Accelerating Rare disease Cures (ARC) Program

TRIAL DESIGN CONSIDERATIONS IN RARE DISEASES

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Rare Diseases Team

DRDMG | ORPURM | CDER | US FDA

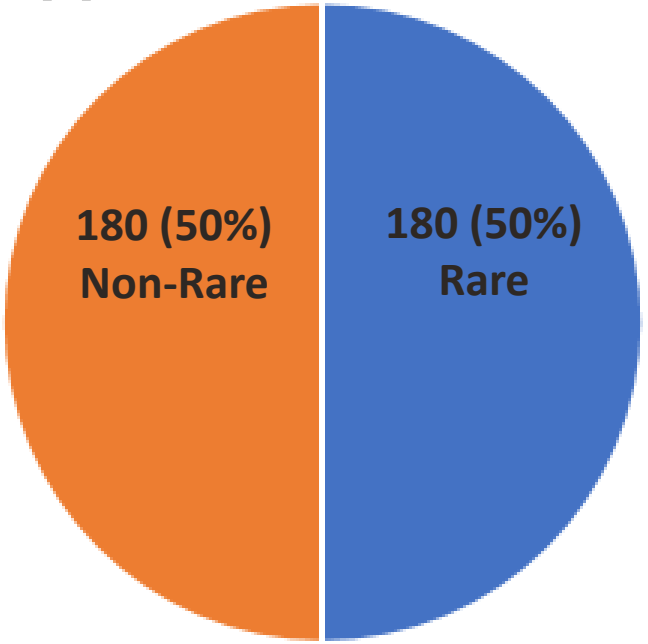
U.S. FOOD & DRUG ADMINISTRATION

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



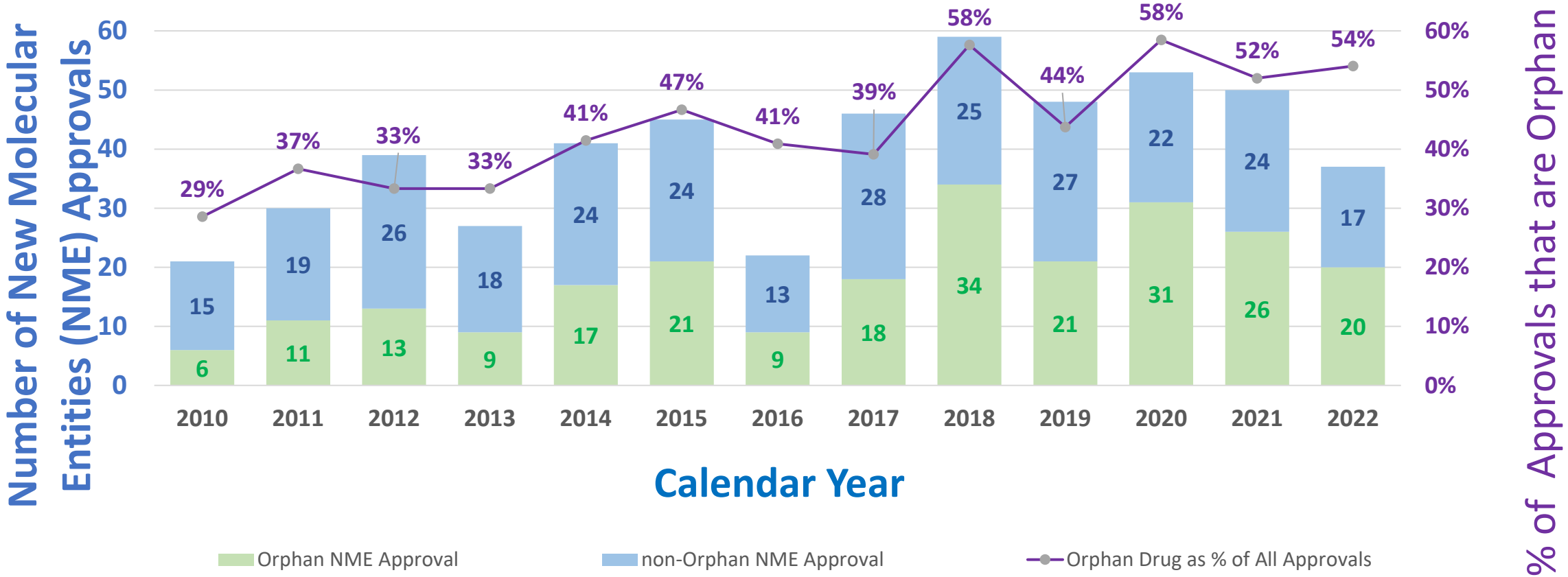
and… FDA has approved over 550 unique drugs and biologics for over 1,100 rare disease indications since the passage of the Orphan Drug Act (1983).

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	• 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**

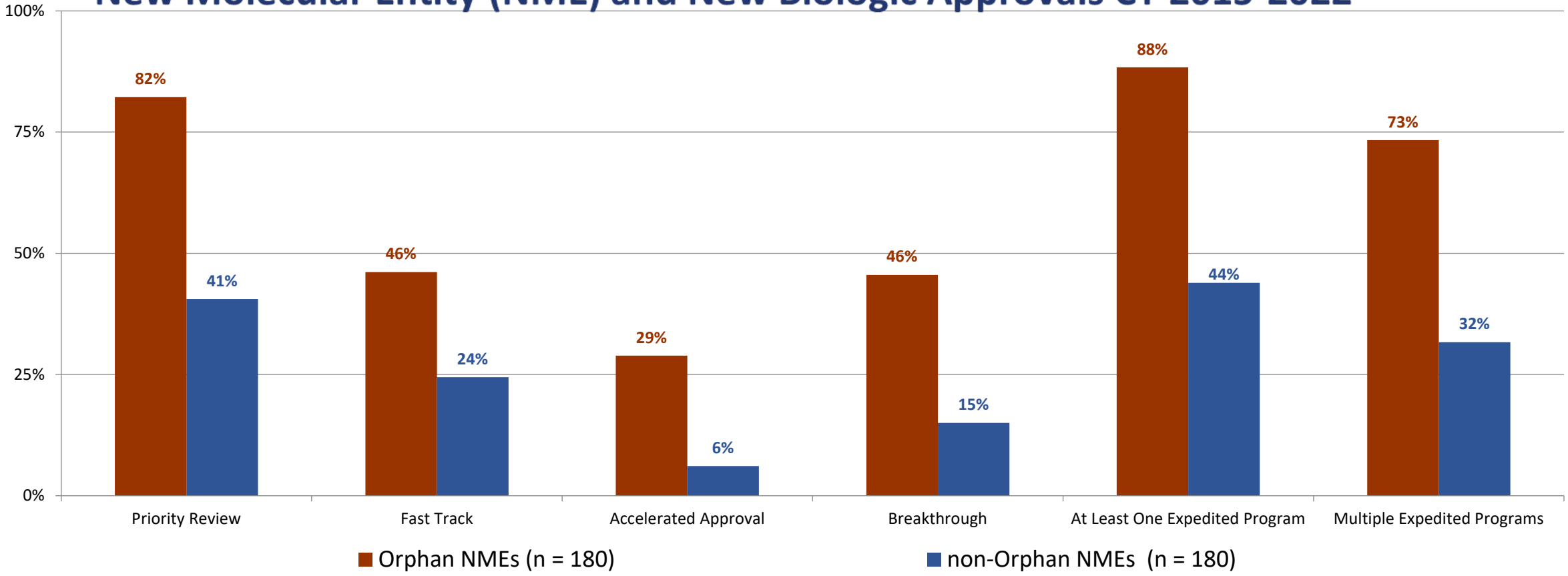
FDA's Expedited Programs (cont.)

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/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

CDER Use of Expedited Development Programs

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



[Final Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics 2014]

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

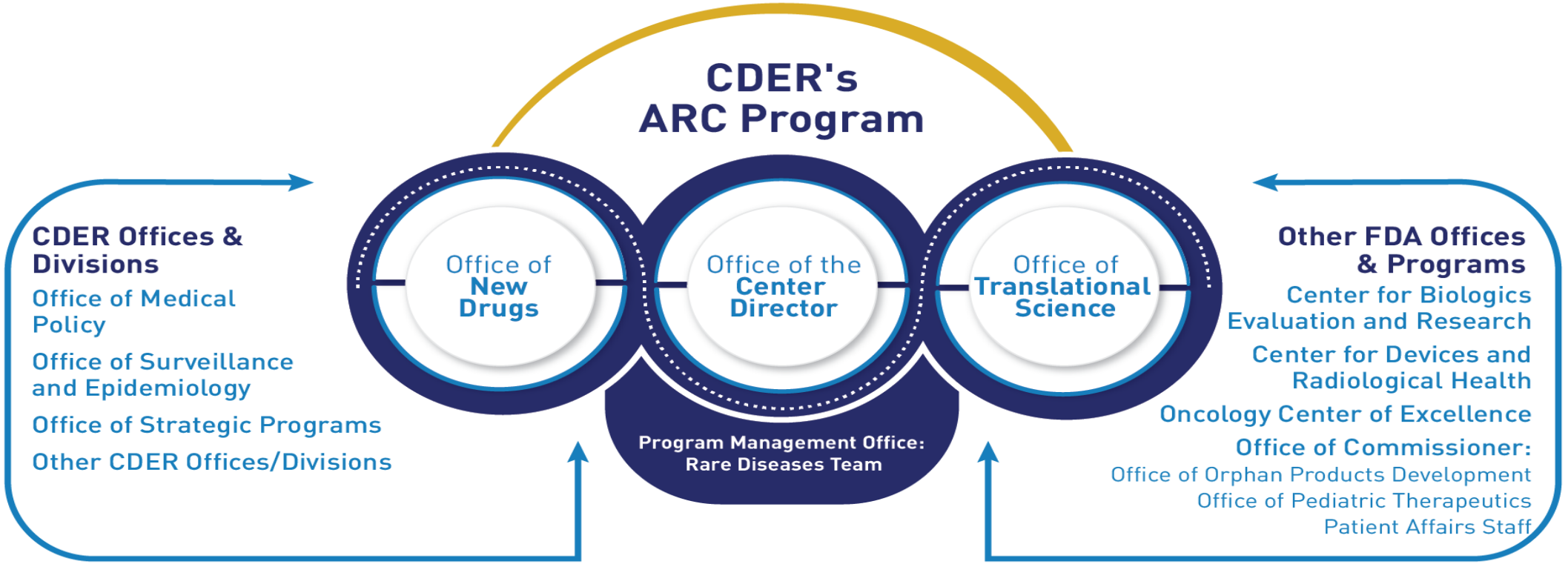
- Vision

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



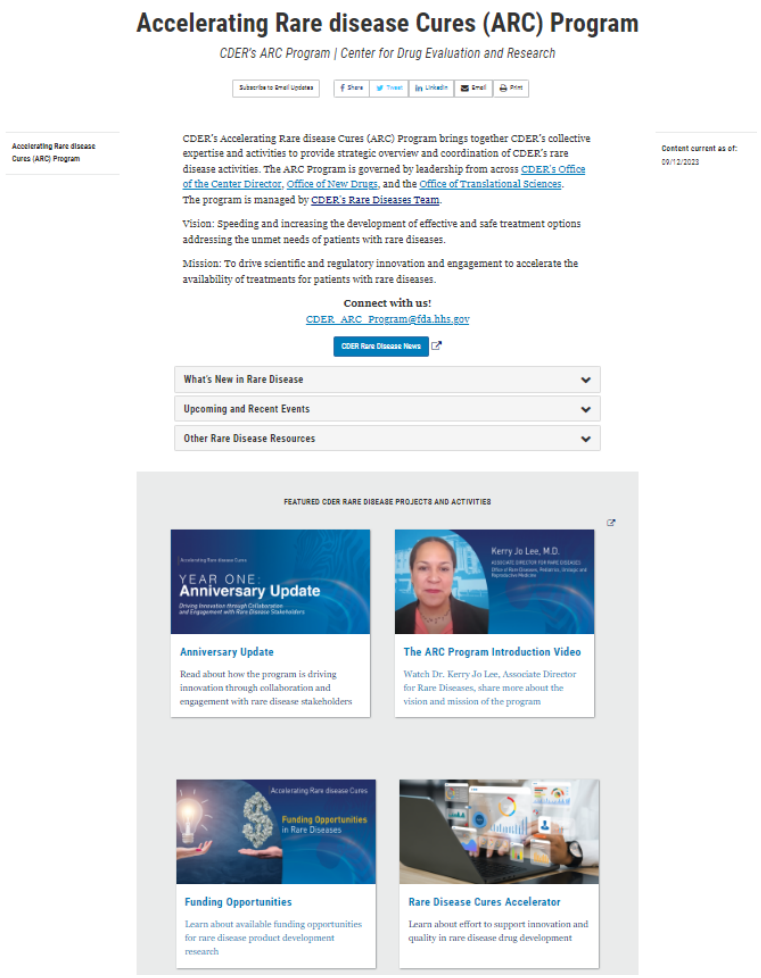
CDER_ARC_Program@fda.hhs.gov

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

Resources for Rare Disease Drug Developers

ARC Website

- 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



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.

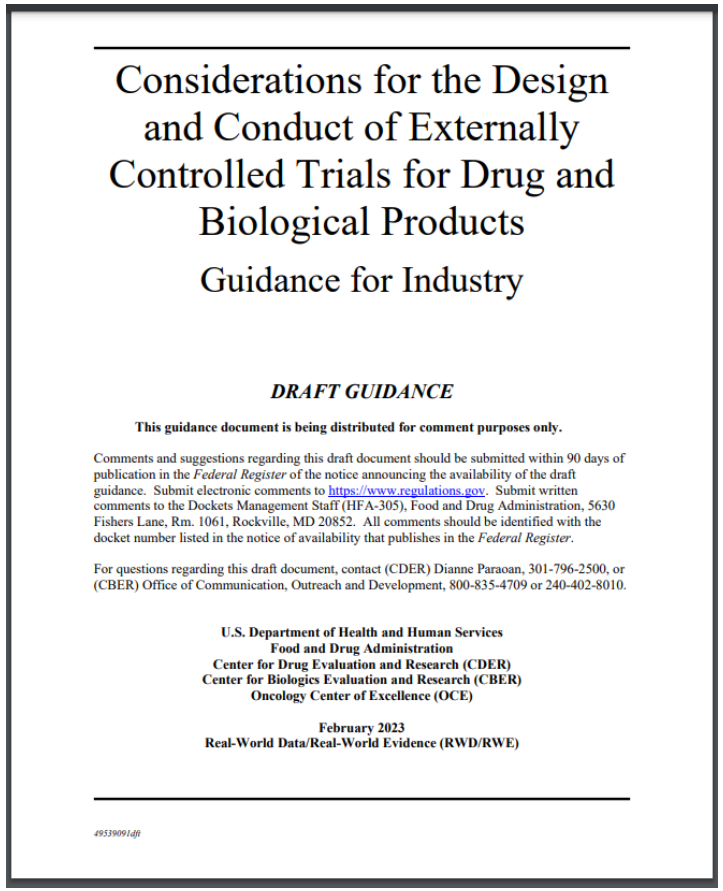
You can search all FDA Guidances by topic, FDA Center, or issue date here.

- 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

Recently Issued Guidances



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.

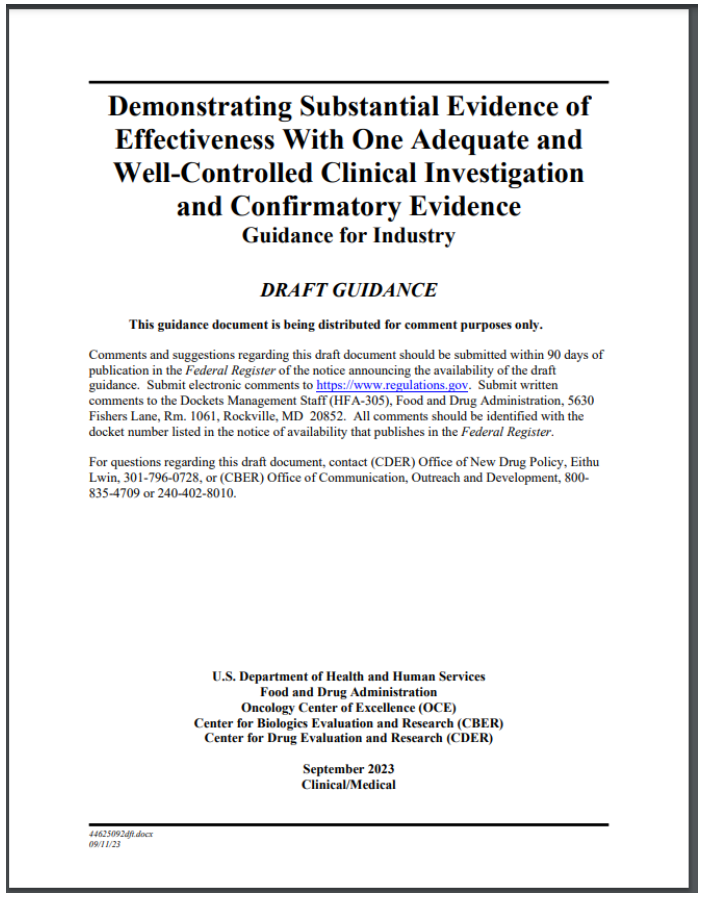
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management 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



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

Guidance for Industry

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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

Funding Opportunities

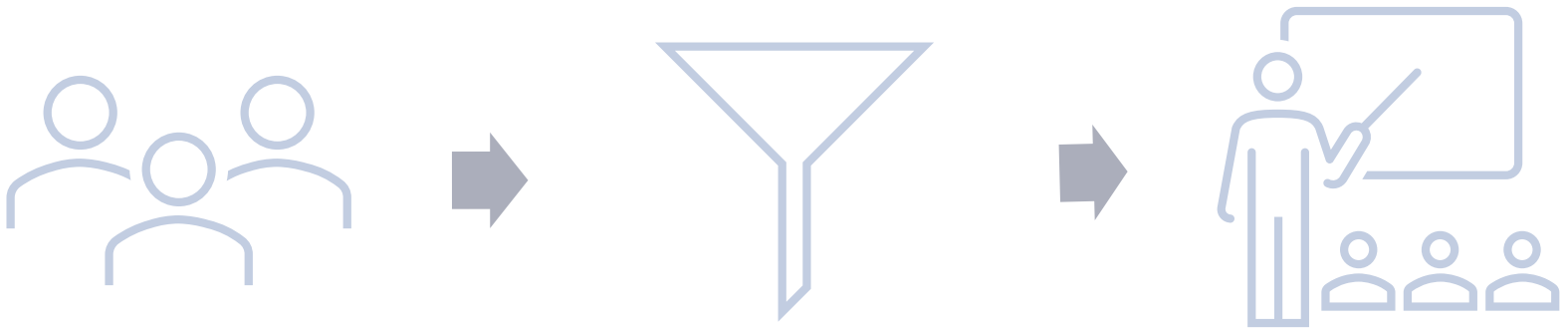
- The ARC webpage lists funding opportunities for rare disease product development research

ARC YEAR 1: ARC's Quarterly Newsletter

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

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

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

https://www.fda.gov/drugs/news-events-human-drugs/fda-cder-and-cber-duke-margolis-center-health-policy-rare-disease-endpoint-advancement-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)**

FDA Launches Pilot Program to Help Further Accelerate Development of Rare Disease Therapies | FDA
Federal Register Notice about the START Pilot Program

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