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

June 7-8, 2023

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Overview

Mark McClellan

Director, Duke-Margolis Center for Health Policy

Remote Participation Instructions

Mute & Slides

- **You have been placed on mute**; speakers can mute/unmute throughout

Questions

- Please feel free to type your question into the Q&A box and we will use your questions to inform the open discussion portion of the event

Submitting Written Comments

- Reminder - stakeholders may submit written comments regarding this event to regulations.gov until July 23, 2023.

Zoom Issues? Please Zoom message Rasheed Willis or email rwillis@newmediamill.com

Day 2 Meeting Agenda

1:00 pm	Welcome and Overview
1:10 pm	Session 5: RDEA Pilot Program Overview
1:40 pm	Session 6: RDEA Pilot Program – Process Overview
2:10 pm	Session 7: Elements of RDEA Proposals and Meetings
2:40 pm	Session 8: RDEA Pilot Program Q&A
3:05 pm	Break
3:20 pm	Session 9: Experiences and Lessons Learned from Other Meeting Pilot Programs
4:00 pm	Session 10: Public Comments
4:25 pm	Closing Remarks and Adjournment

All times listed in ET

Session 5: RDEA Pilot Program Overview

1:10 – 1:40 pm ET

U.S. FOOD & DRUG ADMINISTRATION

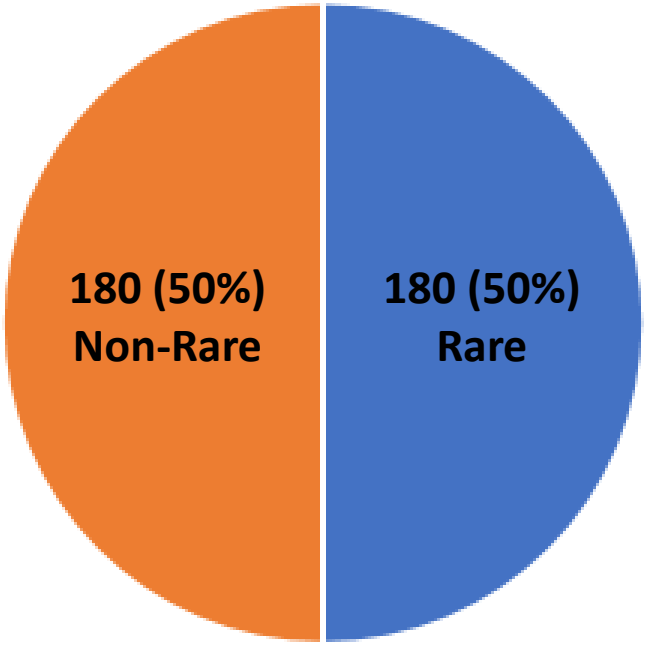
Rare Disease Endpoint Advancement Pilot Program Overview

CDER Perspective

Kerry Jo Lee, M.D.
Associate Director for Rare Diseases
Rare Diseases Team
Division of Rare Diseases and Medical Genetics
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicines
Office of New Drugs (OND) | Center for Drug Evaluation and Research (CDER) | FDA

Rare Disease Progress

Total CDER Novel Drug Approvals 2015-2022



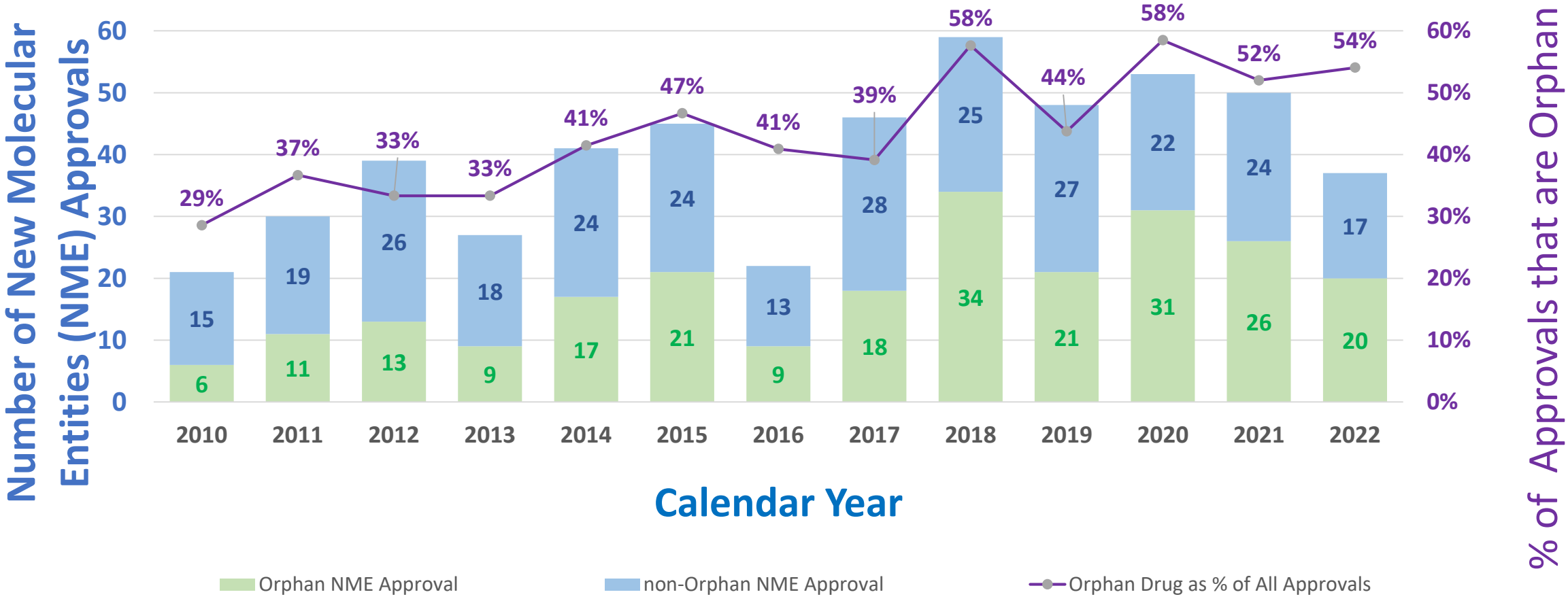
and… FDA has approved over 550 unique drugs and biologics for over 1,100 rare disease indications since the passage of the Orphan Drug Act (1983)

but… ~30 million Americans live with a rare disease

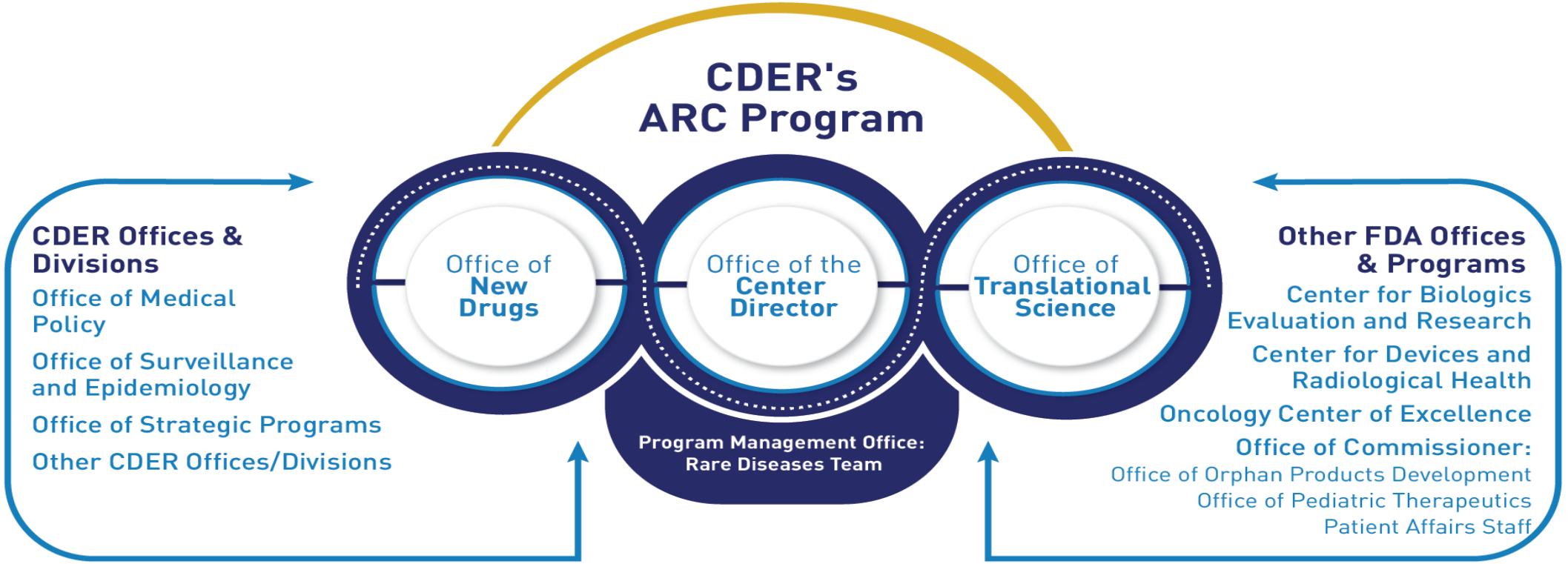
Vast majority do not have approved treatments

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's Accelerating Rare disease Cures Program



CDER_ARC_Program@fda.hhs.gov

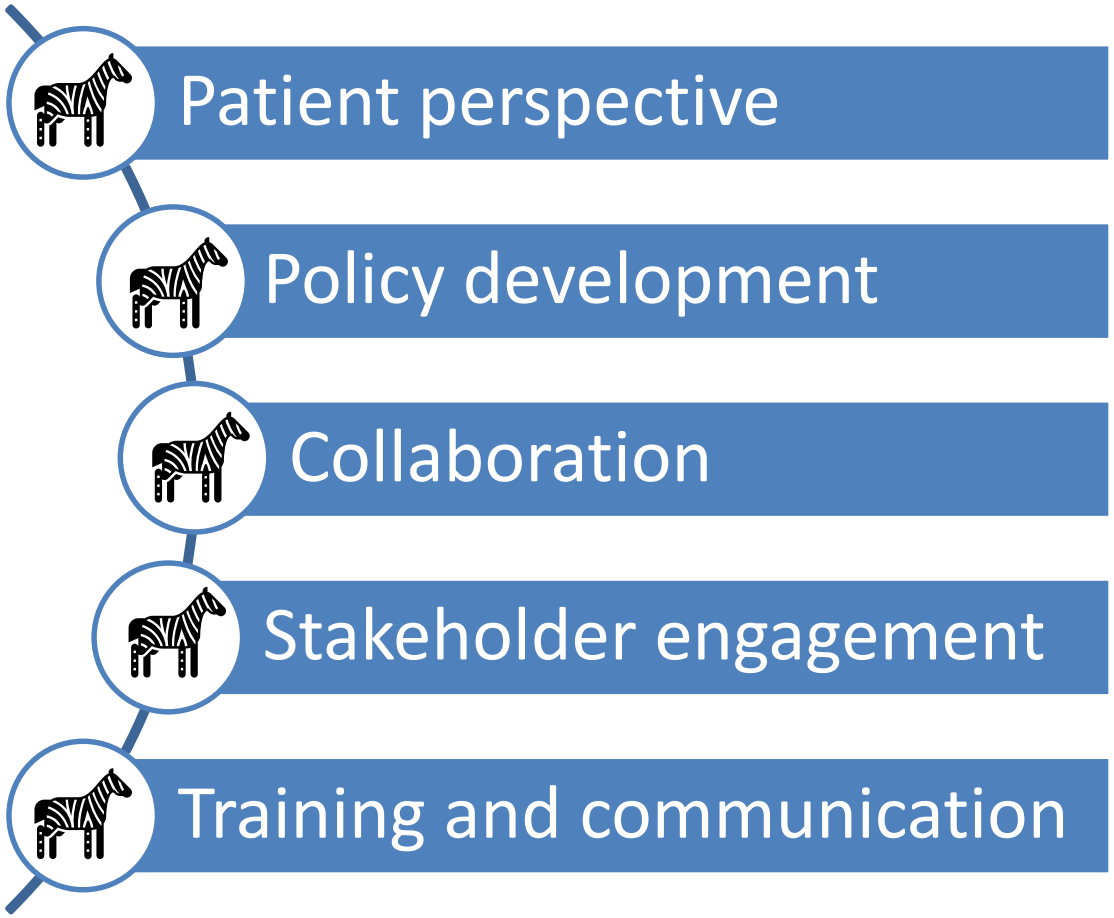
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-arc-program

RDEA Pilot Program Overview: CBER Perspective

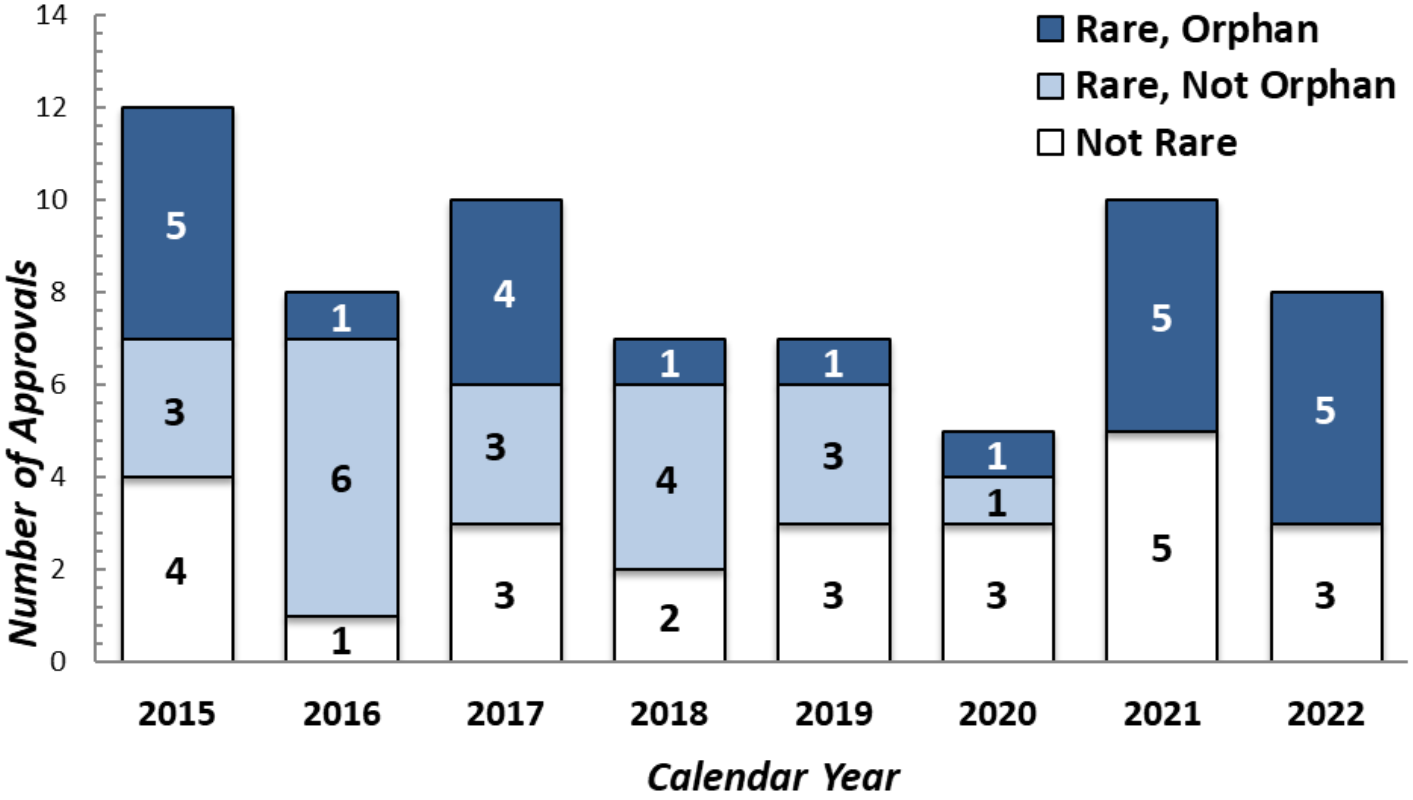
Julienne Vaillancourt, RPh, MPH
Policy Advisor and Rare Disease Liaison
Policy Staff, Office of the Director
Center for Biologics Evaluation and Research

CBER Rare Disease Program

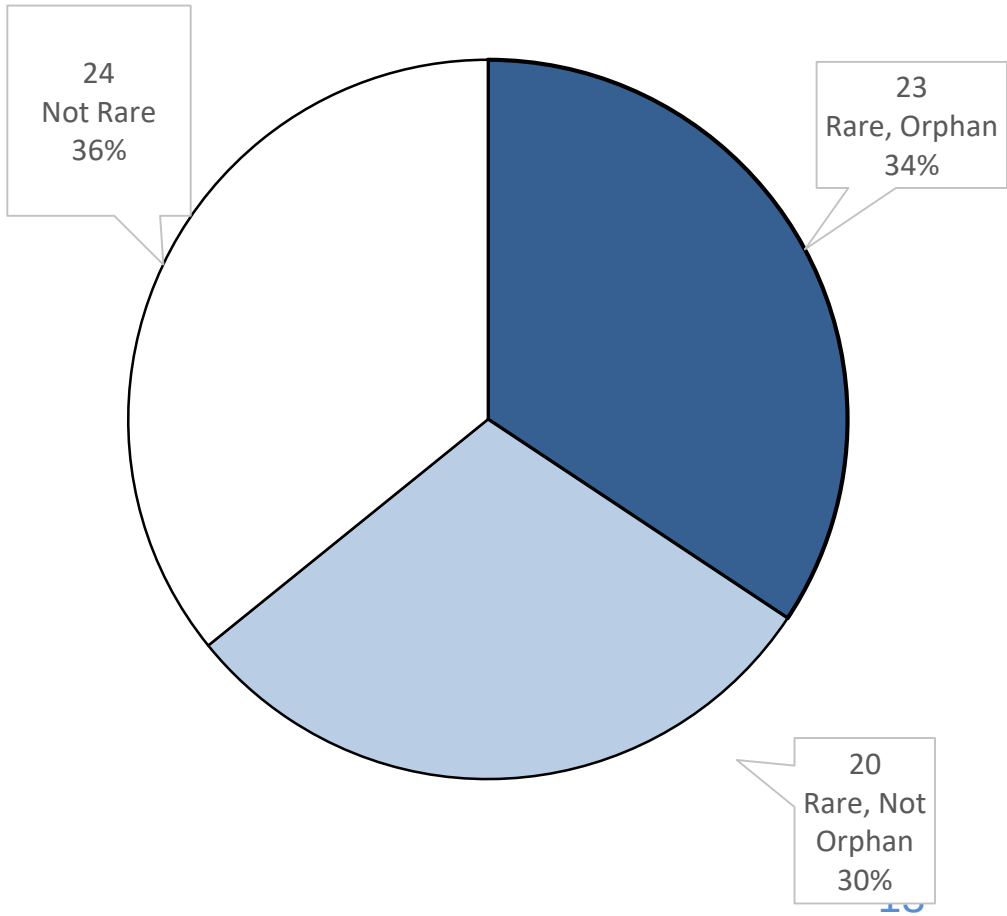
CBER is committed to facilitating and advancing the development and timely approval of safe and effective biologics to improve the lives of children and adults with rare diseases



CBER Novel Biologic Approvals for Use in Rare Diseases 2015-2022

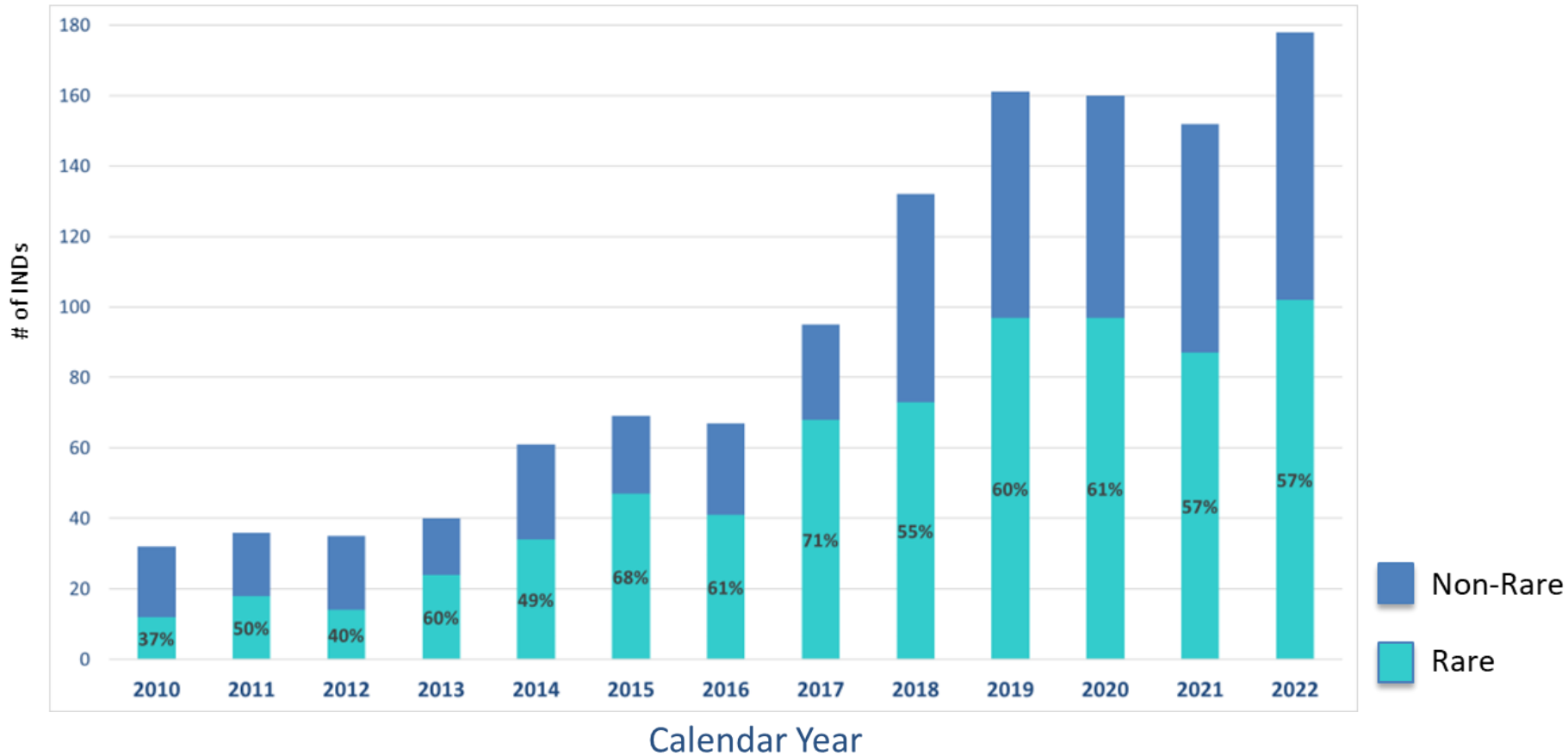


67 Approvals



*Excludes in vitro diagnostic products, reagents and intermediate biological products approved for further manufacture, such as source plasma.

Submitted INDs for Gene Therapy Development Programs for Rare Diseases 2010-2022



Rare Disease Endpoint Advancement Pilot Program

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

Goals of the RDEA Pilot Program

The RDEA Pilot Program is designed to:

- Seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process.
- Promote innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and a public-facing website.
- Develop FDA staff capacity to enable and facilitate the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

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 Proposal Eligibility Criteria

- Sponsor has an active pre-IND or IND for a rare disease
  - Exceptions
    - Sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied are also eligible.
    - The FDA may also consider accepting a proposal for a development program for a common disease that includes innovative or novel endpoint elements, including the specific endpoint and/or the methodology being developed, if there is sufficient justification that the proposal could be applicable to a rare disease
- The proposed endpoint is a novel efficacy endpoint intended to establish substantial evidence of effectiveness for a rare disease treatment.
  - An endpoint is considered novel if it has never been used to support drug approval or if it has been substantially modified from previous use to support drug approval

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session 6: RDEA Pilot Program – Process Overview

1:40 – 2:10 pm ET

RDEA Pilot Program Process Overview

Mary Jo Salerno, MS PT, MPH

Science Policy Analyst | Rare Diseases Team

Division of Rare Diseases and Medical Genetics

Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicines

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

Julienne Vaillancourt, RPh, MPH

Policy Advisor and Rare Disease Liaison

Policy Staff, Office of the Director

Center for Biologics Evaluation and Research

Session Contents

- The RDEA Proposal
- RDEA Process and Timelines
- FDA Processing of RDEA Proposal
- Meeting Process

THE RDEA PROPOSAL

The RDEA Proposal

- Due Dates
- Number of proposals to be admitted into program
- Who can submit an RDEA proposal
- Eligibility Criteria
- RDEA proposal elements will be discussed in detail in session 7.
- How to submit the proposal

RDEA Proposal Due Dates

- Quarterly RDEA Proposal Submission Deadlines:
  - March 31
  - June 30
  - September 30
  - December 31

- Sponsors may submit RDEA program proposals beginning July 1, 2023, through June 30, 2027 (FDA will not receive proposals in Q4FY2027)
- FDA will select a limited number of qualified proposals:

  - *FY 2023*: Sponsors may submit proposals beginning in Q4, and FDA will accept a maximum of one proposal
  - *FY 2024 – FY2027*: FDA will accept up to one proposal per quarter with a maximum of three proposals per year

RDEA Eligibility Criteria

- An RDEA proposal must meet the program eligibility criteria as stated on the RDEA Program webpage and in the October 27, 2022, Federal Register notice announcing the program.

Different Types of RDEA Proposals

- FDA will consider three different types of RDEA proposals for admission into the RDEA pilot program:
  - a proposed rare disease novel endpoint for a sponsor with an active IND or pre-IND.
  - a rare disease natural history study where a proposed novel endpoint is intended to be studied (not associated with a specific drug development program; need to request a pre-IND application number)
  - a development program (with an active IND or pre-IND) for a common disease that includes innovative or novel endpoint elements, including the specific endpoint and/or the methodology being developed, if there is sufficient justification that the proposal could be applicable to a rare disease.

- An endpoint is considered novel if it has never been used to support drug approval or if it has been substantially modified from previous use to support drug approval

Who Can Submit an RDEA Proposal?

For the purposes of the RDEA Pilot Program, consistent with 21 CFR 312.3, a sponsor is a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. Therefore, various types of sponsors can apply to participate in the pilot.

One IND or Multiple INDs?

Q: Can multiple INDs be referenced in an RDEA proposal to explicitly demonstrate and discuss the applicability of an approach across therapeutic areas?

A: To be considered for admission to the RDEA Pilot Program, an RDEA proposal must meet program eligibility criteria, including, generally, that the sponsor has an active pre-IND or IND for a rare disease. While it is possible that an RDEA proposal for a specific development program may have application to another development program, sponsors should reference one IND under which the proposed novel endpoint would be developed, and clearly explain how development of the novel endpoint would be applicable to other INDs.

How to Submit the Proposal

- If you have an active Pre-IND or IND, submit your RDEA Pilot Program proposal to that application.
- If you do not have an active Pre-IND or IND, request a pre-assigned number for your RDEA Pilot Program proposal and then submit the proposal to your newly created Pre-IND application.
- Instructions for electronic submission are available at Electronic Regulatory Submission and Review
- RDEA proposals for natural history studies may be submitted to CDER or CBER at the sponsor's discretion.

Requesting a Pre-assigned Application Number

- Additional information for requesting a pre-assigned number for CBER is available in CBER SoPP 8117

- Additional information for requesting a pre-assigned number for CDER is available at Requesting a Pre-Assigned Application number

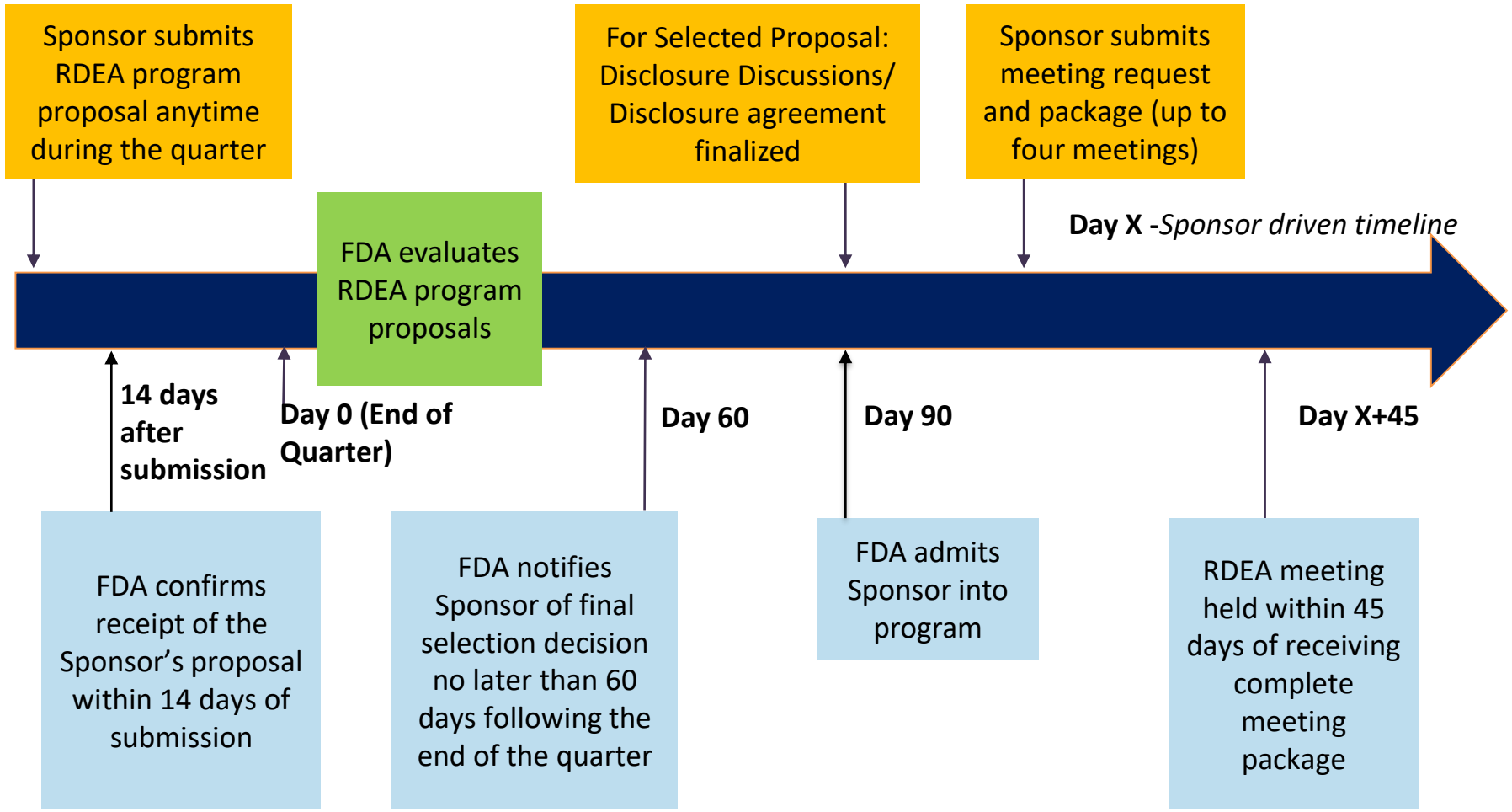
Important Additional Information

- All RDEA Pilot Program submissions should have “RDEA Pilot Program Submission” in the submission header.
- Please send an email to RDEA.Meetings@fda.hhs.gov providing notification that your RDEA Pilot Program proposal has been submitted to the relevant application.

I submitted an RDEA proposal. What happens next?

RDEA PROCESS AND TIMELINES

RDEA Process and Timeline



*Timeline subject to change

FDA PROCESSING OF RDEA PROPOSAL

FDA Processing of RDEA Proposal

- Acknowledgement Letter within 14 days of FDA receipt of proposal
- Eligibility and completeness review
- Internal Selection Process
  - RDEA team members will work in collaboration with the CDER or CBER review division
  - Multidisciplinary reviewers as needed to evaluate the proposal
    - Clinical
    - Statistics
    - Regulatory Project Management
    - As relevant to RDEA proposal:
      - Clinical Outcome Assessments (Psychometrician)
      - Clinical Pharmacology
      - Biomarker Assessment
      - Digital Health Tools
      - Real World Evidence
      - Others if needed
- 60 day notification

*For RDEA proposals with natural history studies studying a proposed endpoint, CDER and CBER will be both involved and will consult each other as needed.

RDEA Proposal Selection

- Given that FDA expects to admit a limited number of RDEA proposals into the pilot program, the agency will give preference to proposals that:
  - Have the potential to impact drug development more broadly, such as one that uses a novel approach to develop an efficacy endpoint or an endpoint that could potentially be relevant to other diseases.
  - Reflect/impact a range of different types of endpoints.
  - For surrogate endpoints, those that use novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints. (If the sponsor is proposing to develop a surrogate endpoint as part of a rare disease application, participation in a prior Type C Surrogate Endpoint meeting is encouraged.)

60 Day Notification to Sponsor

- A PDUFA VII commitment
- 60 days after the end of the quarter in which the RDEA proposal was submitted
- Types of Notification
  - Proceeding to Disclosure Discussions
  - Alternate – Proceeding to Disclosure Discussions
  - RDEA Proposal Denied

Disclosure Agreement

- Required by PDUFA VII to participate in RDEA Pilot Program
- Why a disclosure agreement?
- Process Overview
  - FDA and Sponsor will discuss disclosure elements and come to an agreement
  - Sponsor will submit signed disclosure agreement to FDA
  - Disclosure process will be discussed in more detail in session 8.

Admission to the RDEA Pilot Program

- FDA will notify sponsor of their admission to the RDEA Pilot Program in writing.
- Sponsors admitted to the RDEA pilot may participate in up to four focused meetings with relevant FDA staff to discuss endpoint development.
- Sponsors whose RDEA proposals are admitted into the RDEA pilot program will have the opportunity to interact with interdisciplinary FDA experts in endpoint development as well as the associated review division. The types of interdisciplinary experts will depend on the nature of the proposed novel endpoint.

Will FDA publicly disclose that a sponsor has been admitted to the RDEA Pilot Program?

No. If the sponsor chooses to publicly disclose that it has been admitted into the RDEA Pilot Program, FDA may reference the sponsor as a participant in discussions about the RDEA Pilot Program. FDA will share the overall number of RDEA Pilot Program proposals submitted and the number of proposals the agency selected for admission into the pilot program.

RDEA MEETING PROCESS

The RDEA Meeting Request

- Submit an RDEA meeting request to schedule an RDEA meeting
- Include the RDEA meeting package in the RDEA meeting request
- RDEA meeting package elements will be discussed in detail in session 7.

FDA Processing of the RDEA Meeting Request

- Completeness review
  - Will send formal notification of an incomplete meeting package if the RDEA meeting package does not include all required elements or explanation for why a required element is not included
- RDEA meeting will be scheduled within 45 days following FDA's receipt of the RDEA meeting request and a complete RDEA meeting package

RDEA Meeting

- FDA Attendees will include all FDA interdisciplinary experts appropriate for the nature of the proposed novel endpoint
- RDEA Meeting Summary will be sent after the meeting

RDEA Pilot Program Completion

- Sponsors who have completed the maximum of four RDEA meetings or do not have additional endpoint-focused questions or issues to discuss with FDA may proceed with the standard regulatory submission process. The sponsor can request additional input from FDA through other formal meeting mechanisms, such as Type B, Type C, Type C Surrogate Endpoint, or Type D meetings.
- FDA's advice provided during and between RDEA meetings does not constitute a regulatory decision and is considered non-binding. Completing the four RDEA meetings does not guarantee approval for a regulatory submission that includes efficacy endpoints discussed during RDEA meetings.

Questions

- Please enter your questions via Zoom.
- We will answer as many questions as we can during Session 8.

Thank you!


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session 7: Elements of RDEA Proposals and Meetings

2:10 – 2:40 pm ET

Elements of Proposals and Meeting Packages for RDEA Pilot Program

RDEA Pilot Program Workshop

June 8, 2023

Sepideh Haghpanah, M.D.
Team Lead
Rare Diseases Team
CDER Office of New Drugs

Objectives

- Learn about **required elements** for a complete **RDEA proposal**
- Learn about **required elements** for a complete **RDEA meeting package**
- Learn about available **resources** to assist with the development of a complete RDEA proposal and meeting package

- **Proposal Elements**
- **Meeting Package**

Proposal Elements: General Information

- Executive summary: 1 – 2 page(s)
- Overall proposal: maximum 12 pages
  - Include all required information
  - Provide additional information deemed relevant

Required Proposal Information (1)

1. Product name
2. IND or pre-IND Application Number
3. Proposed indication
4. If proposal is for a rare disease natural history study:
    - Disease being studied
    - Prior knowledge of disease epidemiology and natural history
    - The additional information the proposed natural history study will provide
    - How the design of the natural history study will support endpoint selection for future studies
    - Projected timeline to design and conduct the natural history study (if not already initiated)

Required Proposal Information (2)

5. If proposal is for a **common disease** that includes novel endpoint(s) applicable to a rare disease:
   - Justification to support that the **novel endpoint could apply to a rare disease**

6. Justification that the proposed endpoint is a **novel efficacy endpoint** intended to establish **substantial evidence of effectiveness** for a rare disease treatment

   An endpoint is considered novel if:
   - it has never been used to support drug approval, or
   - if it has been substantially modified from previously used

Required Proposal Information (3)

7. Scientific justification for why the endpoint **measures meaningful clinical benefit** in the disease/condition and **detailed description of endpoint attributes and characteristics**, to include:

- Basis of endpoint: COA, biomarker, digital-health technology, multicomponent
- Disease characteristics measured by the endpoint
- How the endpoint will be developed, verified, and validated
- How patient and caregiver input is considered
- High level description of how the endpoint measures a clinically meaningful change in the studied population

Required Proposal Information (4)

8. As applicable: Brief history of the development program, status of product development, etc.

9. Brief overview of study design, objectives, conduct, analysis methods, etc.

10. Elements of the proposed novel endpoint development and/or study design the sponsor considers **non-disclosable**, along with a rationale for exclusion

11. A list of questions for discussion with the Agency

- Proposal Elements
- **Meeting Package**

Required RDEA Meeting Package Elements

1) Product Name

2) IND or pre-IND Application Number

3) Proposed agenda and estimated time for discussion of agenda items

4) List of questions for discussion

5) If follow up meeting, summary of new information

For All Novel Endpoints (1)

1) Population in which the endpoint is being studied

2) Description of the concept of interest and context of use

3) Description of existing measures to assess the concept of interest in the context of use

4) Rationale for the selection, construction, and use of the novel endpoint:
   - natural history of disease
   - pathophysiology of the disease
   - use of novel endpoint in medical product development programs for similar diseases
   - the rationale for the selection of the assessment(s) used to develop the endpoint and a description of how the proposed endpoint measures the concept of interest

For All Novel Endpoints (2)

5) Sponsor's plan to engage with patients

6) If the novel endpoint is a type of multiple endpoint: a detailed description of each specified component and how they will be combined to construct the novel endpoint

7) Pre-specified plans to validate the novel endpoint

8) Description of study design, objectives, schema, eligibility criteria, analysis methods, etc.

9) Estimand(s) of interest in clinical trials

For All Novel Endpoints (3)

10) Real-world data sources, if applicable
    - Category (e.g., electronic health records, registries, etc.) and brief description of data sources
    - Data reliability, including data accrual and assurance processes
    - Relevance of data to the research question being addressed
    - Timing and completeness of key data elements
    - Validation efforts related to key data elements
    - Linkage to other data sources and additional data collection

11) Plans and procedures to prevent and handle missing data

12) Ethical and human subjects' protections information

For a Biomarker as a Surrogate Endpoint

Refer to BEST glossary, Biomarkers Guidances and Reference Materials, List of Qualified Biomarkers, and Surrogate Endpoint Resources for Drug and Biologic Development webpage

1) Information outlined in "Considerations for Discussion of a New Surrogate Endpoint(s) at a Type C PDUFA Meeting request"
   - the clinical outcome the surrogate endpoint (SE) is proposed to predict
   - relationship of the SE to the causal pathway(s) of the disease
   - evidence to support the relationship between the SE and the clinical outcome of interest
   - evidence that a therapeutic-induced change in the SE will be predictive of a change in the clinical outcome
   - analytical performance characteristics of the measurement tool

2) If information is not available, please describe plans to generate relevant evidence

For a Clinical Outcome Assessment (COA)

Refer to PFDD Guidance series and List of Qualified Clinical Outcome Assessments

1) Evidence to support a clear rationale that a proposed COA measure is fit-for-purpose
Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments (June 2022)

2) Evidence to support the construction and selection of a COA-based endpoint
Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making (April 2023)

- Clear description of the COA-based endpoint
- Considerations for constructing and selecting the COA-based endpoint (e.g., trial objective/hypothesis, trial duration and timing of COA assessments, etc.)

3) Description of prespecified plans to evaluate the meaningfulness of changes in the COA-based endpoint to support the treatment benefit

For Use of a Digital Health Technology (DHT) (1)

Refer to Draft FDA Guidance for Industry, Investigators, and Other Stakeholders *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2021)

1) Rationale to support that the DHT is fit-for-purpose
2) Description that DHT captures a concept that is clinically meaningful to patients
3) Description of how the endpoint using measures from a DHT relates to existing endpoints, if applicable, or how the DHT provides a new means of measuring an endpoint
4) Description of how to create and interpret the endpoint from the data collected
5) What aspect of the data collected will be used to support the endpoint

For Use of a Digital Health Technology (DHT) (2)

6) Description of the design and operation of the DHT
7) Rationale for use of a participant's own DHT or a general-purpose computing platform
8) Evidence that the physical parameter (e.g., acceleration, temperature, pressure) measured by the DHT is measured accurately and precisely over time
9) Evidence that the selected DHT appropriately assesses the clinical event or characteristic in the intended population of interest
10) Usability studies to test the ability of future trial participants to use the DHT
11) Description of plans and procedures to address and mitigate potential risks

For Multiple Endpoints (including Multi-component Endpoints) (1)

Refer to:

- Final FDA Guidance for Industry, *Multiple Endpoints in Clinical Trials* (October 2022) and
- Draft FDA Guidance for Industry, FDA Staff, and Other Stakeholders *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making* (April 2023)

1) Individual components (e.g., of composite and multi-component endpoints), including information for each component as applicable
2) Suitability of the multiple endpoints for the context of use, including clinical importance of the components
3) Aspects of the concept of interest captured by the overall endpoint and each component
4) Measurement strategy and endpoint model
5) Instructions, training

For Multiple Endpoints (including Multi-component Endpoints) (2)

6) Endpoint scoring method and relation to the concept of interest
7) Score and endpoint sensitivity to detect consequential changes within patients over time
8) Interpretation of meaningfulness of treatment benefit in the context of the product's benefits and risks
9) Limitations of interpretation
10) Relevant subgroups, as applicable
11) Validation approach

For a Natural History Study

Refer to Draft FDA Guidance for Industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019)

1) Type of proposed natural history study and rationale
2) Summary of the available literature for the natural history data relevant to the endpoint development
   - Senior author or protocol number (with hyperlink)
   - Year study completed or published (in ascending order)
   - Population size and characteristics (diagnostic criteria, age range, duration of observation, etc.)
   - Key study design elements (e.g., cross-sectional, retrospective, prospective)
   - Summary measure
3) The additional information the proposed natural history study will provide
4) Current care options for disease (regionally and globally)

Summary

- **Required elements** for a complete **RDEA proposal**
  - General requirements for all proposals
  - Specific requirements, e.g., for natural history studies
- **Required elements** for a complete **RDEA meeting package**
  - General requirements for all meeting packages and all endpoints
  - Specific requirements, e.g., for each type of endpoint
- Available **resources** to assist with the development of a complete RDEA proposal and meeting package

Thank you!


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session 8: RDEA Pilot Program Q&A

2:40 – 3:05 pm ET

Session 8: RDEA Pilot Program Q&A

Moderator:

- **Nancy Allen Lapointe,** Duke-Margolis Center for Health Policy

Panelists:

- **Sepideh Haghpanah,** U.S. Food and Drug Administration
- **Stefanie Kraus,** U.S. Food and Drug Administration
- **Kerry Jo Lee,** U.S. Food and Drug Administration
- **Mary Jo Salerno,** U.S. Food and Drug Administration
- **Julienne Vaillancourt,** U.S. Food and Drug Administration

Break

3:05 pm – 3:20 pm ET

Reminder - stakeholders may submit written comments regarding this event to regulations.gov until July 23, 2023.

For further information on submitting comments for the workshop, please visit: https://www.federalregister.gov/documents/2023/04/17/2023-08066/rare-disease-endpoint-advancement-pilot-program-workshop-novel-endpoints-for-rare-disease-drug

Session 9: Experiences and Lessons Learned from Other Meeting Pilot Programs

3:20 – 4:00 pm ET

U.S. FOOD & DRUG ADMINISTRATION

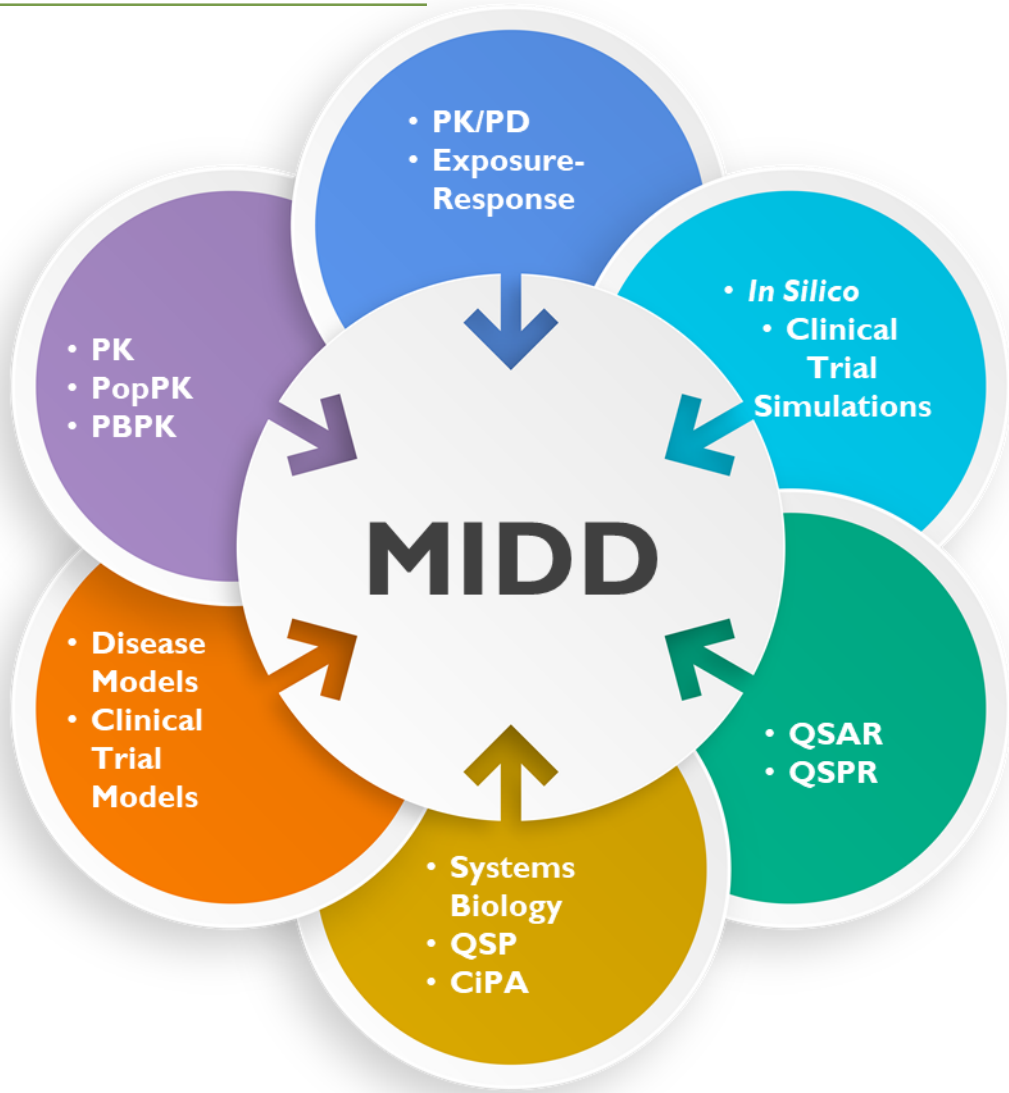
PDUFA VI MIDD Paired Meeting Pilot Program

Rajanikanth (Raj) Madabushi, PhD
Associate Director, Guidance and Scientific Policy
CDER Lead for MIDD Paired Meeting Pilot Program
Office of Clinical Pharmacology
Office of Translational Sciences
U.S. Food and Drug Administration

Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development
Duke-Margolis Center for Health Policy | Virtual Public Meeting
June 7 – 8, 2023

Model-informed Drug Development (MIDD)

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*



* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

Huang SM 2019 AAPS

PDUFA VI
MIDD Paired Meeting Pilot Program

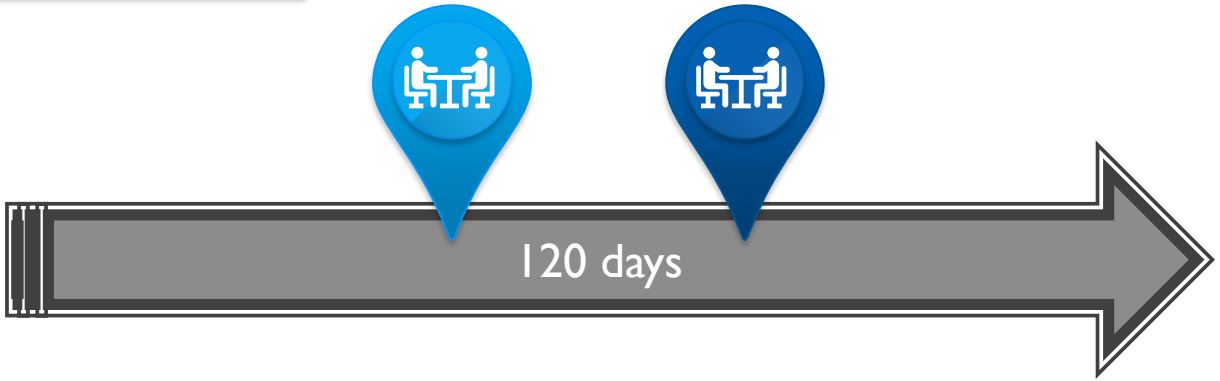
A dedicated forum for regulatory interaction on MIDD applications in specific drug development programs

Dose Section and Optimization

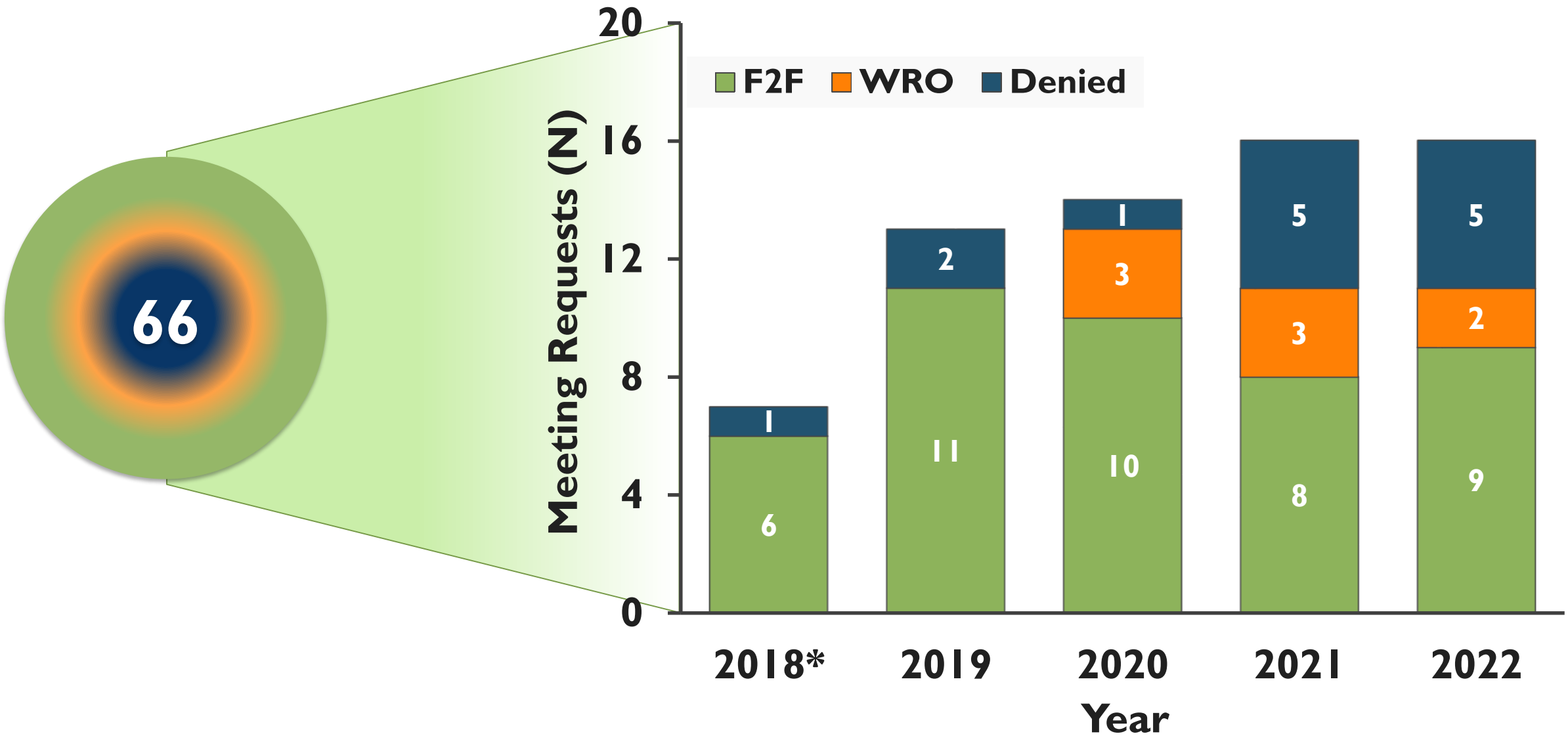
Clinical Trial Simulation

Mechanistic Safety Evaluation

2 – 4 proposals/ quarter



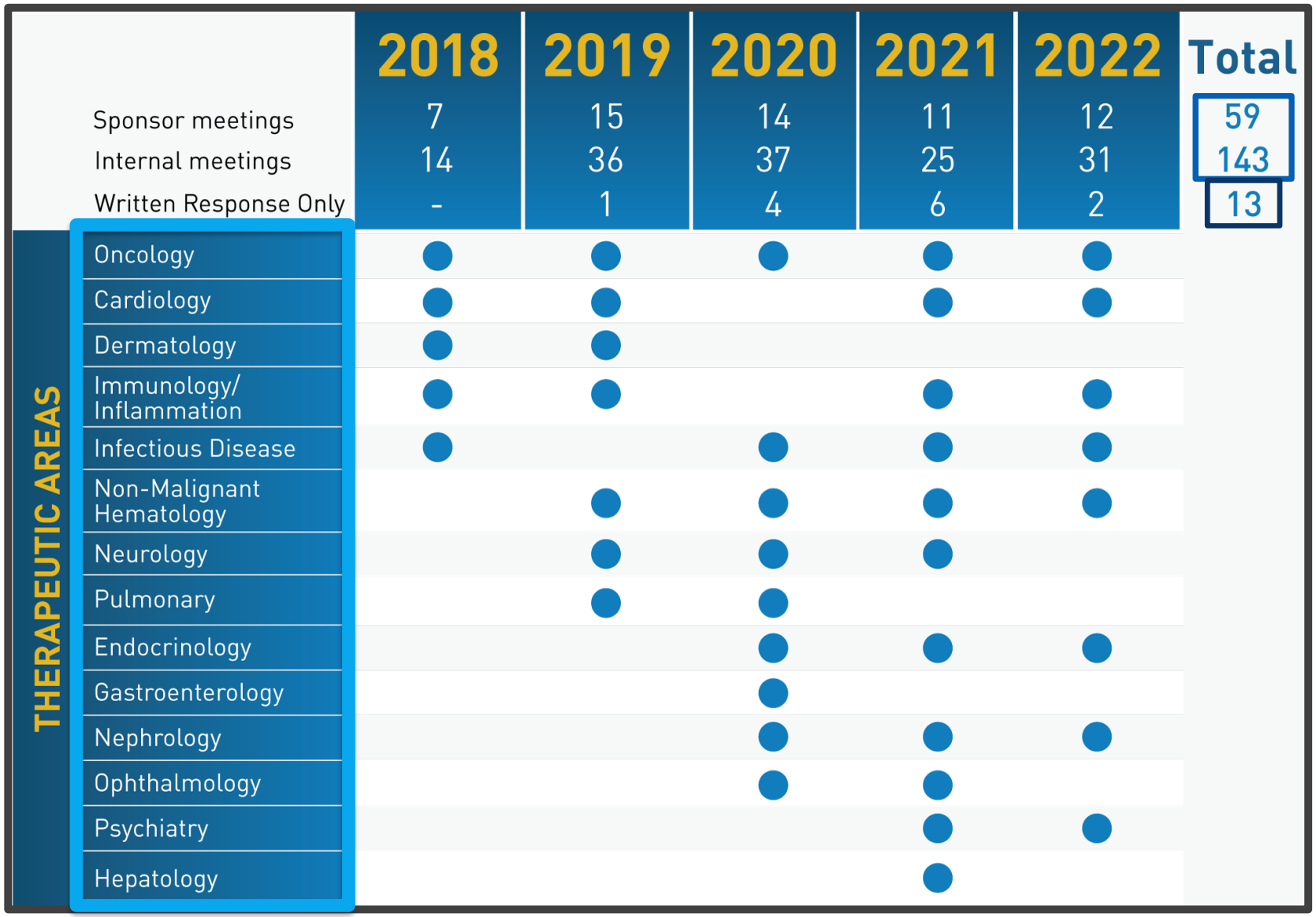
CDER/OCP Pilot Program Experience



* *Partial year #s*

¤ *Conducted as of Dec 31, 2022*

Pilot Program Experience



	2018	2019	2020	2021	2022	Total
Sponsor meetings	7	15	14	11	12	59
Internal meetings	14	36	37	25	31	143
Written Response Only	-	1	4	6	2	13
THERAPEUTIC AREAS						
Oncology	●	●	●	●	●	
Cardiology	●	●		●	●	
Dermatology	●	●				
Immunology/ Inflammation	●	●		●	●	
Infectious Disease	●		●	●	●	
Non-Malignant Hematology		●	●	●	●	
Neurology		●	●	●		
Pulmonary		●	●			
Endocrinology			●	●	●	
Gastroenterology			●			
Nephrology			●	●	●	
Ophthalmology			●	●		
Psychiatry				●	●	
Hepatology				●		

Applicable across wide spectrum of therapeutic areas

Resource intensive and involves engagement of multidisciplinary stakeholders

Flexibility, transparency, and clarity in feedback

Office of Clinical Pharmacology – 2022 Annual Report https://www.fda.gov/media/164793/download

Pilot Program Impact

Drug Development

Model validation & clinical trial simulation to inform trial design and patient selection

Strategies for dose selection, optimization and risk mitigation

Alternative approaches for therapeutic individualization

Regulatory pathway seeking approval of new dose, dosing regimen, formulation, etc.

Regulatory Approvals

- **Ramucirumab**

  Approval of shorter infusion option

- **Sotalol Hydrochloride**

  Approval of a new dosing strategy that reduces the hospital stay from 3 days to 1 day

- **Cetuximab**

  Approval of a dosing regimen with extended inter-dosing interval

- **Valbenazine**

  Approval of a new dose option as part of titration

Full prescribing information is available at:

Ramucirumab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s036lbl.pdf
Sotalol Hydrochloride: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022306s005lblrpl.pdf
Cetuximab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s277s280lbl.pdf
Valbenazine: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209241s020lbl.pdf

Designed by PresentationGO.com

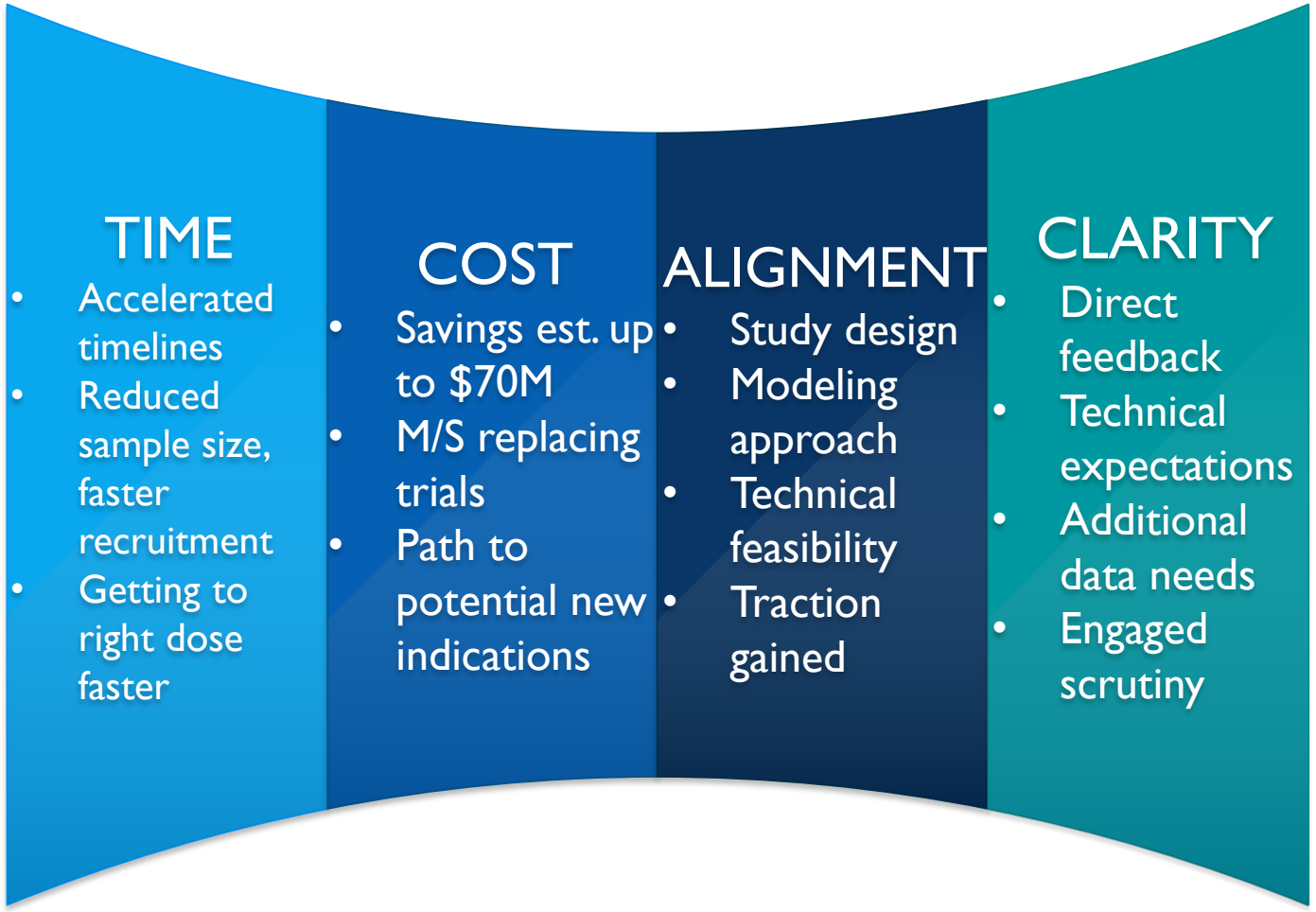
Pilot Program Impact

Industrial Benefit

U.S. FOOD & DRUG ADMINISTRATION

Industrial Perspective on the Benefits Realized From the FDA's Model-Informed Drug Development Paired Meeting Pilot Program

Gerald R. Galluppi[1,*], Satjit Brar[2], Luzelena Caro[3], Yuan Chen[4], Nicolas Frey[5], Hans Peter Grimm[5], Deanne Jackson Rudd[3], Chi-Chung Li[6], Mindy Magee[7], Arnab Mukherjee[8], Lee Nagao[9], Vivek S. Purohit[10], Amit Roy[11], Ahmed Hamed Salem[12,13], Vikram Sinha[3,†], Ahmed A. Suleiman[14], Kunal S. Taskar[15], Vijay V. Upreti[16], Benjamin Weber[17] and Jack Cook[18,*]



Source: Results from International Consortium for Innovation and Quality in Pharmaceutical Development survey
Clin Pharmacol Ther 2021;110(5):1172-1175

Slide Courtesy: Kim Bergman & Issam Zineh

Summary

- MIDD Paired Meeting Pilot Program meet/exceeded the PDUFA VI goals
- Pilot Program under PDUFA 6 demonstrated tangible benefits to drug development and regulatory decision-making
- Pilot Program provided an opportunity:
  - to standup and operationalize the regulatory interaction
  - gain valuable experience across the spectrum of drug development and therapeutic landscape
  - explore pragmatic solutions to meet the demand

Complex Innovative Designs

PDUFA VI Complex Innovative Trial Designs Pilot Meeting Program

Dionne L. Price, Ph.D.

Deputy Director, Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research

June 8, 2023

FDA U.S. FOOD & DRUG ADMINISTRATION

Complex Innovative Trial Designs (CID)

Guidance for Industry, Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products, reads:

Although CID has been considered to refer to complex adaptive, Bayesian, and other novel clinical trial designs, there is no fixed definition of CID because what is considered innovative, or novel can change over time. For the purposes of this guidance, CID includes trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications. CID can also include the novel application of complex trial design features to a given indication even when those design features have been used in other indications.

CID includes (but not limited to)….

- Complex Adaptive Designs
- Formal incorporation of “prior” information
- Use of a posterior probability to determine trial success criteria
- Master protocols
- Sequentially Multiple Assignment Randomized Trial (SMART) designs

Motivation

- Potential to increase trial efficiencies
  - Decrease number of patients
  - Accelerate product development
  - Optimize product development

- Limited use of CIDs to provide substantial evidence of effectiveness across a broad range of therapeutic areas

PDUFA VI: CID Pilot Meeting Program

- Joint effort of the Center for Drug Evaluation and Research and Center for Biologic Evaluation and Research
- Sponsors
  - submit designs
  - have the opportunity to engage with **regulatory team** on designs via two meetings
- Agency
  - select up to 2 submissions per quarter
  - **uses the design as a case study for continuing education and information sharing**
- Meetings led by statistical units with participation from all relevant disciplines
- Five-year duration

Eligibility Criteria

- The sponsor must have a pre-IND or IND number for the medical product(s) included in the CID proposal with the intent of implementing the CID in the pilot program application.
- The proposed CID is intended to provide substantial evidence of effectiveness to support regulatory approval of the medical product.
- The trial is not a first in human study, and there is sufficient clinical information available to inform the proposed CID.
- **The sponsor and FDA reach agreement on the trial design information to be publicly disclosed.**

CID Pilot Meeting Program

- 6 accepted submissions span several therapeutic areas
  - Neurology
  - Analgesia
  - Rheumatology
  - Oncology
  - Includes adult and pediatric rare diseases
- Designs incorporated
  - Bayesian hierarchical modeling
  - Use of formal priors
  - Formulation of a master protocol

Case Examples

Case Example 1	Case Example 2	Case Example 3

• Randomized, double-blind, placebo-controlled, phase 2/3 trial
• Population: Duchenne muscular dystrophy
• Bayesian adaptive design
• Also proposed to explore placebo augmentation with historical controls
	• Randomized, double-blind, group sequential, non-inferiority trial
	• Population: pediatric multiple sclerosis
	• Bayesian framework utilizing meta-analytic predictive priors to leverage information from external adult and pediatric studies
		• Randomized, double-blind, placebo-controlled, master protocol to evaluate multiple interventions across multiple pain conditions
		• Possible adaptations
		  • Stop for futility
		  • Modify sample size
		  • Add or remove arms
		• Bayesian hierarchical model to leverage placebo and treatment effect information

Case Examples

Case Example 4	Case Example 5	Case Example 6

• Randomized, double-blind, Bayesian adaptive design
• Population: Systemic lupus erythematosus
• Features
  ○ Response adaptive randomization
  ○ Bayesian hierarchical model for dose selection
• Interim analyses for futility and to inform dose and endpoint selection for future studies
	• Randomized, open-label, controlled trial
	• Population: Diffuse large B-cell lymphoma
	• Incorporation of external controls using a Bayesian dynamic borrowing approach
		• Randomized, double-blind, placebo-controlled, parallel group study
		• Population: pediatric patients with epilepsy with myoclonic-atonic seizures
		• Bayesian hierarchical model that dynamically borrows treatment effect information from external studies

Resources for Case Examples

Design

CLINICAL TRIALS

Clinical Trials
1–5
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/17407745211050580
journals.sagepub.com/home/ctj
SAGE

The U.S. Food and Drug Administration's Complex Innovative Trial Design Pilot Meeting Program: Progress to date

Dionne Price and John Scott

Abstract

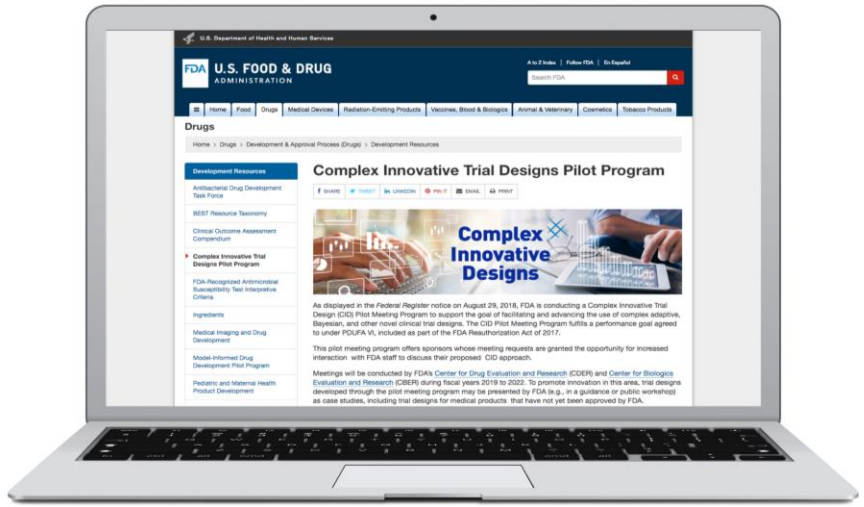
Background: The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration have been leaders in advancing science to protect and promote public health by ensuring that safe and effective drugs and biological products are available to those who need them. Recently, new therapeutic discoveries, increased understanding of disease mechanisms, the need for innovation to optimally use resources, and global public health crises have led to an evolving drug development landscape. As a result, the U.S. Food and Drug Administration and medical product developers are faced with unique challenges and opportunities. The U.S. Food and Drug Administration is proactively meeting the challenges of this evolving landscape through various efforts, including the Complex Innovative Trial Design Pilot Meeting Program. Our focus, here, will be on the pilot meeting program.

Methods: The U.S. Food and Drug Administration has defined a process to facilitate the implementation of the Complex Innovative Trial Design Pilot Meeting Program. The process is transparent and outlines the steps and timeline for submission, review, and meetings.

Results: Five submitted meeting requests have been selected for participation in the Complex Innovative Trial Design Pilot Meeting Program.

Conclusion: The pilot meeting program has been successful in further educating stakeholders on the potential uses of complex innovative designs in trials intended to provide substantial evidence of effectiveness. The selected submissions, thus far, have all utilized a Bayesian framework. The reasons for the use of Bayesian approaches may be due to the flexibility provided, the ability to incorporate multiple sources of evidence, and a desire to better understand the U.S. Food and Drug Administration perspective on such approaches. We are confident the pilot meeting program will have continued success and impact the collective goal of bringing safe and effective medical products to patients.

Keywords
Food and Drug Administration, complex innovative trial designs, pilot program



https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

Lessons Learned

- Resource requirements
- Timing
- Content of submissions
- Consistency
- Education and shared learning

Observations from CID Pilot Program

- Each proposal raised novel questions
- Clarification on terminology
- Some increase in CIDs
  - In late phase development in CBER
  - More common in exploratory and early phase trials
  - Increase in master protocols during pandemic
- Iterative nature of innovative designs
- Importance of multi-disciplinary dialogue around designs
- Use of Bayesian designs

Summary

- Continuance of Paired Meeting Program under PDUFA VII indicates FDA commitment to advancing innovative designs and analysis

- Scientific thought, education, and communication continue to be key when considering innovative aspects of trial designs and analyses

Session 9: Experiences and Lessons Learned from Other Meeting Pilot Programs

Moderator:

- **Mark McClellan,** Duke-Margolis Center for Health Policy

Panelists:

- **Rajanikanth Madabushi,** U.S. Food and Drug Administration
- **Dionne Price,** U.S. Food and Drug Administration
- **Susan Warner,** Eli Lilly and Company

Session 9: Experiences and Lessons Learned from Other Meeting Pilot Programs

1. What are the key lessons learned from experiences with the Complex Innovative Trial Design (CID), Model-Informed Drug Development (MIDD) programs? How might these lessons be applied to best support stakeholders engaging through the new RDEA program?
2. What are some additional reflections regarding experience with the sponsor disclosure component of the CID program? What are the different stakeholder perspectives on the disclosure component and how has this aligned with the experiences to date?
3. How can stakeholders and regulators best work together to achieve the goals of participation in various FDA pilot meeting programs?
4. What are the key recommendations you have for sponsors who submit a request (proposal) to participate in a PDUFA pilot meeting program?
5. How were other pilot programs evaluated to assess their effectiveness and transition to a non-pilot program?

Session 10: Public Comments

4:00 – 4:25 pm ET

Day 2 Adjournment

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

June 8, 2023

Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at
dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

Follow Us

DukeMargolis

@DukeMargolis

@DukeMargolis

Duke Margolis