



Accelerating Rare disease Cures (ARC) Program

# TRIAL DESIGN CONSIDERATIONS IN RARE DISEASES

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*DRDMG | ORPURM | CDER | US FDA*



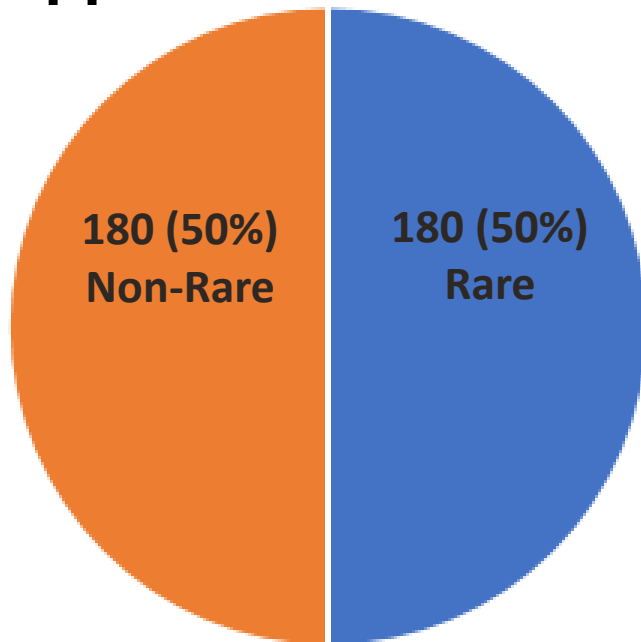
**U.S. FOOD & DRUG**  
ADMINISTRATION

# 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

# 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...

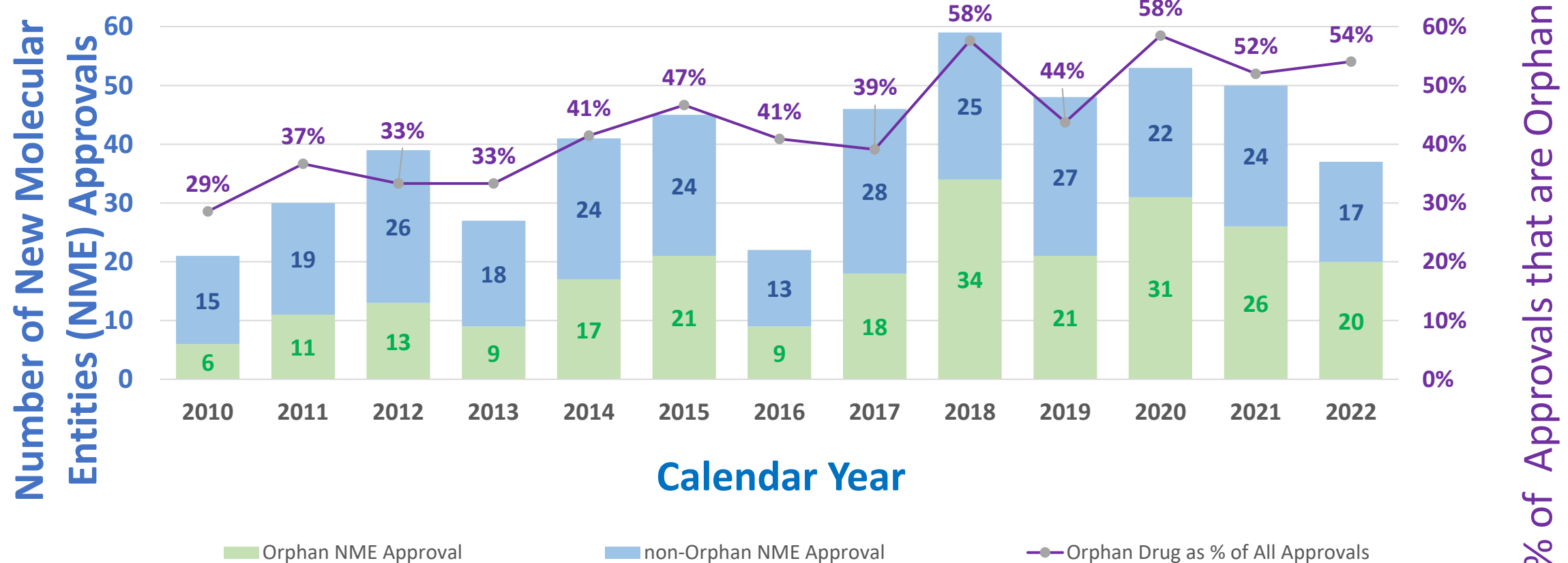
~30 million Americans live with a rare disease.  
Vast majority do not have approved treatments.

<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	<ul style="list-style-type: none"><li>• Drug that treats a <b>serious condition</b></li><li>• nonclinical or clinical data <b>demonstrate the potential to address unmet medical need</b></li></ul>	<ul style="list-style-type: none"><li>• Drug that treats a <b>serious condition</b></li><li>• <b>preliminary clinical evidence</b> indicates that the drug <b>may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</b></li></ul>	<ul style="list-style-type: none"><li>• Drug that treats a <b>serious condition</b></li><li>• provides a <b>meaningful advantage over available therapies</b></li><li>• demonstrates an effect on a <b>surrogate endpoint</b> that is <b>reasonably likely to predict clinical benefit</b> or on a <b>clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM)</b> that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical benefit)</li></ul>	<ul style="list-style-type: none"><li>• Application (original or efficacy supplement) for a drug that treats a <b>serious condition</b></li><li>• If approved, would provide a <b>significant improvement in safety or effectiveness</b></li></ul>

# FDA's Expedited Programs (cont.)

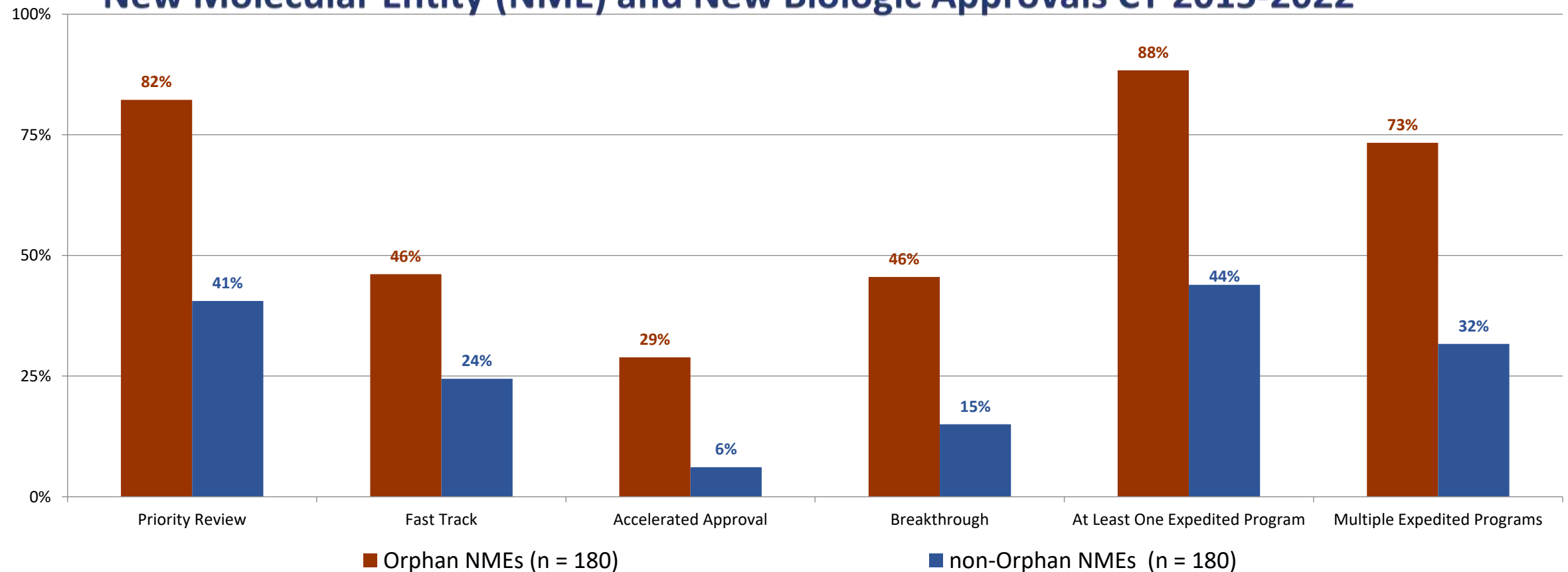


EXPEDITED PROGRAMS	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Features	<ul style="list-style-type: none"><li>• Actions to expedite development and review</li><li>• Rolling review</li></ul>	<ul style="list-style-type: none"><li>• Intensive guidance on efficient drug development</li><li>• Organizational commitment</li><li>• Rolling review</li><li>• Other actions to expedite review</li></ul>	<ul style="list-style-type: none"><li>• 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</li></ul>	<ul style="list-style-type: none"><li>• Shorter clock for review of marketing application (6 months compared with the 10-month standard review from filing date)</li></ul>



# CDER Use of Expedited Development Programs

## New Molecular Entity (NME) and New Biologic Approvals CY 2015-2022



# 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](mailto: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

- Building the ARC site with the goal of becoming a “1 stop shop” for Rare Disease Drug Development resources
- <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program>

## Accelerating Rare disease Cures (ARC) Program

CDER's ARC Program | Center for Drug Evaluation and Research

Accelerating Rare Disease Cures (ARC) Program

Accelerating Rare Disease Cures (ARC) Program

CDER's Accelerating Rare Disease Cures (ARC) Program brings together CDER's collective expertise and activities to provide strategic oversight and coordination of CDER's rare disease activities. The ARC Program is governed by leadership from across CDER, including the Center Director, Office of New Drugs, and the Office of Translational Sciences. The program is managed by CDER's Rare Diseases Team.

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

Mission: To drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

Website content as of: 08/15/2020

Connect with us:  
[CDER ARC Program on Facebook](#)  
[CDER ARC Program on Twitter](#)

What's New in Rare Disease

Upcoming and Recent Events

Other Rare Disease Resources

FEATURED CDER RARE DISEASE PROJECTS AND ACTIVITIES



**Anniversary Update**  
 Read about how the program is driving innovation through collaboration and engagement with rare disease stakeholders.



**The ARC Program Introduction Video**  
 Watch Dr. Henry J. Lee, Associate Director for Rare Diseases, share more about the vision and activities of the program.



**Funding Opportunities**  
 Learn about available funding opportunities for rare disease product development research.



**Rare Disease Cures Accelerator**  
 Learn about efforts to support innovation and quality in rare disease drug development research.



# Educational Conferences and Workshops

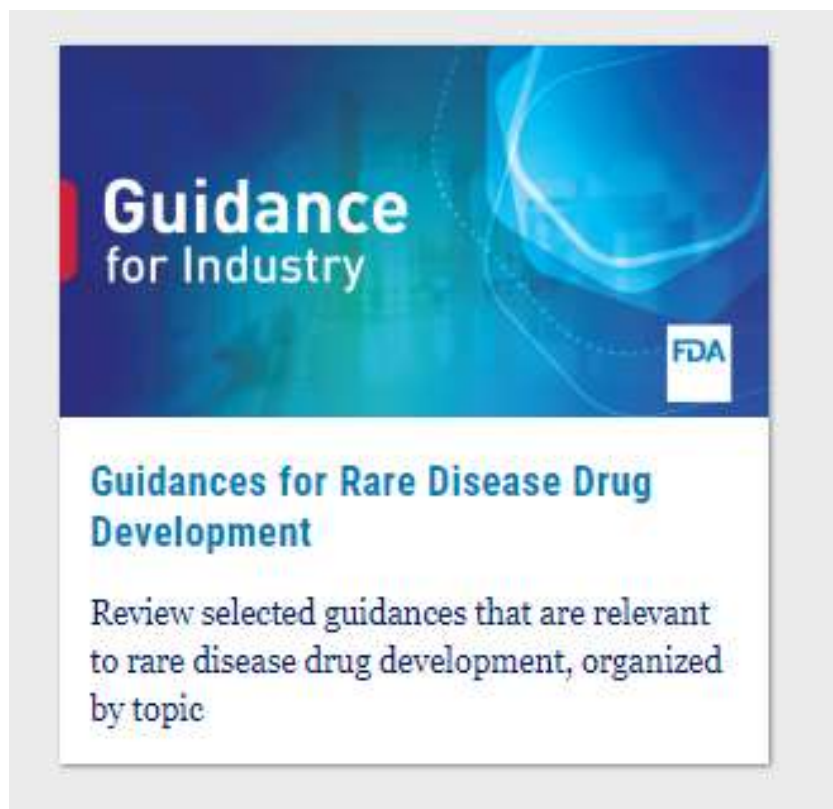
- FDA/NIH Regulatory Fitness in Rare Disease Clinical Trials conference, May 16-17, 2022
  - CDER's Rare Diseases Team and National Center for Advancing Translational Sciences (NIH)
  - Focus on academic investigators and those looking to learn how to bridge the gap between academic investigation and the regulatory aspects of drug development
- FDA and Duke Margolis Virtual Public Workshop: Translational Science in Drug Development: Surrogate Endpoints, Biomarkers, and More, May 24-25, 2022
  - CDER'S Office of Drug Evaluation Science and Office of Clinical Pharmacology
  - Focus on translational science and the development of surrogate endpoints



# Educational Conferences and Workshops - 2

- FDA CDER & Johns Hopkins Center of Excellence in Regulatory Science and Innovation (CERSI) Workshop: Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools, May 2-3, 2023
  - How to collect high quality and fit-for-purpose data for rare disease clinical trials
  - Use of real-world data to inform rare disease drug development
  - Design and analysis methodologies for use in rare disease clinical trials
- FDA CDER & University of Maryland Center of Excellence in Regulatory Science and Innovation (CERSI) Workshop: Creating a Roadmap to Quantitative Systems Pharmacology-Informed Rare Disease Drug Development, May 11, 2023

# Guidances



## Guidance Documents for Rare Disease Drug Development

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### 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.

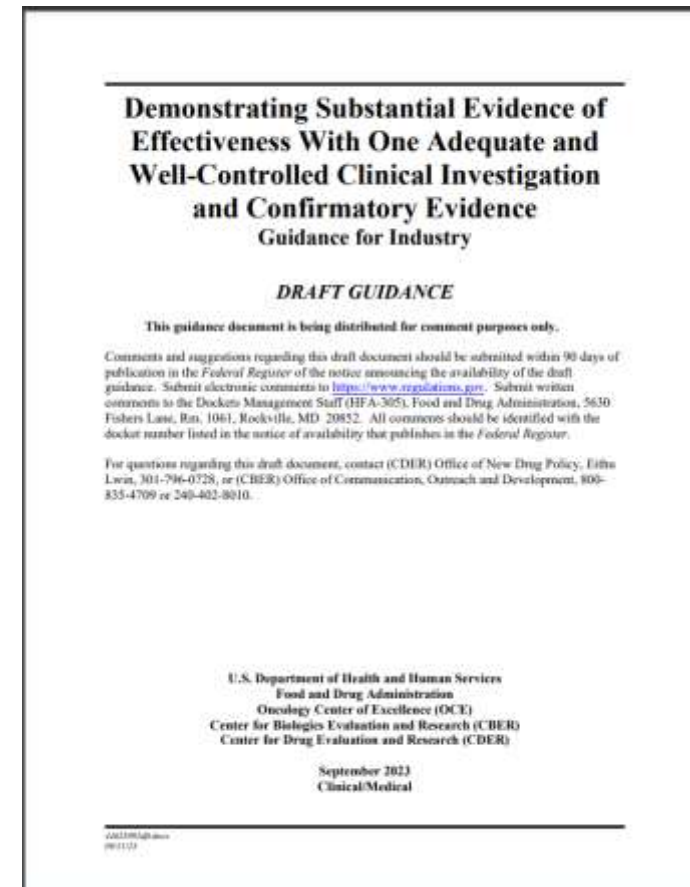
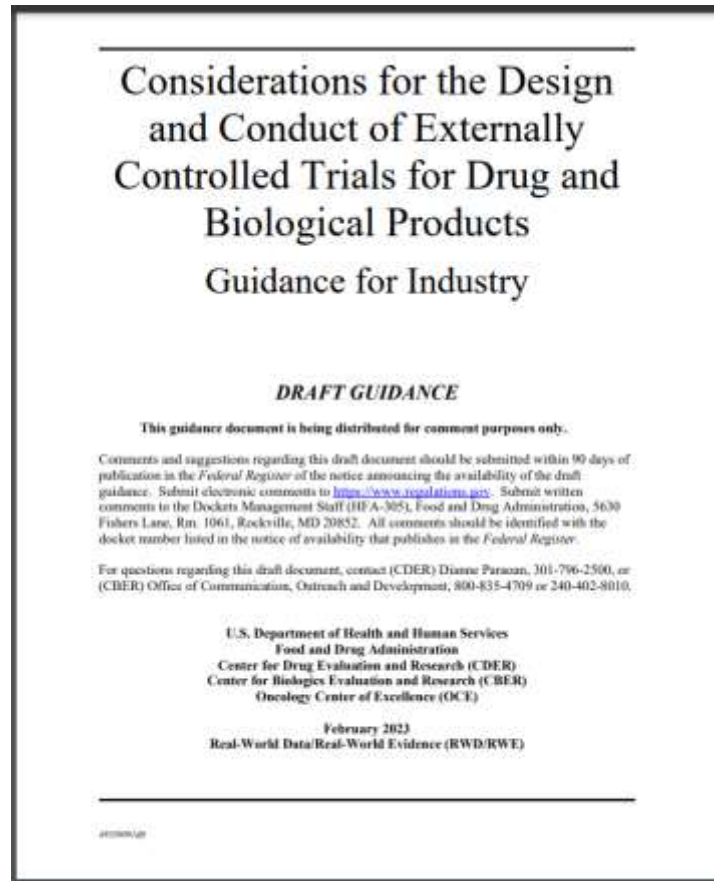
You can search all FDA Guidances by topic, FDA Center, or issue date [here](#).

Content current as of:  
04/19/2023

Regulated Product(s):  
Drugs

- [Rare Disease](#)
- [Benefit-Risk](#)
- [Biomarkers](#)
- [Clinical Pharmacology](#)
- [Clinical Trials](#)
- [Complex Innovative Trial Design](#)
- [Communication with FDA](#)
- [Digital Health](#)
- [Effectiveness](#)
- [Expanded Access](#)
- [Expedited Programs](#)
- [Individualized Antineoplastic Oligonucleotide Drug 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](#)

# Recently Issued Guidances



# Funding Opportunities

- The ARC webpage lists funding opportunities for rare disease product development research





# ARC YEAR 1: ARC's Quarterly Newsletter

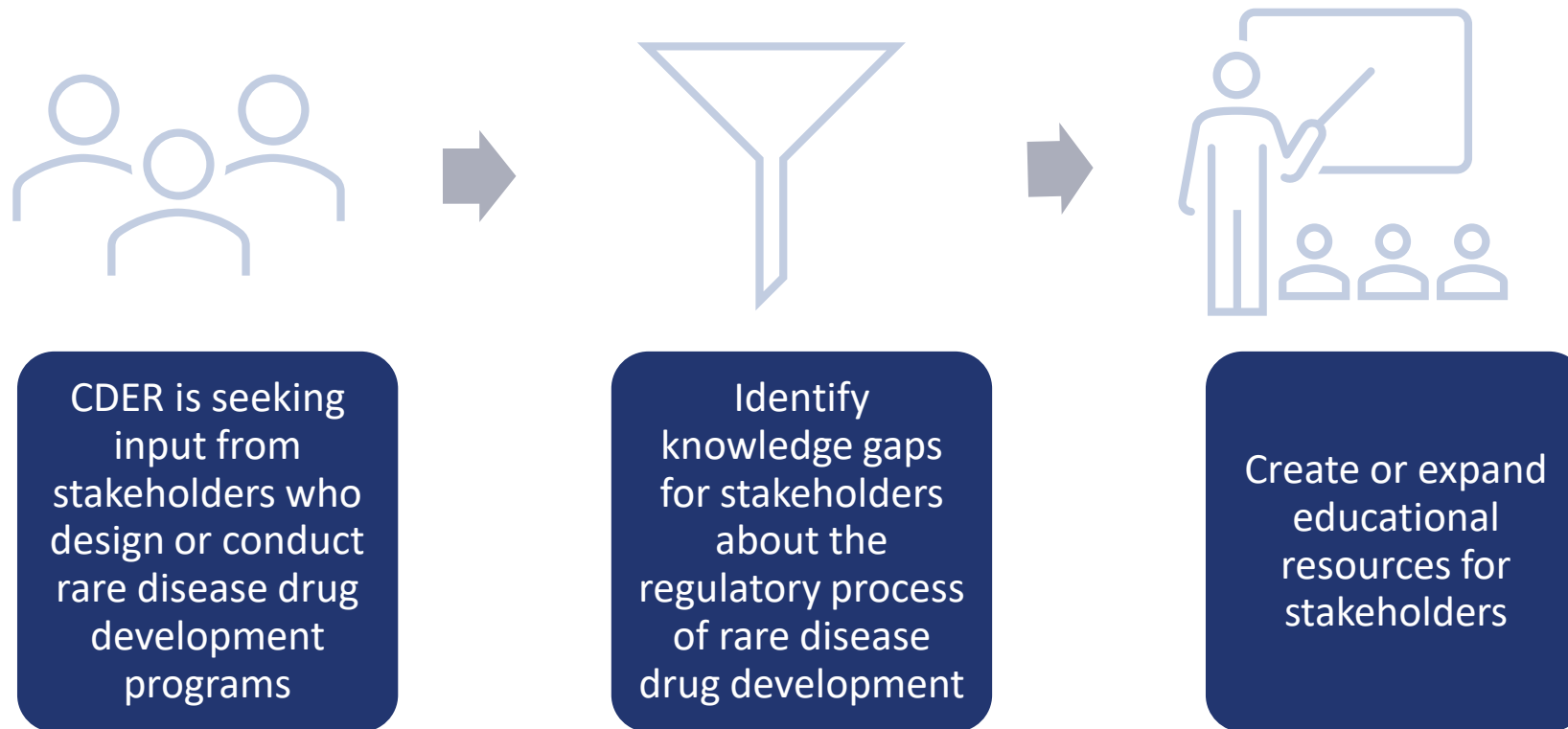
- To subscribe: [U.S. Food and Drug Administration \(govdelivery.com\)](https://www.fda.gov/govdelivery)



**LEARNING AND EDUICATION TO ADVANCE AND  
EMPOWER RRARE DISEASE DRUG DEVELOPERS  
(LEADER 3D)**



# What is **LEADER 3D**?



## 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>



# Focusing on Endpoints: PDUFA VII RDEA Pilot Program Overview

- **Scope:** The Rare Disease Endpoint Advancement (RDEA) pilot program will seek 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 endpoint** intended to establish substantial evidence of effectiveness for a rare disease treatment

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

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



- FDA CDER and CBER & Duke-Margolis Center for Health Policy Workshop, June 2023
  - This workshop discussed:
    - RDEA Pilot Program, including application process and required elements for the RDEA proposal
    - Scientific and technical issues associated with developing study endpoints for rare diseases
    - Lessons learned from previous PDUFA meeting programs that can be applied to the RDEA Pilot Program

# 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



# Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program - Overview



- Intended to further accelerate the pace of development of certain CBER- and CDER- regulated products (novel drug and biological products) that are intended to treat a rare disease
- The pilot program is designed to be:
  - **Product-focused and augment** the currently available formal meetings between FDA and sponsors by addressing issues related to the development of individual products through more rapid communications with FDA
  - **Milestone-driven**, (i.e., to facilitate the progression of a development program to pivotal clinical study stage or the pre-BLA or pre-NDA meeting stage) where product development programs selected would benefit from enhanced communications with FDA
  - **Address a variety of specific programmatic issues** that individual products sponsors might need help with, such as clinical, manufacturing, or nonclinical considerations
  - For CDER, focus on products intended to treat **rare neurodegenerative conditions (including those of rare genetic metabolic etiology)**

# Application Process Overview



## When can sponsors apply?

Applications will be open from January 2, 2024, to March 1, 2024



## How can sponsors apply?

Interested sponsors will be asked to submit their request to participate as an amendment to their Investigational New Drug (IND) application.



## How many participants will be selected?

Up to three sponsors per Center (CDER & CBER) will be chosen to participate in the initial pilot, but in the future, the program may expand and/or there could be a second iteration of the program announced.



## When will selected participants be notified?

FDA will issue a letter to each to applicant to notify them of their decision regarding their participation in the pilot program within 90 days of the application deadline.

# 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
- Need for additional meetings for development issues
  - Support for clinical Trials Advancing Rare disease Therapeutics (START)

# 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.

# Challenge Question #1

**Educational content on the ARC website includes:**

- A. A list of guidances organized by topic area
- B. Recordings of public workshops
- C. Listing of funding opportunities
- D. All of the above

# Challenge Question #2

**Challenges in rare disease drug development include:**

- A. Small populations
- B. Lack of precedent, including clinically meaningful endpoints
- C. Phenotypic and genotypic diversity within a disorder
- D. All of the above