Common Challenges in Rare Disease Drug Development

- **Natural history** is often poorly understood
- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs,** many have **pediatric onset**
- **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

Common Challenges in Rare Disease Drug Development

- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs,** many have **pediatric onset**
    - **AM is a serious disease that can lead to death in early childhood and to progressive and severe motor impairment in later onset forms.**
- **Small populations** often restrict study design options
    - **AM has a prevalence of 1:500,000**
- **Phenotypic and genotypic** diversity within a disorder
    - **AM has highly variable clinical manifestations, severity, and progression.**

Common Challenges in Rare Disease Drug Development

- **Drug development tools** - **outcome measures** and **biomarkers** often **lacking**
  - **Trial demonstrated a statistically significant reduction in serum oligosaccharides.**
  - **This supports the proposed mechanism but is not a validated surrogate endpoint**
- Lack of **precedent**, including **clinically meaningful endpoints**, for drug development in many rare diseases
  - **Clinical endpoints included the trial 3-minute stair climb test, 6-minute walk test, and FVC percent of predicted normal value.**

Resources to Address Challenges

- Velmanase was approved based on 1 Adequate and Well-Controlled Trial and Confirmatory Evidence
  - Use ARC's Guidance list to find guidances related to rare disease drug development
- Endpoint selection is key
  - Rare Disease Endpoint Advancement (RDEA) program
  - Rare Disease Endpoint Advancement Workshop recording on the ARC website

Case Study 2

- Vutrisiran
- Indication: Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
- Approved: June 13, 2022

Hereditary Transthyretin-mediated Amyloidosis

- Autosomal dominant disorder
- Caused by mutations in the TTR gene, leading to protein misfolding, aggregation, and deposition in the nervous system, heart, kidneys, eyes, bone, and GI tract
- Vutrisiran is a small interfering RNA that targets TTR mRNA (both mutant and wild type)
- At the indicated dose, vutrisiran reduced TTR levels by an average of 85%

Common Challenges in Rare Disease Drug Development

- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs,** many have **pediatric onset**
  - **Death occurs within 5 to 12 years of onset**
  - **There remains a significant unmet clinical need for effective treatments for hATTR because not all patients are able to receive or tolerate the currently available clinical treatments.**
- **Small populations** often restrict study design options
  - **Global prevalence of hATTR-PN is estimated to be between 5,000 and 10,000 persons**
- **Development programs often lack solid translational background**
  - **Reduction in serum TTR provided strong mechanistic support**

Resources to Address Challenges

- Vutrisiran was approved based on 1 Adequate and Well-Controlled Trial and Confirmatory Evidence
  - Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
  - Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biologic Products
- Educational Conferences and Workshops from 2022
  - FDA/NIH Regulatory Fitness in Rare Disease Clinical Trials
  - FDA and Duke Margolis Virtual Public Workshop: Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More

Conclusions

- In recent years, over 50% of CDER's novel drug approvals were for rare diseases
- CDER's ARC program will help CDER work more effectively with our rare disease drug development partners
- CDER and ARC have multiple resources to assist with the challenges of rare disease drug development.