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

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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

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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/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

Calendar Year

Number of New Molecular Entities (NME) Approvals

- Orphan NME Approval
- non-Orphan NME Approval
- Orphan Drug as % of All Approvals

% of Approvals that are Orphan
CDER Use of Expedited Development Programs
New Molecular Entity (NME) and New Biologic Approvals CY 2015-2022

- Priority Review: 82%
- Fast Track: 46%
- Accelerated Approval: 29%
- Breakthrough: 46%
- At Least One Expedited Program: 88%
- Multiple Expedited Programs: 73%

Orphan NMEs (n = 180)
- Priority Review: 41%
- Fast Track: 24%
- Accelerated Approval: 6%
- Breakthrough: 15%
- At Least One Expedited Program: 44%
- Multiple Expedited Programs: 32%

non-Orphan NMEs (n = 180)

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’s ARC Program

CDER Offices & Divisions
- Office of Medical Policy
- Office of Surveillance and Epidemiology
- Office of Strategic Programs
- Other CDER Offices/Divisions

Office of New Drugs
Office of the Center Director
Office of Translational Science

Program Management Office: Rare Diseases Team

Other FDA Offices & Programs
- Center for Biologics Evaluation and Research
- Center for Devices and Radiological Health
- Office of Commissioner: Office of Orphan Products Development
  Office of Pediatric Therapeutics
  Patient Affairs Staff

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

  - 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.

CDER’s ARC Quarterly Newsletter

• To subscribe: U.S. Food and Drug Administration (govdelivery.com)
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 endpoint 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 – FY 2027:** 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

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

Rare Diseases: Common Issues in Drug Development Guidance for Industry

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

Recent Additional Selected Cross-Cutting Guidances

- **Real-World Data: Registries**
  - Additional FDA Real-World Data guidances and information: [https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence](https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence)

- **“N of 1” Therapies**
Conclusions

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