Considerations in Rare Disease Drug Development and How CDER is Accelerating Rare Disease Treatments

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Office of New Drugs (OND) | Center for Drug Evaluation and Research (CDER) | FDA

May 2023

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

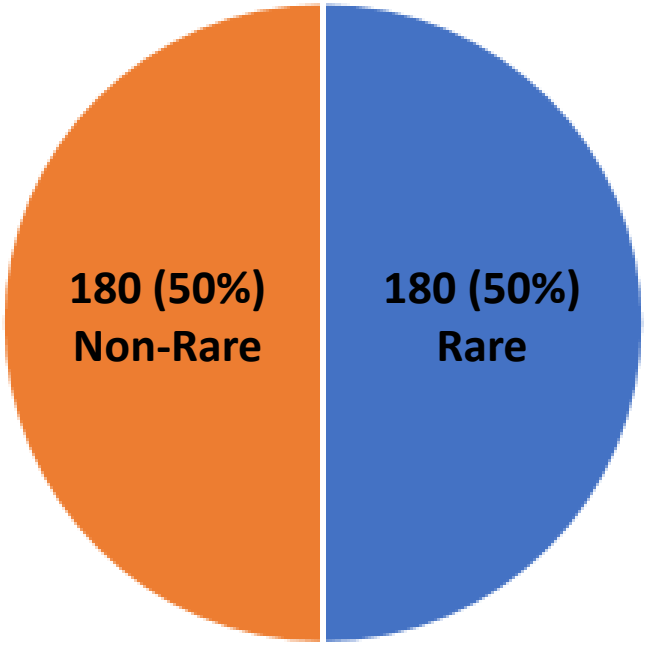
Agenda

- Overview of Progress in Rare Disease Drug Development
- Challenges and Considerations in Rare Disease Drug Development
- Collaborations are Key in Rare Disease Drug Development:
  CDER's Accelerating Rare disease Cures Program and Rare Disease Initiatives

OVERVIEW OF PROGRESS IN RARE DISEASE DRUG DEVELOPMENT

Rare Disease Progress

Total CDER Novel Drug Approvals 2015-2022



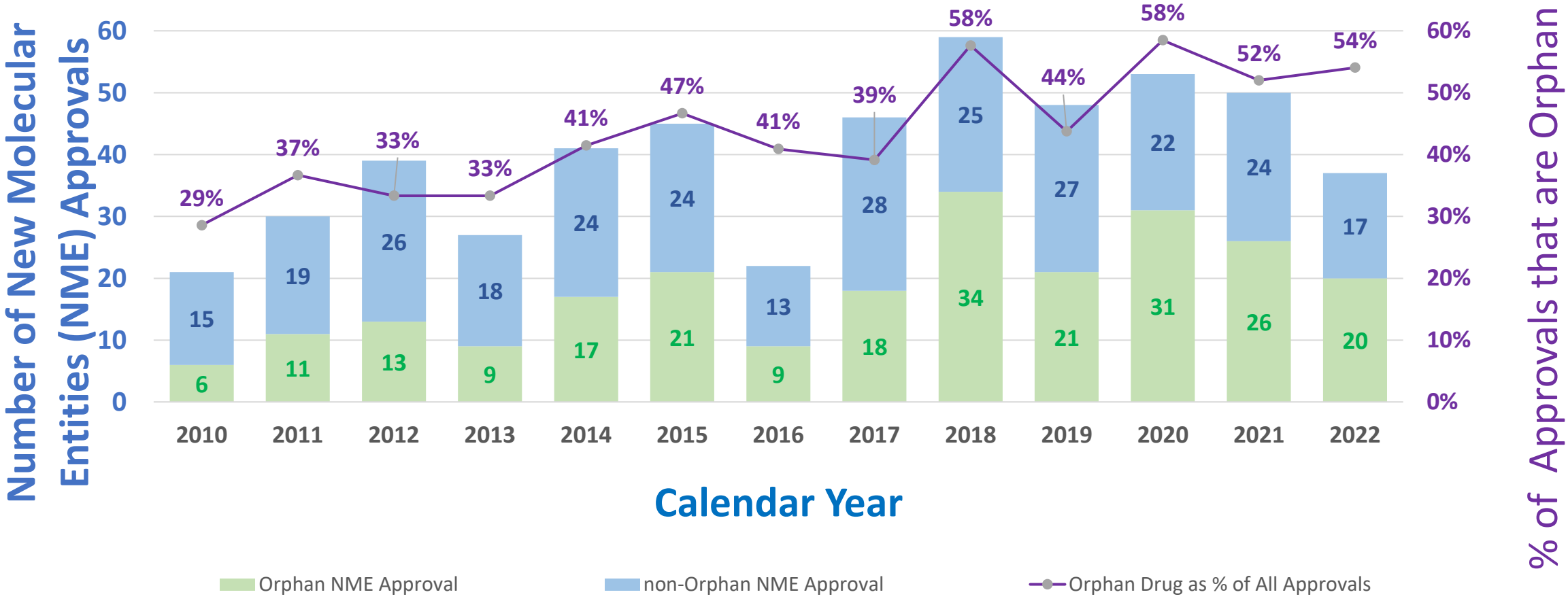
and… FDA has approved over 550 unique drugs and biologics for over 1,100 rare disease indications since the passage of the Orphan Drug Act (1983)

but… ~30 million Americans live with a rare disease

Vast majority do not have approved treatments

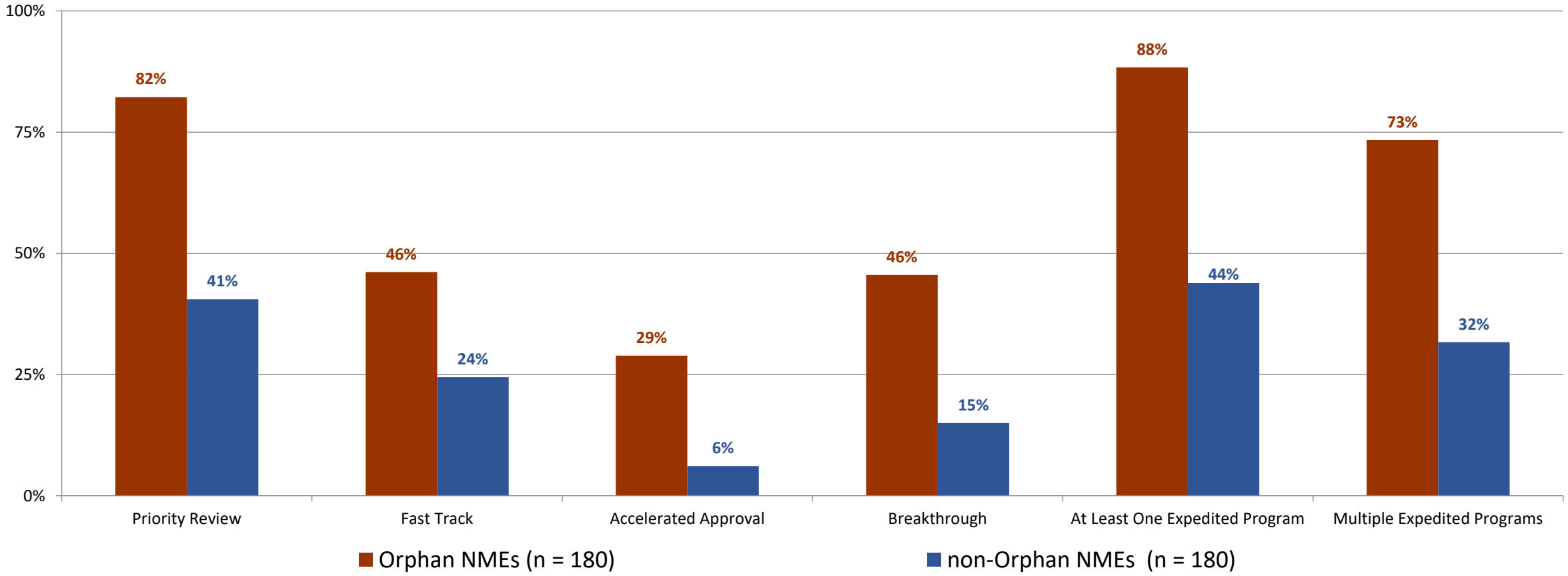
https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
https://www.fda.gov/drugs/news-events-human-drugs/cder-continues-advance-rare-disease-drug-development-new-efforts-including-accelerating-rare-disease
https://www.fda.gov/news-events/fda-voices/fda-continues-important-work-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



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]

Challenges and Considerations in Rare Disease Drug Development

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

Collaborations are Key in Rare Disease Drug Development:
CDER's Accelerating Rare disease Cures (ARC) Program and Rare Disease Initiatives

Vision

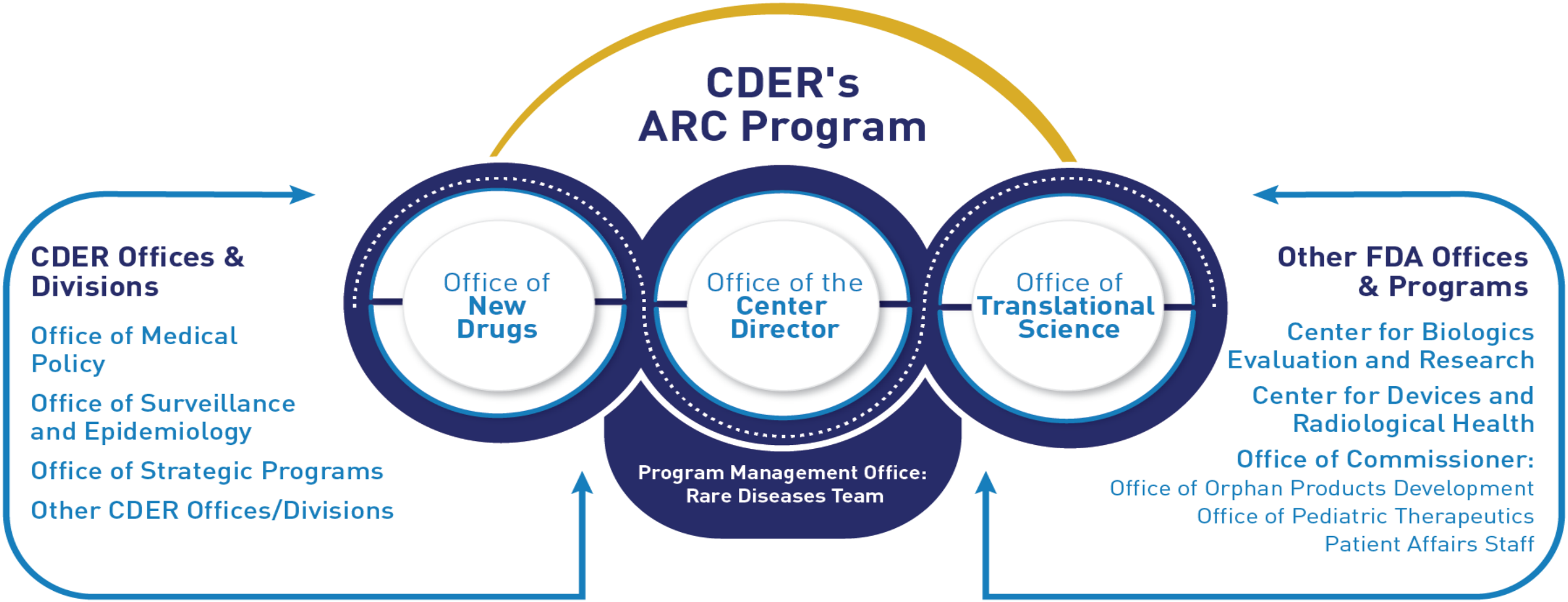
Speeding and increasing the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.

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.

https://www.fda.gov/drugs/CDERARC

CDER's Accelerating Rare disease Cures Program

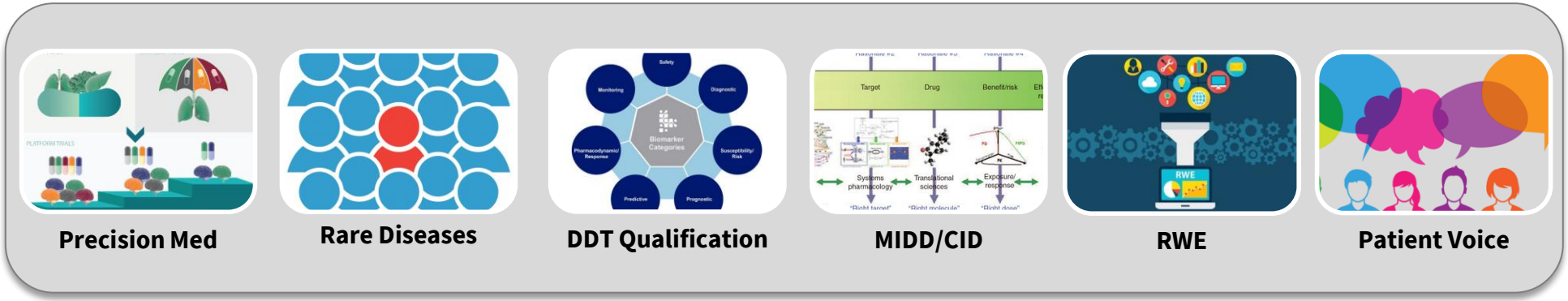


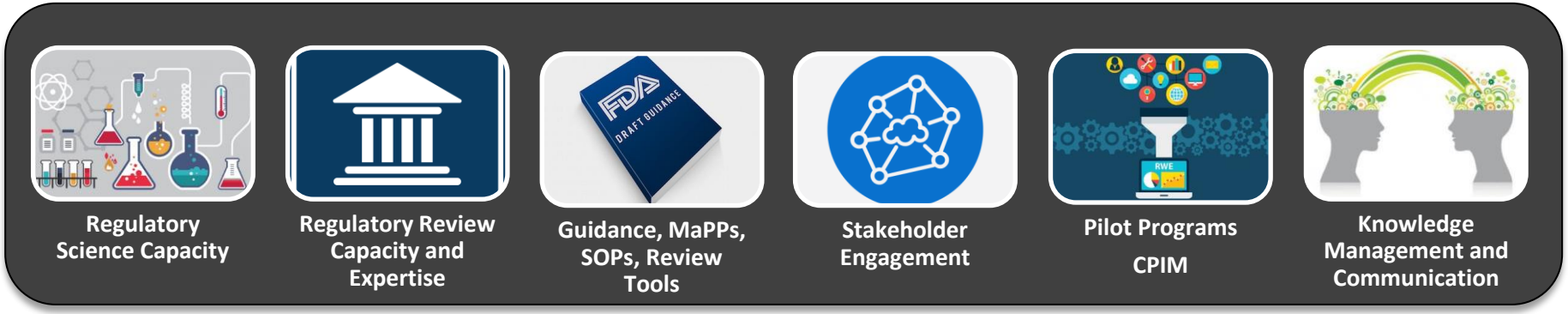
CDER_ARC_Program@fda.hhs.gov

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

Found in Translation:
The Office of Translational Science
Commitment to ARC

"So what is…'translational science'…the field of investigation which seeks to understand the **scientific and operational** principles underlying each step of the translational process." - Austin 2018





Office of Clinical Pharmacology

GOALS

Drive the development and use of regulatory and scientific tools

Platforms to facilitate natural history studies

Methodologies to construct novel endpoints

Drug/disease modeling

Dose selection

Translational medicine

Engage stakeholders

Deepen understanding of regulatory requirements

Collaborate to develop novel tools

Patient-centered engagement

REGULATORY REVIEW

- Model-informed approaches to expand access and optimize dosing
- Experimental models to characterize efficacy
- Biomarkers to provide confirmatory evidence

POLICY

- Tailoring treatment for outliers/therapeutic individualization
- Development of genetically targeted therapies for rare subsets

RESEARCH

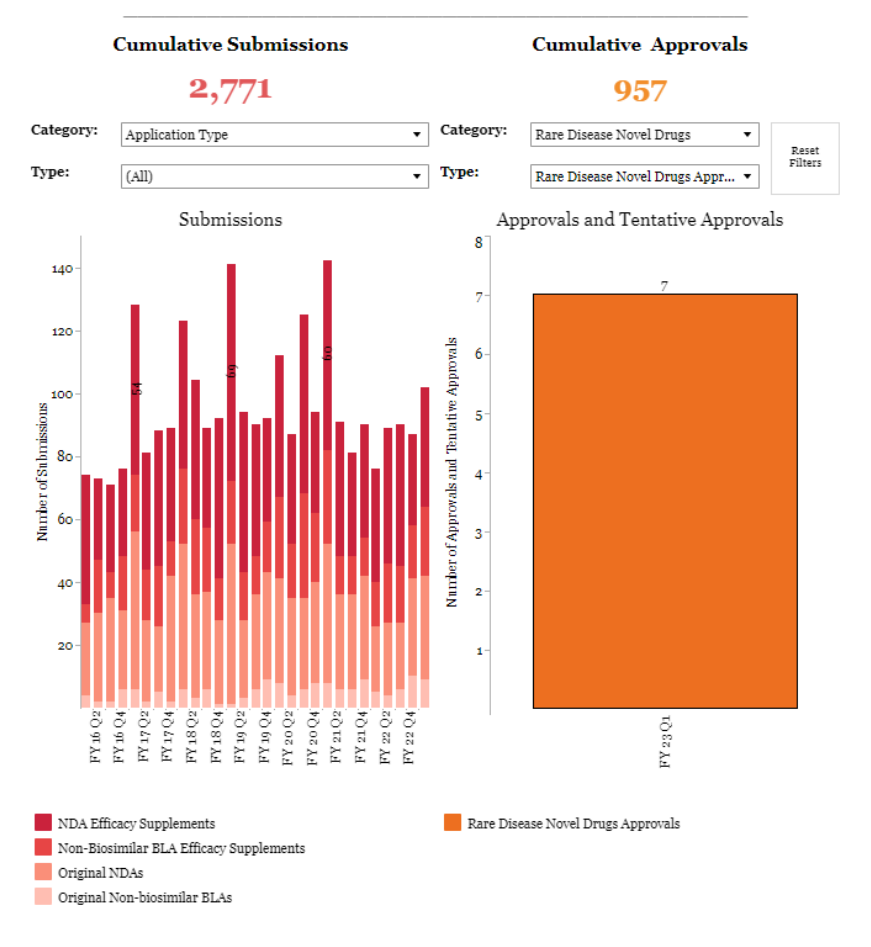
- Drug-Trial-Disease modeling
- Multi-omic biomarker approaches to support EoE and dose finding

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 (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 and Science and Office of Clinical Pharmacology
  - Focus on translational science and the development of surrogate endpoints
- FDA CDER & Johns Hopkins Center of Excellence in Regulatory Science and Innovation (CERSI) Workshop, May 2-3, 2023
  - CDER's Rare Diseases Team and Office of Biostatistics
  - 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
- 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

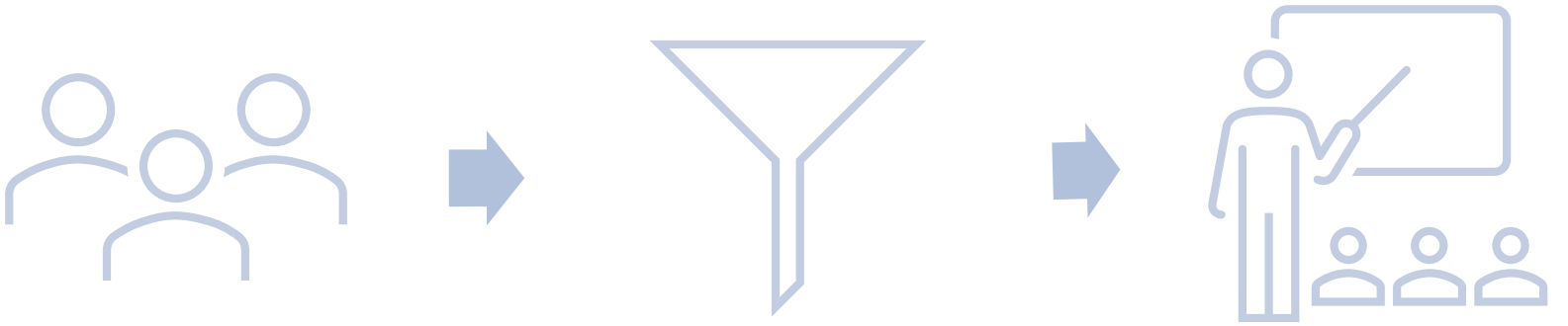
Tracking Rare Disease Approvals



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

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

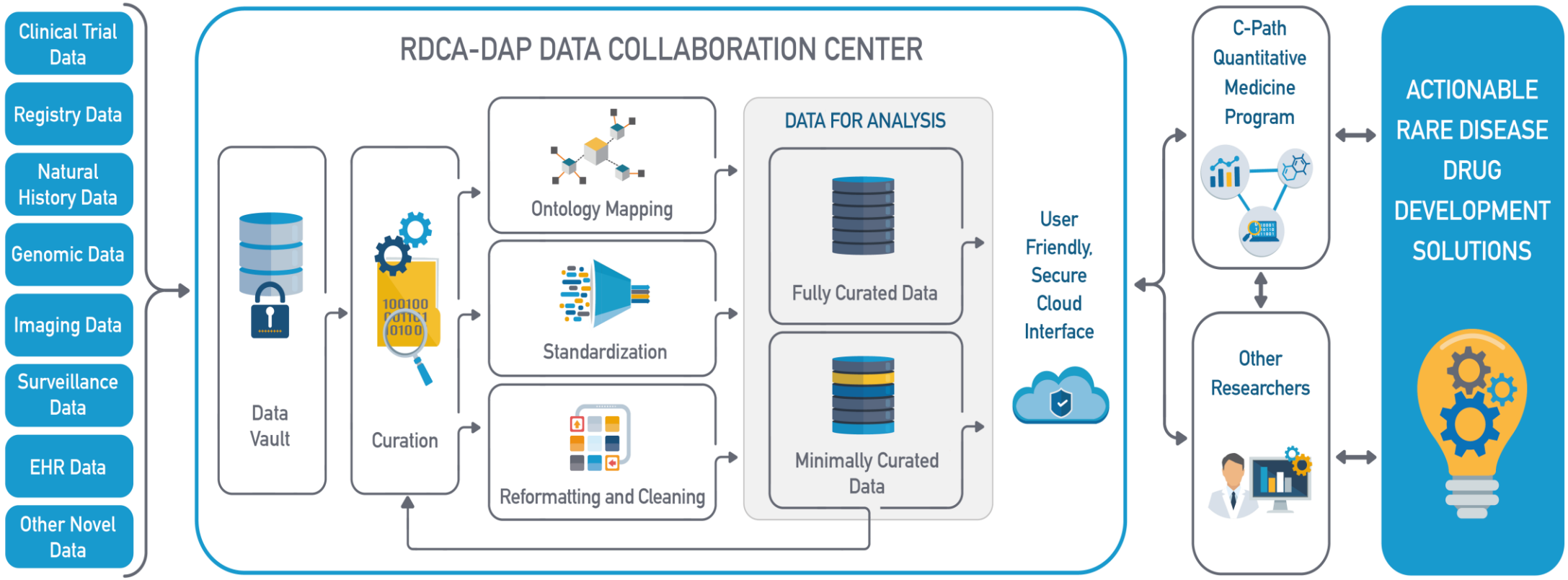
In parallel with the LEADER 3D effort, CDER is working with the National Organization for Rare Disorders to develop an advanced drug development education series for patients and patient groups.

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

CDER's ARC Quarterly Newsletter

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

Rare Disease Cures Accelerator Data and Analytics Platform



Rare Disease Cures Accelerator Data and Analytics Platform
WHY SHARE DATA

- People who take part in studies want the data used
- Industry, clinicians and academics can use data for all kinds of purposes beyond what it was originally collected for
- Combined data can be incredibly informative
- Every piece of rare disease data is valuable
- Data should be shared in a responsible way that enables it to be interpreted and used well

Focusing on Endpoints: PDUFA VII RDEA Pilot Program Overview

- **Scope**: The RDEA pilot program is a joint CDER and CBER program that 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 endpoin**t intended to establish substantial evidence of effectiveness for a rare disease treatment

PDUFA=Prescription Drug User Fee Act
https://www.fda.gov/media/151712/download

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

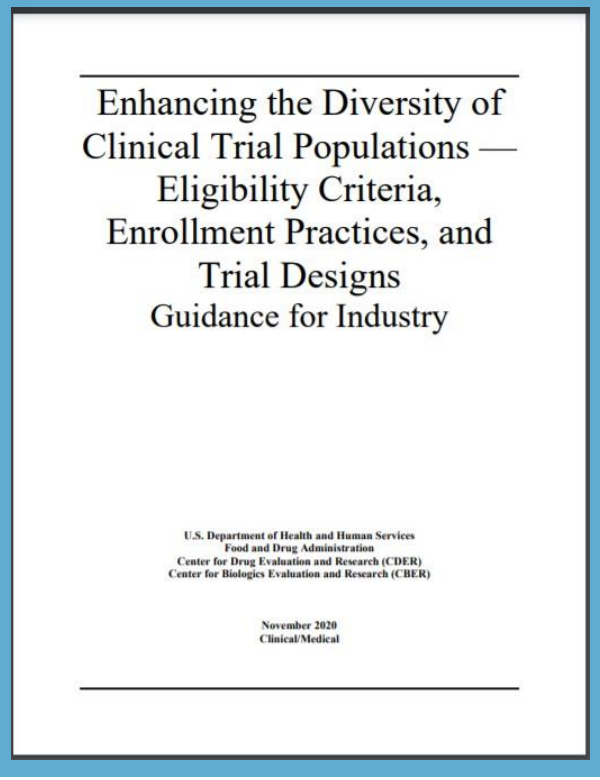
- **Transparency**:
  - FDA will conduct **up to 3 public workshops** by the end of FY 2027 to discuss various topics related to endpoint development for rare diseases
  - To promote innovation and evolving science, **novel endpoints developed through RDEA may be presented by FDA**, such as in guidance 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 -

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

Relevant Guidances for Rare Disease Drug Development

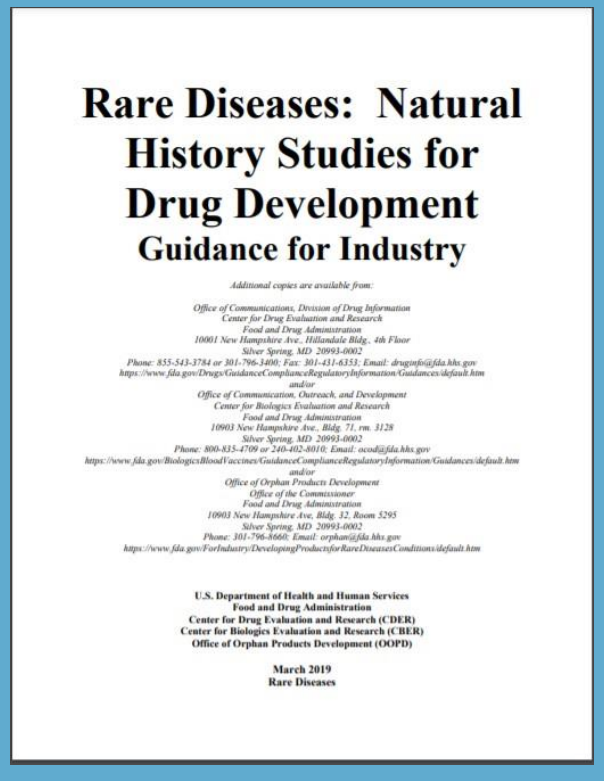


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

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

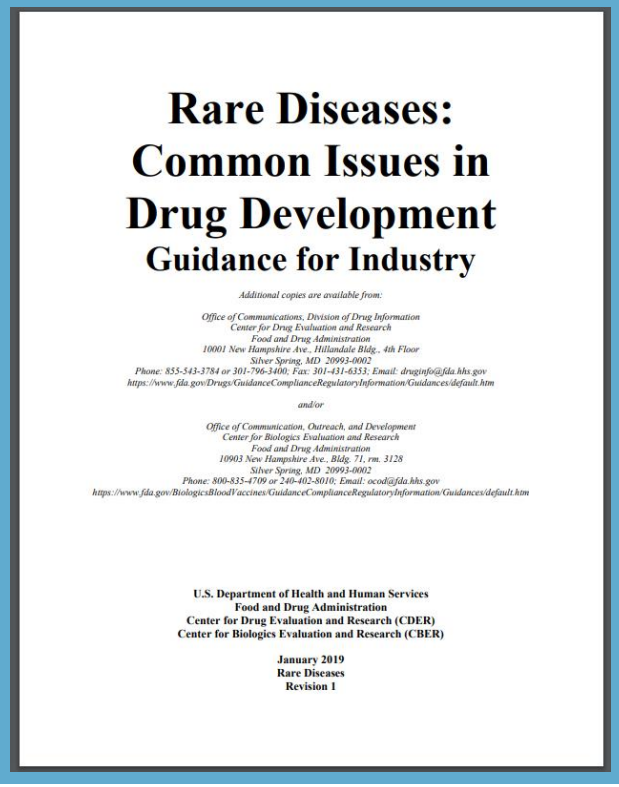
Additional copies are available from:

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
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
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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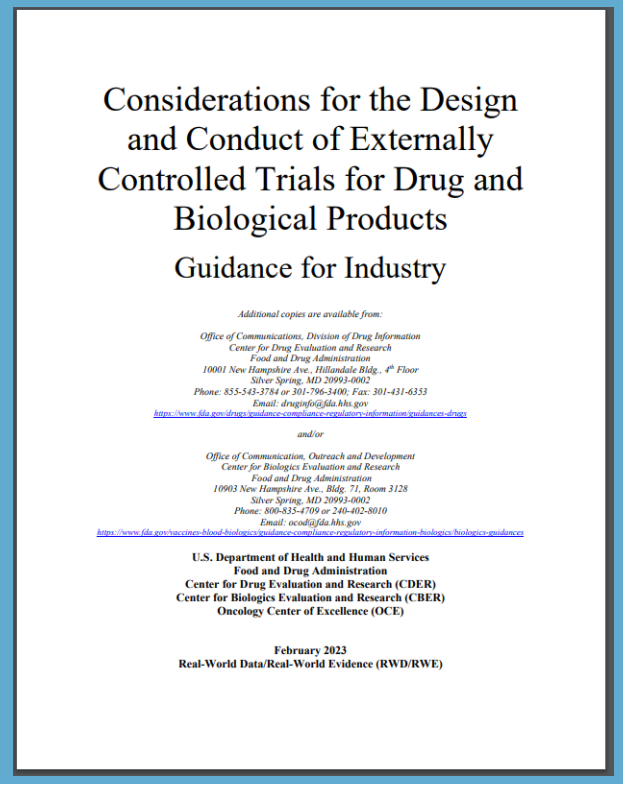
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)

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

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/guidance-compliance-regulatory-information/guidances-drugs

and/or

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Email: ocod@fda.hhs.gov
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

Recent Additional Selected Cross-Cutting Guidances

- Real-World Data: Registries
  - Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drugs and Biological Products—Draft Guidance for Industry
  - Additional FDA Real-World Data guidances and information: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

- "N of 1" Therapies
  - IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations—Draft Guidance for Sponsor-Investigators
  - IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls—Draft Guidance for Sponsor-Investigators
  - IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations—Draft Guidance for Sponsor-Investigators
  - Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases—Draft Guidance for Sponsor-Investigators

Conclusions

- Rare diseases are challenging, engage with FDA early and often
- CDER has numerous programs to facilitate rare disease drug development


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