U.S. FOOD & DRUG ADMINISTRATION

FDA/National Academies of Sciences, Engineering, and Medicine (NASEM) Committee Meeting

November 6, 2023

Agenda

Agenda Item:	Presenter	Time
Rare Disease Overview	**Sandra Retzky** **Kerry Jo Lee** **Julienne Vaillancourt**	2:30 – 2:40 PM
Expedited Programs and Utilization for Rare Diseases	**Miranda Raggio**	2:40 – 2:55 PM
Selected FDA Programs to Support Rare Disease Drug Development	**Kerry Jo Lee** **Robyn Bent** **Julienne Vaillancourt**	2:55 – 3:15 PM
International Collaboration and Clusters	**Katherine Tyner** **Kerry Jo Lee** **Sarah Zaidi** **Judith Arcidiacono**	3:15 – 3:35 PM
Q&A	**FDA** **NASEM Committee**	3:35 – 4:35 PM

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Rare Disease Overview

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Office of Orphan Products Development
Office of the Commissioner

Kerry Jo Lee, MD
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
Center for Drug Evaluation and Research

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Senior Policy Advisor and Rare Disease Liaison
Policy Staff
Office of the Director
Center for Biologics Evaluation and Research

Disclosure

- This presentation reflects the views of the speaker and should not be construed to represent FDA's views on policies.

Orphan Drugs: Designation & Exclusivity

- Goal: Stimulate development of drugs/biologics for rare diseases
- "Orphan drug" is a drug or biological product for prevention, diagnosis, or treatment of a rare disease or condition, generally defined as affecting < 200,000 individuals in the United States (21 U.S.C. 360bb(a)(2)).
- A sponsor may request orphan-drug designation (ODD) any time before submission of a marketing application. ODD may be granted to products that meet eligibility criteria and are for a rare disease or condition.
  - A sponsor may request ODD of a previously unapproved drug, or of a new use for an already marketed drug. 21 C.F.R 316.16(a).
  - A sponsor of a drug that is otherwise the same drug as an already approved drug may obtain ODD for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. 21 C.F.R 316.20(a).
- Designated products may qualify for financial incentives:
  - Tax credits for qualified clinical trial expenses, exemption from user fees, and
  - Upon approval for an indication or use within the scope of the designation, 7-years of market exclusivity.

7-year Orphan Exclusivity

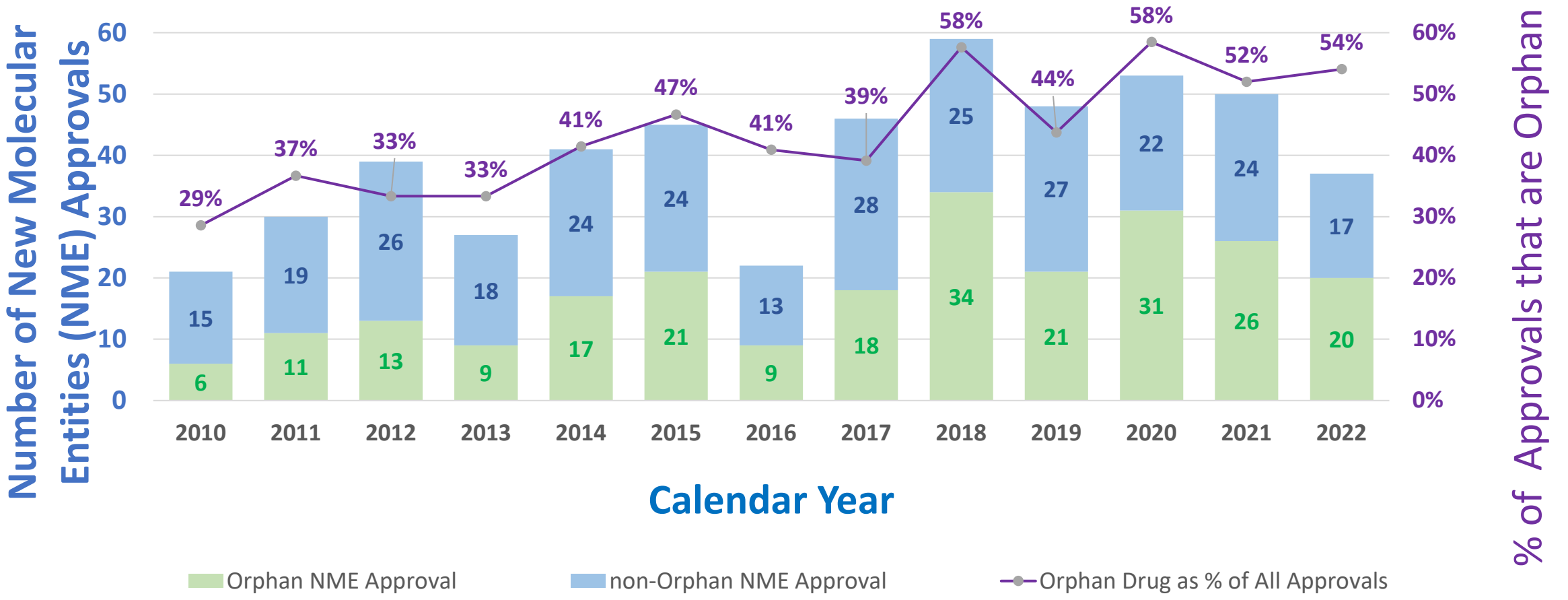
- Seven years of market exclusivity means:
  - FDA cannot approve an application from a different sponsor for a subsequent “same drug” for the same use or indication during the seven-year period of exclusivity. 21 U.S.C. 360cc(a); 21 CFR 316.31; 21 CFR 316.3(b)(14).
  - If a drug is otherwise the same drug as a previously approved drug for the same use or indication, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug. 21 U.S.C. 360cc(c); 21 CFR 316.34(c); 21 CFR 316.3(b)(3).

Rare Pediatric Disease Designation and Priority Review Voucher (PRV) Programs

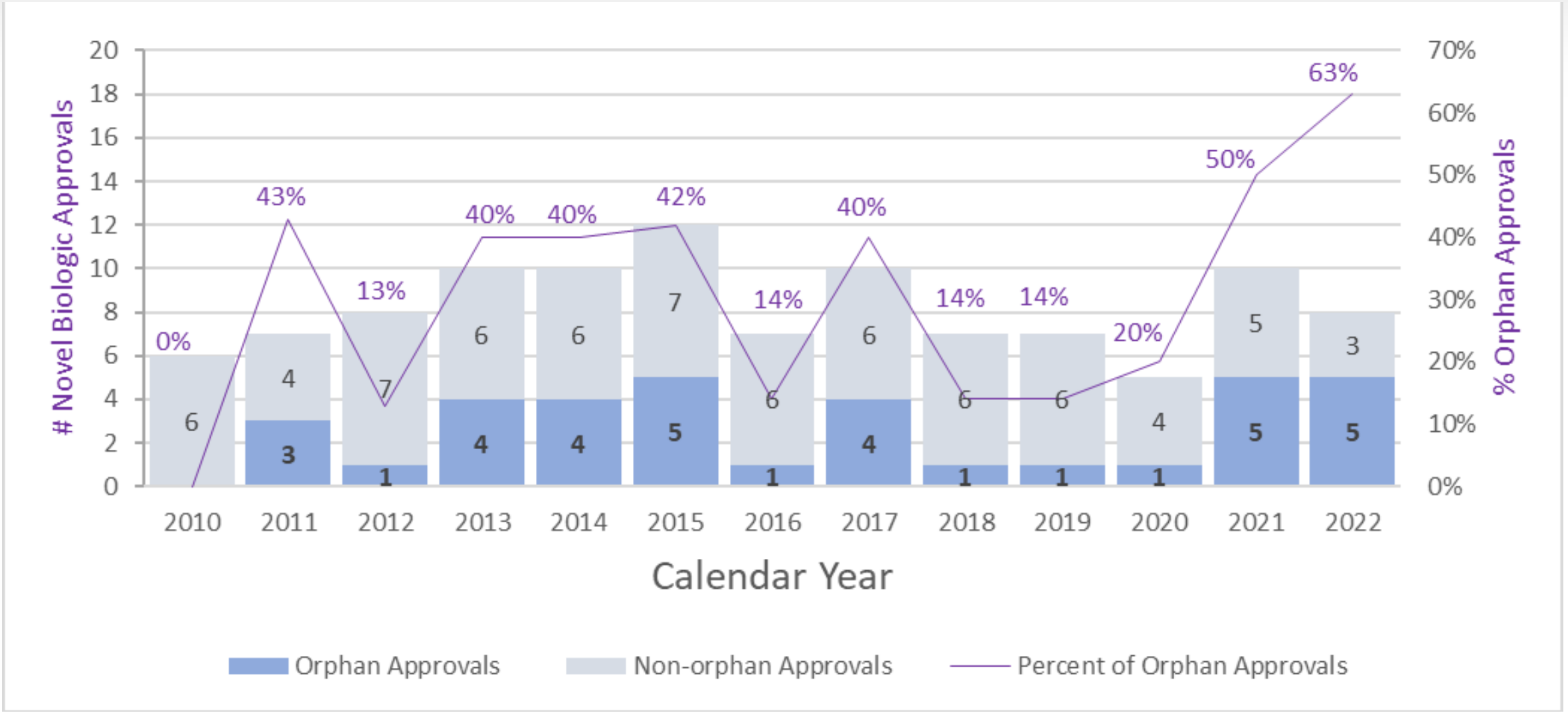
- Goal: Incentivizes development of therapies for rare pediatric diseases
  - Approval of a “rare pediatric disease product application,” the sponsor is eligible to receive a PRV which can be redeemed, or transferred, to obtain priority review of another application that would otherwise be ineligible for priority review. 21 U.S.C. 360ff(a)(2).
  - Prior to filing of an application, a sponsor may choose to request rare pediatric disease designation. 21 U.S.C. 360ff(d). Such RPD designation does not guarantee voucher award upon approval of the product.
  - Whether or not a sponsor receives rare pediatric disease designation for its drug, the sponsor must include a request for a rare pediatric disease PRV in its original NDA/BLA submission in order to be eligible for a voucher. 21 U.S.C. 360ff(b)(4)(A)(i).

See also Rare Pediatric Disease Priority Review Vouchers Guidance for Industry

Proportion of CDER Novel Drug Approvals that are Orphan



Proportion of CBER Novel Biologic Approvals that are Orphan



Note: these data exclude in vitro diagnostic products, reagents and intermediate biological products approved for further manufacture, such as source plasma.

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FDA Expedited Programs

Miranda Raggio MA, BA, BSN, RN
CDER Expedited Programs Manager
Office of Program Operation
Office of News Drugs
Center for Drug Evaluation and Research

Four Expedited Programs for Eligible Drugs and Biologics – The Laws

Accelerated Approval: An Approval Pathway- Section 506(c) of the Food, Drug, and Cosmetic (FD&C) Act, as amended by section 901 of the Food and Drug Innovation Act (FDASIA) of 2012, and section 3210 of the Consolidated Appropriations Act, 2023

Priority Review: A Designation- Prescription Drug User Fee Act of 1992

Fast Track: A Designation- Section 506(b) FD&C Act as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), amended by section 901 of FDASIA 2012

Breakthrough Therapy: A Designation- Section 506(a) of the FD&C Act, as added by Section 902 of FDASIA 2012

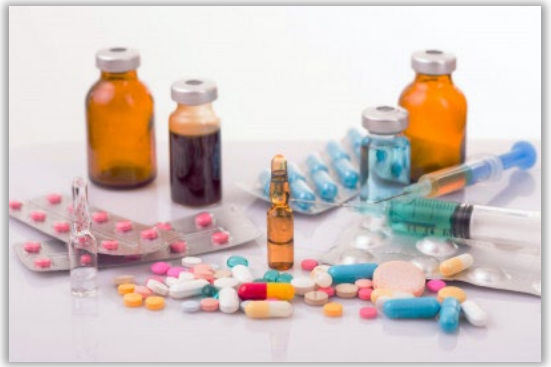
Common Goal of Expedited Programs

All programs are intended to:

- To facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition
- To help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the approval standard has been met, including that the therapies' benefits justify their risks

Concepts of Expedited Programs

- **Serious Condition:** A disease or condition associated with morbidity that has substantial impact on day-to-day functioning
- **Available Therapy:** Is approved or licensed in the United States for the same indication being considered for the new drug and is relevant to current U.S. standard of care for the indication
- **Unmet Medical Need**: A condition whose treatment or diagnosis is not addressed adequately by available therapy



Detailed information on these concepts can be found in the FDA Guidance on Expedited Programs (next slide)

FDA Guidance on Expedited Programs

Guidance to Industry: *Expedited Programs for Serious Conditions-Drugs and Biologics*, Final May 2014

- Resource for information on FDA's policies & procedures for 4 expedited programs
- Describes threshold criteria applicable to concluding that a drug is a candidate for an expedited development & review program

Note: This Guidance to Industry is a joint guidance that applies to drugs and biologics from both Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Accelerated Approval Pathway

- **Qualifying Criteria:**
  - A drug that treats a serious condition **AND** generally provides a meaningful advantage over available therapies **AND** 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 endpoint)
- **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
- **Confirmatory post-marketing trials are required** to verify and describe the anticipated effect on IMM or other clinical benefit
- **Approval is subject to expedited withdrawal** if confirmatory trial(s) are not done or fail to verify clinical benefit
- **If confirmatory trials verify clinical benefit**, the AA will be converted to a standard (i.e., "traditional") approval
- https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

Priority Review Designation

- **Qualifying Criteria:**
  - A marketing application (original or efficacy supplement) for a drug that treats a serious condition **AND**, if approved, would provide a significant improvement in safety or effectiveness **OR**
  - Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A **OR**
  - An application for a drug that has been designated as a qualified infectious disease product **OR**
  - Any application or supplement for a drug submitted with a priority review voucher
- **Request is submitted** with original BLA, NDA, or efficacy supplement
- **Features:** Shorter clock for review of marketing application (6 months compared with the 10-month standard review)

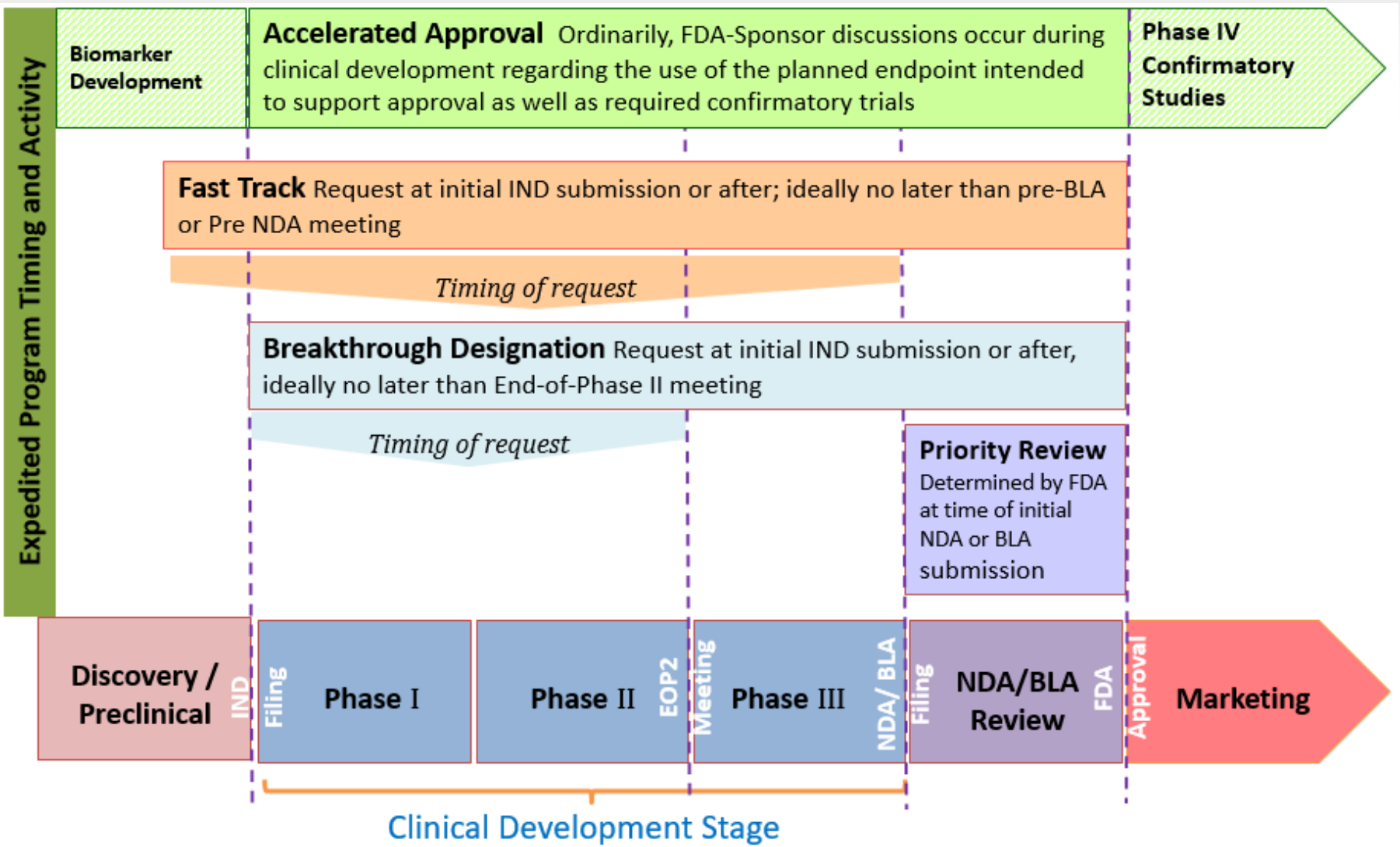
Fast Track Designation

- **Qualifying Criteria:**
  - A drug that is intended to treat a serious condition **AND nonclinical or clinical** data demonstrate the potential to address unmet medical need OR A drug that has been designated as a qualified infectious disease product
- **Designation is for a drug and specific indication**
- **Submitted** with an active IND or anytime thereafter
- **Features:** If granted - actions to expedite development and review are enhanced and the application is eligible for rolling review
- **FTD may be rescinded** if the qualifying criteria are no longer met

Breakthrough Therapy Designation

- **Qualifying Criteria:**
  - A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
- **Designation is for a drug and specific indication**
- **Submitted with** an active IND or anytime thereafter
- **Features of BTD:**
  - Intensive guidance on efficient drug development
  - Organizational commitment to involve senior leadership
  - Rolling review eligibility
  - Other actions to expedite review, such as enhanced communications, more meetings
- **BTD may be rescinded** if the qualifying criteria are no longer met

Timing of Evidence and Expedited Program Use During Drug Development



See Guidance for Industry *Expedited Programs for Serious Conditions- Drugs and Biologics*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

One Expedited Program for Certain Eligible Biologics – The Law

Regenerative Medicine Advanced Therapy (RMAT): A Designation- Section 506(g) of the FD&C Act, as added by Section 3033 of the 21st Century Cures Act

FDA Guidance on Expedited Programs (cont.)

Guidance for Industry: *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions,* Final February 2019

- Single resource for information on FDA's policies & procedures for the five expedited programs available to sponsors of regenerative medicine therapies for serious conditions
- Describes threshold criteria applicable to concluding that a drug is a candidate for an expedited development & review program

Note: This Center for Biologics Evaluation and Research (CBER)-issued guidance applies to a drug that meets the definition of a regenerative medicine therapy

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions

Regenerative Medicine Advanced Therapy (RMAT) Designation

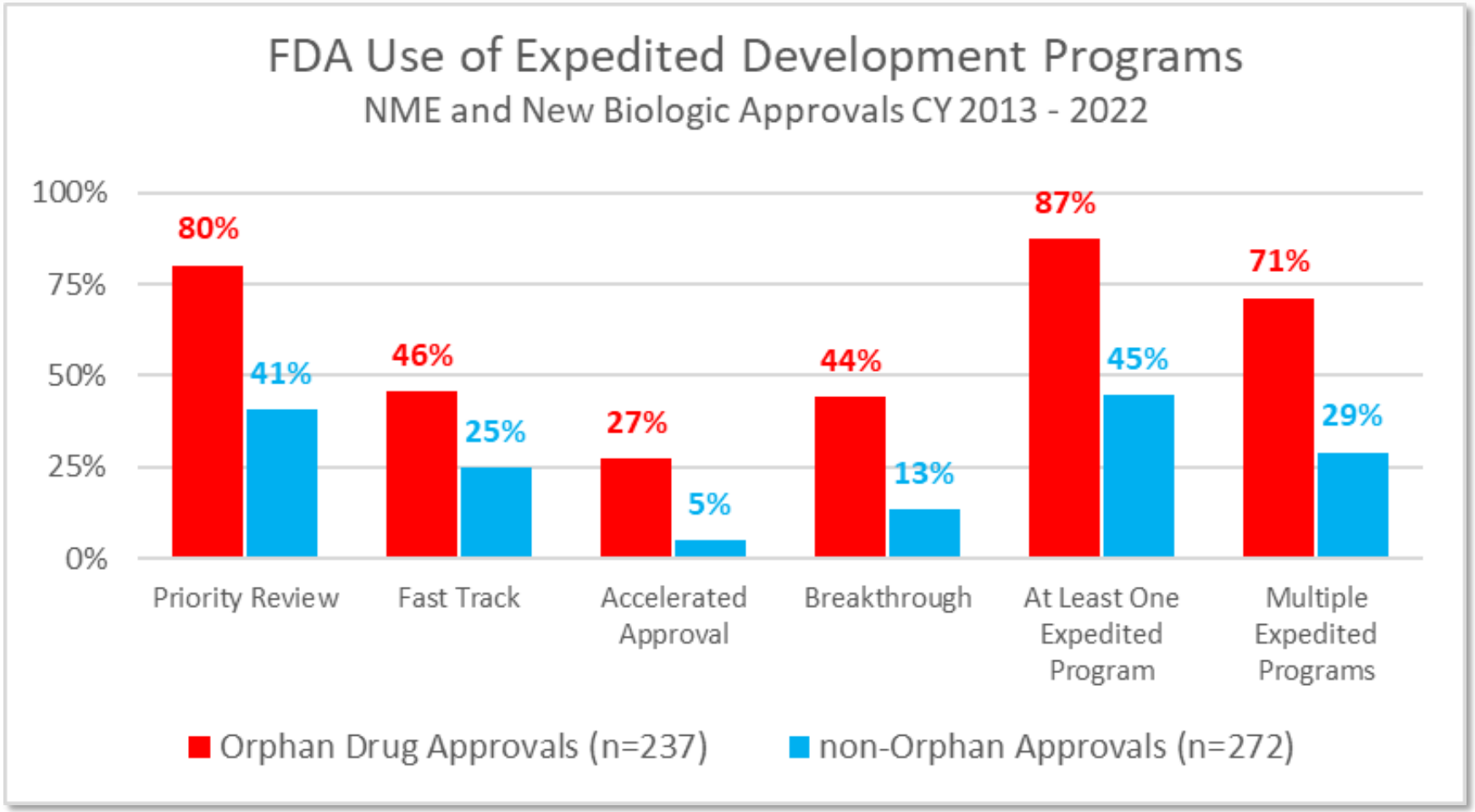
- **Qualifying Criteria:**
  - The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition
- **Designation is for a drug and specific indication**
- **Request for RMAT designation** must be made either concurrently with submission of an IND or as an amendment to an existing IND
- **Features of RMAT Designation:**
  - all breakthrough therapy features, including early interactions to discuss any potential surrogate or intermediate endpoints
  - possible priority review and accelerated approval (if eligible)
  - statutory flexibility with regard to accelerated approval and post-approval requirements
- **RMAT Designation may be rescinded** if the qualifying criteria are no longer met

Important to Note

- These programs expedite development and review of new drugs, but **do not change FDA's standards for approval.**
- To approve any new drug, whether or not it is part of an expedited program, the FDA must determine that it is safe and effective for its intended use; this requires the finding of substantial evidence of effectiveness, which must be based, as defined in law, upon adequate and well-controlled investigation(s).
- Substantial evidence of effectiveness is necessary but not sufficient for FDA approval. FDA must also determine that the drug is safe for the intended use, which requires a showing that the benefits of the drug outweigh its risks.

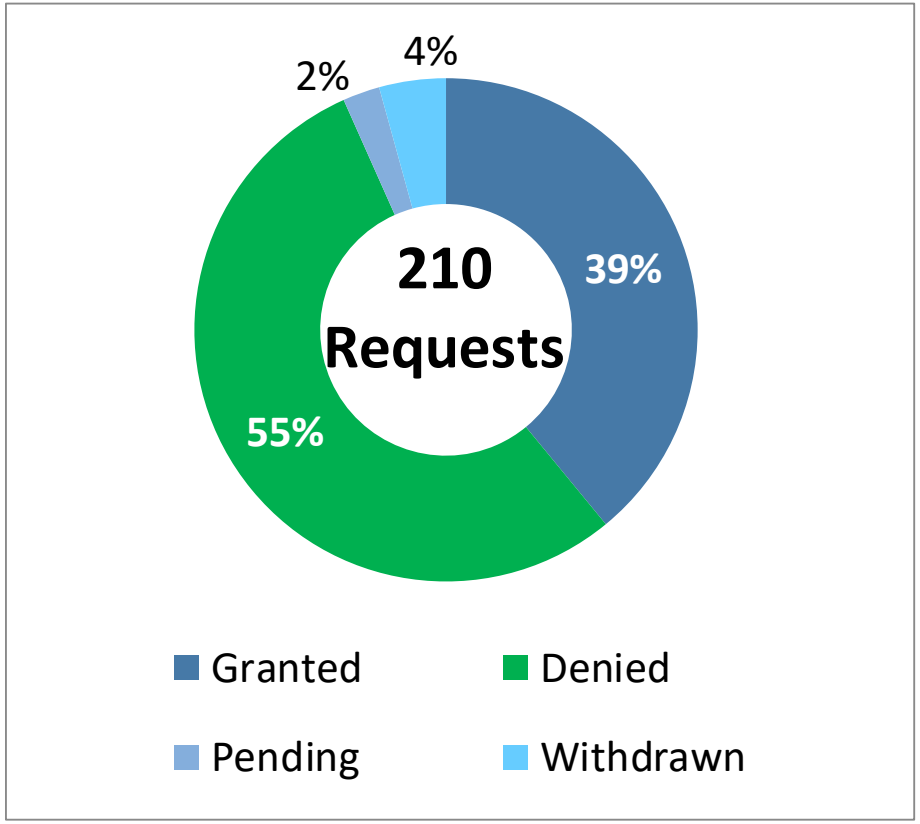
Use of Expedited Programs in CDER and CBER

Orphan NMEs are more likely to utilize expedited programs.



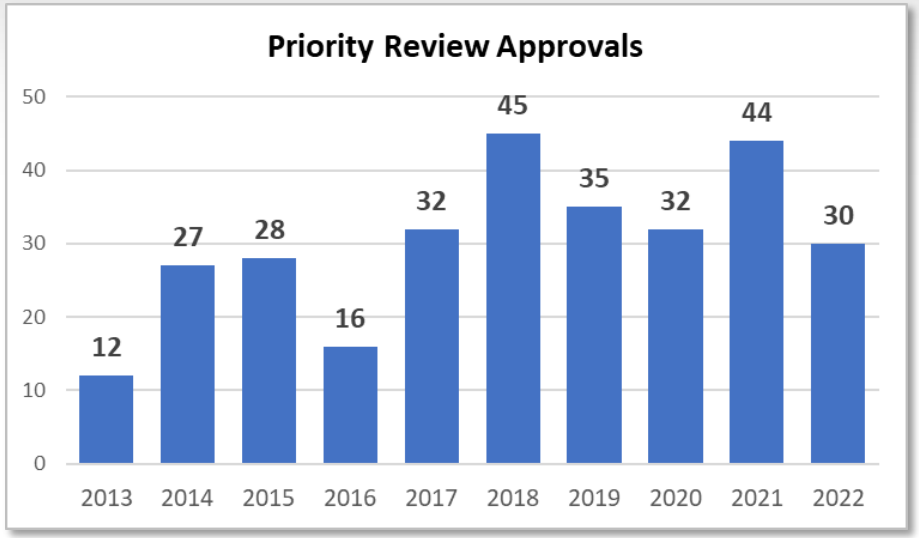
Regenerative Medicine Advance Therapy (RMAT)

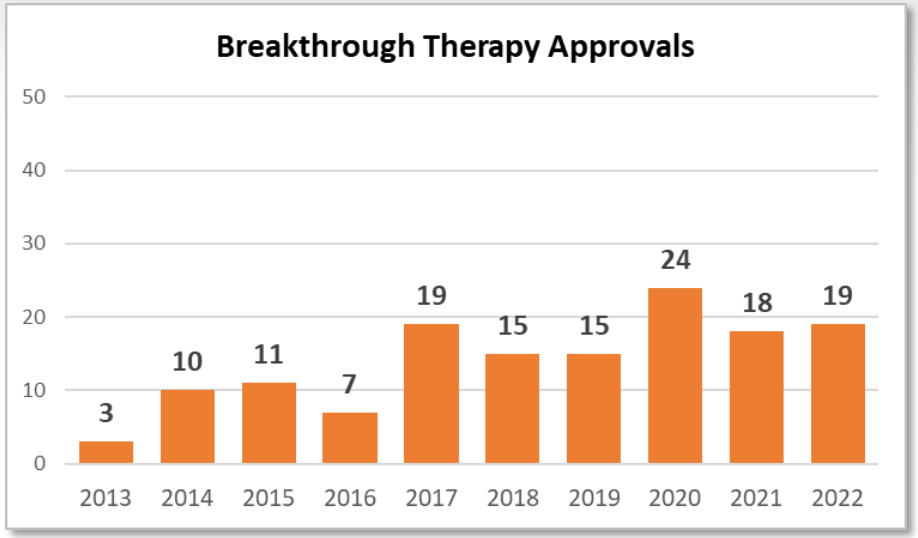
35 (43%) of the 82 Regenerative Medicine Advanced Therapy (RMAT) designations granted by CBER since program inception have orphan product designation

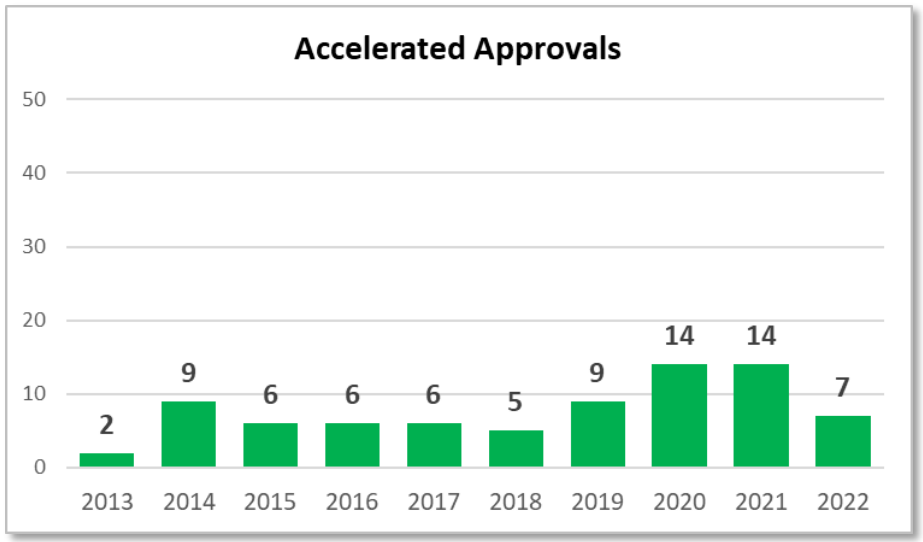


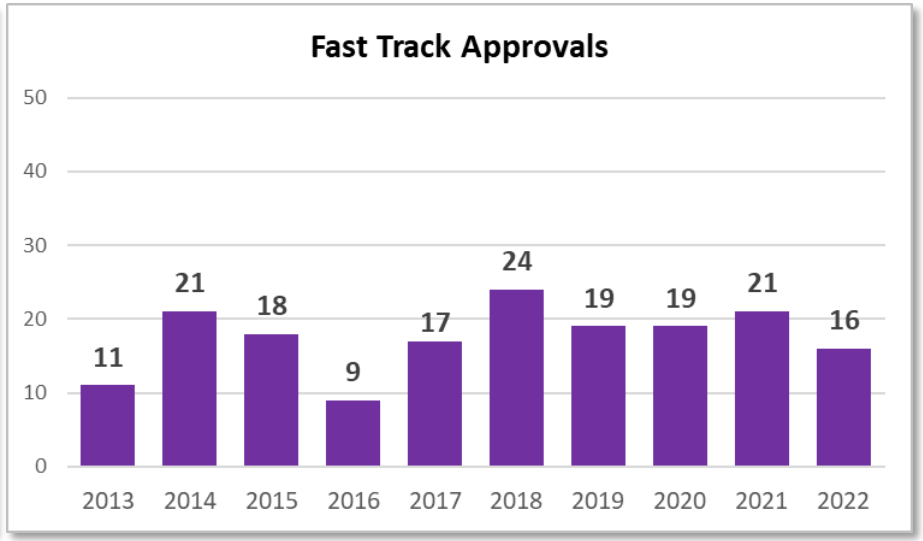
Data as of December 31, 2022

FDA Expedited Program Approvals for New Molecular Entities and Novel Biologics in CDER and CBER









Years 2013-2022

* Each drug or biologic approval may have qualified for more than one expedited program

Breakthrough Therapy Designation: Orphan Diseases *or* Available Therapy

Center for Drug Evaluation & Research (CDER) decisions to grant or deny breakthrough therapy designation requests (n=240) for non-oncology drugs/biological products: 1 Jan 2017 thru 31 Dec 2019

Category; n (% of total)	Granted	Denied
Orphan, no available therapy; n=63 (26%)	35 (56%)	28 (44%)
Orphan, available therapy; n=27 (11%)	12 (44%)	15 (56%)
Not an orphan, no available therapy; n=70 (29%)	28 (40%)	42 (60%)
Not an orphan, available therapy; n=80 (33%)	18 (22.5%)	62 (77.5%)
Total; N=240	93	147

Analyses by Atasi Poddar, Miranda Raggio, John Concato (CDER)

Selected FDA Programs on Rare Disease

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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
Center for Drug Evaluation and Research

Robyn Bent, MS, RN
Director, CDER Patient Focused Drug Development
Office of the Center Director
Center for Drug Evaluation and Research

Julienne Vaillancourt, RPh, MPH
Captain, U.S. Public Health Service Commissioned Corps
Senior Policy Advisor and Rare Disease Liaison
Policy Staff
Office of the Director
Center for Biologics Evaluation and Research

Introduction

We Face Common Challenges in Rare Disease Drug Development including:

- Small and sometimes very **small patient populations**
- **Genotypic/phenotypic** heterogeneity within a disease
- **Natural history** often poorly understood
- Often **serious/life-threatening**, progressive, **childhood onset**, and often lack adequate **approved therapies – urgent needs**
- **Drug development tools – outcome measures** and **biomarkers** often **lacking**
- Often limited, if any, **precedent**, including **clinically meaningful endpoints**, for drug development in many rare diseases

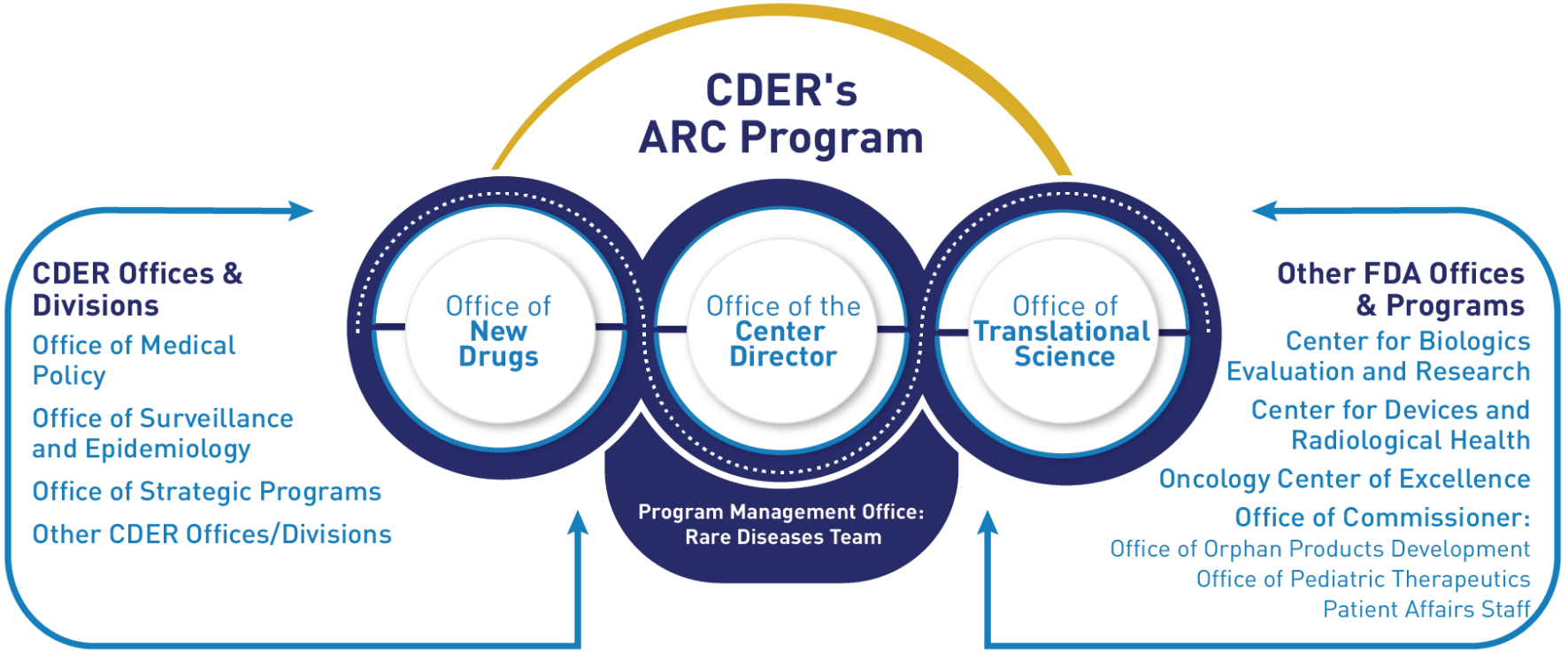
And, Common Considerations in the "Environment" for Rare Diseases Drug Development

- 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

Accelerating Rare disease Cures Program (ARC)

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

Accelerating Rare disease Cures Program (ARC)

ARC Year One by the Numbers

- **22** rare disease drug approvals
- **25+** public speaking engagements featuring the ARC Program
- **19** externally-led Patient-Focused Drug Development Meetings on rare disease supported by CDER staff
- **23** patient listening sessions on rare diseases supported by CDER staff
- **4** ARC Quarterly Newsletters
- **10k+** CDER Rare Disease News subscribers

Accelerating Rare disease Cures Program (ARC)

ARC Website

- “Upcoming and Recent Events” tab – serves as a hub for educational conferences relevant to rare disease topics
- “Guidances” tab – selected guidances relevant to rare disease drug development organized by topic
- “Funding Opportunities” tab – available funding and fellowship opportunities for rare disease product development research
- ARC Year 1: “Anniversary Update”

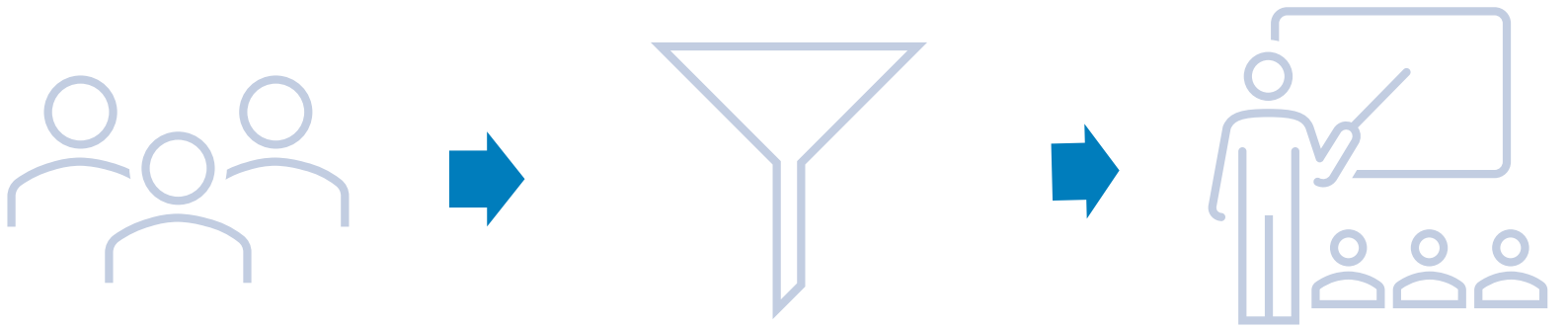
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program

Accelerating Rare disease Cures Program (ARC)

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)



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

Patient Focused Drug Development (PFDD)

- Patient-focused drug development (PFDD) is a systematic approach to help ensure that **patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated** into drug development and evaluation.

PFDD MEETINGS

PFDD METHODOLOGIC G UIDANCE SERIES

STANDARD CORE COA GRANT PROGRAM

INTERNATIONAL COUNCIL FOR HARMONISATION PFDD REFLECTION PAPER

REPORT ON USE OF PATIENT EXPERIENCE DATA IN REGULATORY DECISION MAKING

NORD EDUCATION SERIES

International Council for Harmonisation PFDD Reflection Paper

This Reflection Paper:

- Identifies key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making.
- Presents opportunities for development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both regulated industry and regulatory authorities.

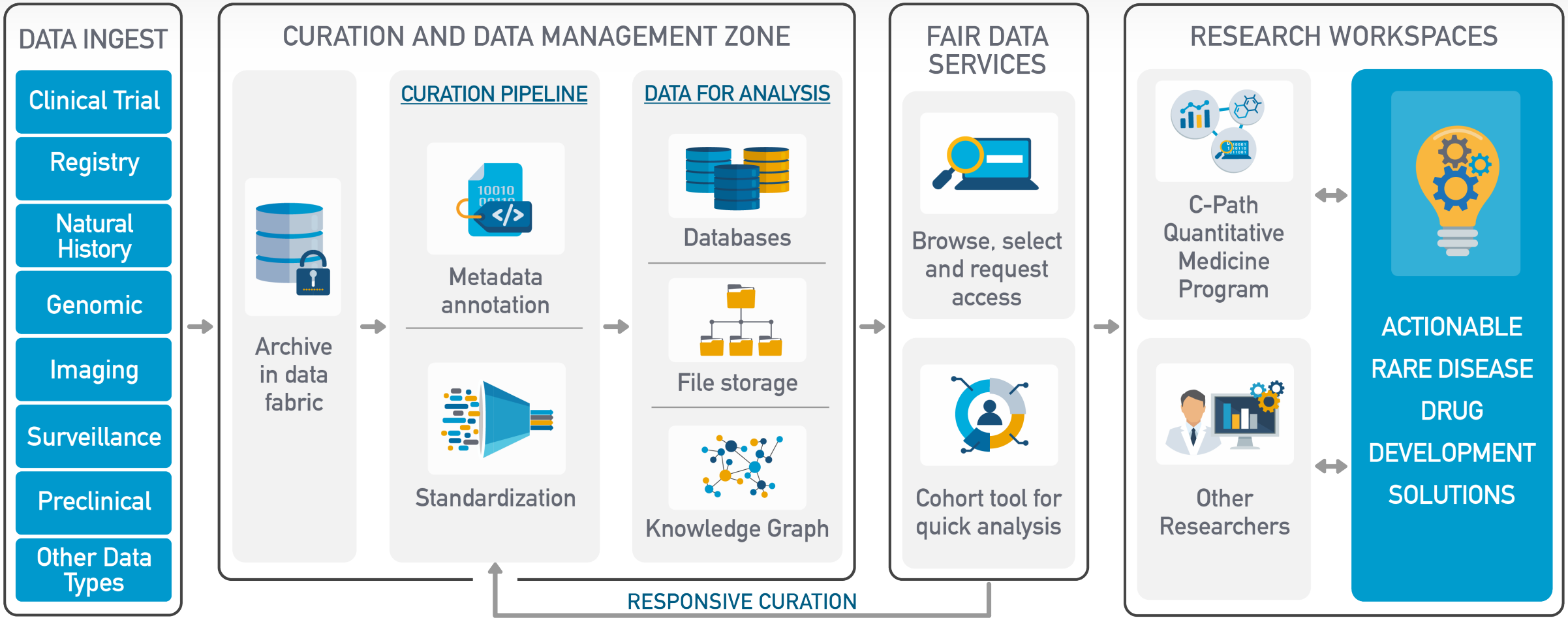
https://www.ich.org/page/reflection-papers

Rare Disease Cures Accelerator-Data and Analytics Platform

RDCA-DAP: a neutral, independent data collaboration and analytics hub to **promote the sharing of critical data across rare diseases** in order to accelerate the understanding of disease progression and optimize clinical trial design.

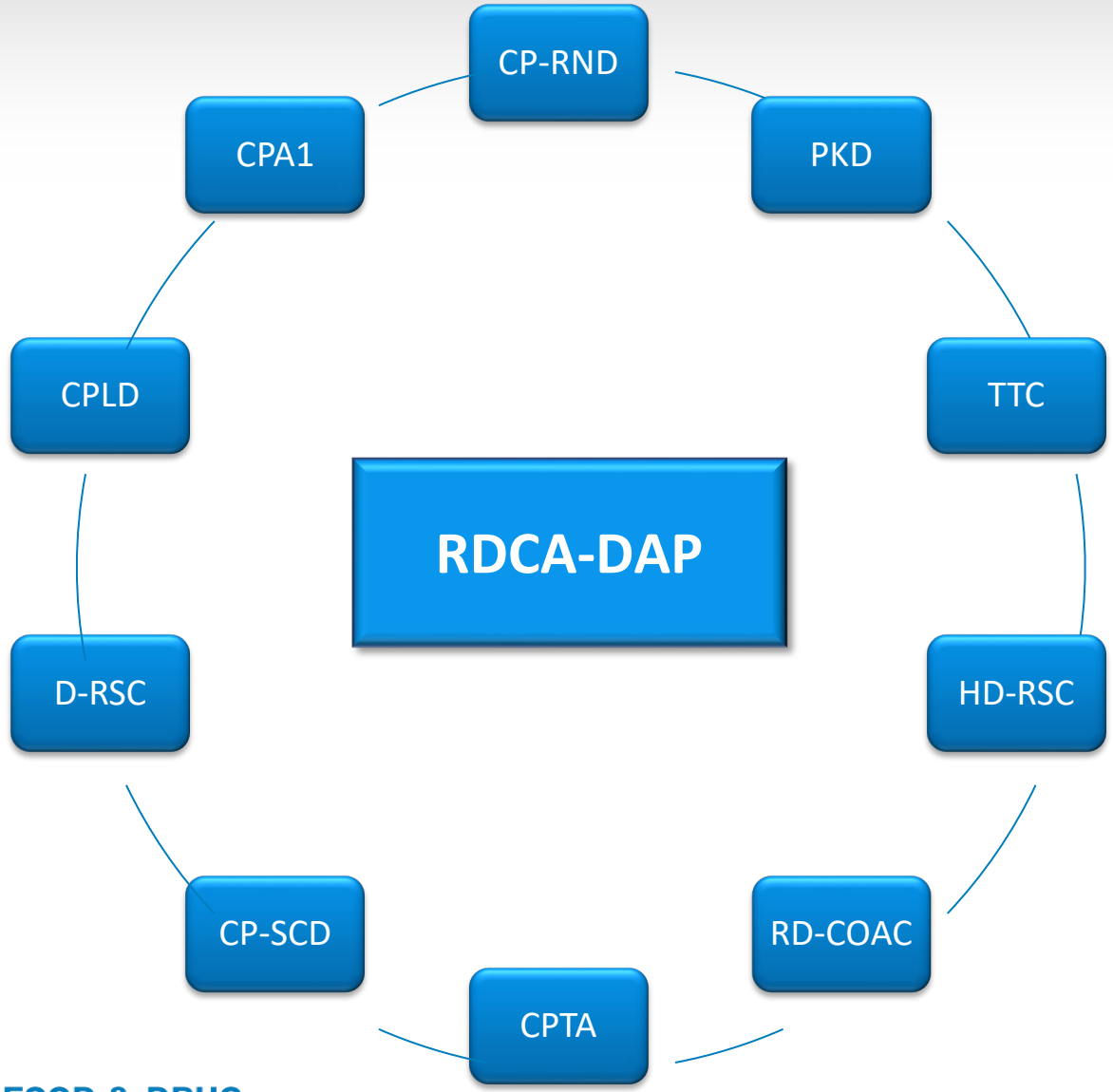
RDCA-DAP is an initiative led by Critical Path Institute in collaboration with FDA and NORD

The RDCA-DAP Platform



(Europe – GDPR compliant)

C-Path's Active Rare and Orphan Disease Programs



D-RSC
DUCHENNE REGULATORY SCIENCE CONSORTIUM

CP-RND
CRITICAL PATH FOR RARE NEURODEGENERATIVE DISEASES

PKD
POLYCYSTIC KIDNEY DISEASE OUTCOMES CONSORTIUM

TTC
TRANSPLANT THERAPEUTICS CONSORTIUM

HD-RSC
HUNTINGTON'S DISEASE REGULATORY SCIENCE CONSORTIUM

RD-COAC
RARE DISEASE CLINICAL OUTCOME ASSESSMENT CONSORTIUM

CPTA
CRITICAL PATH TO THERAPEUTICS FOR THE ATAXIAS

CP-SCD
CRITICAL PATH FOR SICKLE CELL DISEASE

CPA-1
CRITICAL PATH FOR ALPHA-1 ANTITRYPSIN DEFICIENCY

CPLD
CRITICAL PATH FOR LYSOSOMAL DISEASES

CRITICAL PATH INSTITUTE

RDCA-DAP®
Rare Disease Cures Accelerator
Data and Analytics Platform

Rare Disease Endpoint Advancement Pilot Program (RDEA)

- **Scope**: The Rare Disease Endpoint Advancement (RDEA) pilot program is a **joint CDER and CBER program** that seeks 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
- For each RDEA proposal admitted into the pilot program, the agency will conduct an initial meeting and, if requested, up to three follow-up meetings.
- Current application quarter closes on December 31st, 2023

Rare Disease Endpoint Advancement Pilot Program (RDEA)

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 (RDEA)

- 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
- RDEA First Public Workshop:
  - Jointly hosted by CDER/CBER and Duke-Margolis Center for Health Policy, June 7-8, 2023
    - https://www.fda.gov/drugs/news-events-human-drugs/fda-cder-and-cber-duke-margolis-center-health-policy-rare-disease-endpoint-advancement-pilot-program
- Questions?
  - Email: RDEA.Meetings@fda.hhs.gov

Complex Innovative Trial Design Meeting Program

"*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*" – *Guidance for Industry: Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products*

- Meeting Program is a joint effort of the Center for Drug Evaluation and Research and Center for Biologic Evaluation and Research
- Sponsors submit designs and have the opportunity to engage with **regulatory team** on designs via two meetings
- The Agency selects up to 2 submissions per quarter and **uses the designs as case studies for continuing education and information sharing (**under a disclosure agreement**)**
- Five-year duration

Support for clinical Trials Advancing Rare disease Therapeutics (START)

➢ Joint CBER and CDER Pilot Program – announced September 29, 2023

- To further accelerate the pace of development of certain CBER- and CDER-regulated products that are intended to address an unmet medical need as a treatment for a rare disease
- Augment currently available formal meetings by addressing issues with more rapid, ad hoc communication
- Open period for submitting requests: January 1, 2024, to March 1, 2024
- Up to three participants from each Center (CBER and CDER)

Federal Register Notice: https://www.federalregister.gov/public-inspection/2023-21235/support-for-clinical-trials-advancing-rare-disease-therapeutics-pilot-program

➢ Eligibility

- IND in eCTD form or granted a waiver from eCTD
- CMC development strategy aligns with clinical development plans
- For CBER-regulated products:
  - Cell or gene therapy under IND and being developed toward a BLA
  - Intended to address an unmet medical need as a treatment for a rare disease or serious condition, which is likely to lead to significant disability or death within the first decade of life
- For CDER-regulated products:
  - Must be intended to treat rare neurodegenerative conditions, including those of rare genetic metabolic type

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International Clusters and Collaboration

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FDA Liaison to the EMA
Europe Office
Office of Global Policy and Strategy
Office of the Commissioner

Kerry Jo Lee, MD
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
Center for Drug Evaluation and Research

Judith Arcidiacono, M.S.
International Regulatory Expert
Policy and Special Project Staff
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Sarah Zaidi, MD
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Office of Pediatric Therapeutics (OPT)
Office of Clinical Policy and Programs (OCPP)|Office of the Commissioner(OC)

Foundational Collaborations with the EMA

➢ Confidentiality Commitment (CC)

- Ability to share non-public pre-and post-market activities as part of cooperative regulatory activities
- https://www.fda.gov/international-programs/confidentiality-commitments/ema-europe-fda-confidentiality-commitment
- Allows for ad hoc communication on product discussions, regulatory practices, guidelines, standards, etc.

➢ Liaison Program

- Senior officials embedded in each agency to serve as a primary point of contact
- Ensure timely information exchange and development of strategies to facilitate engagement

➢ Mutual Recognition Agreement (MRA)

- Mechanism to allow sharing and reliance of human drugs GMP inspection reports

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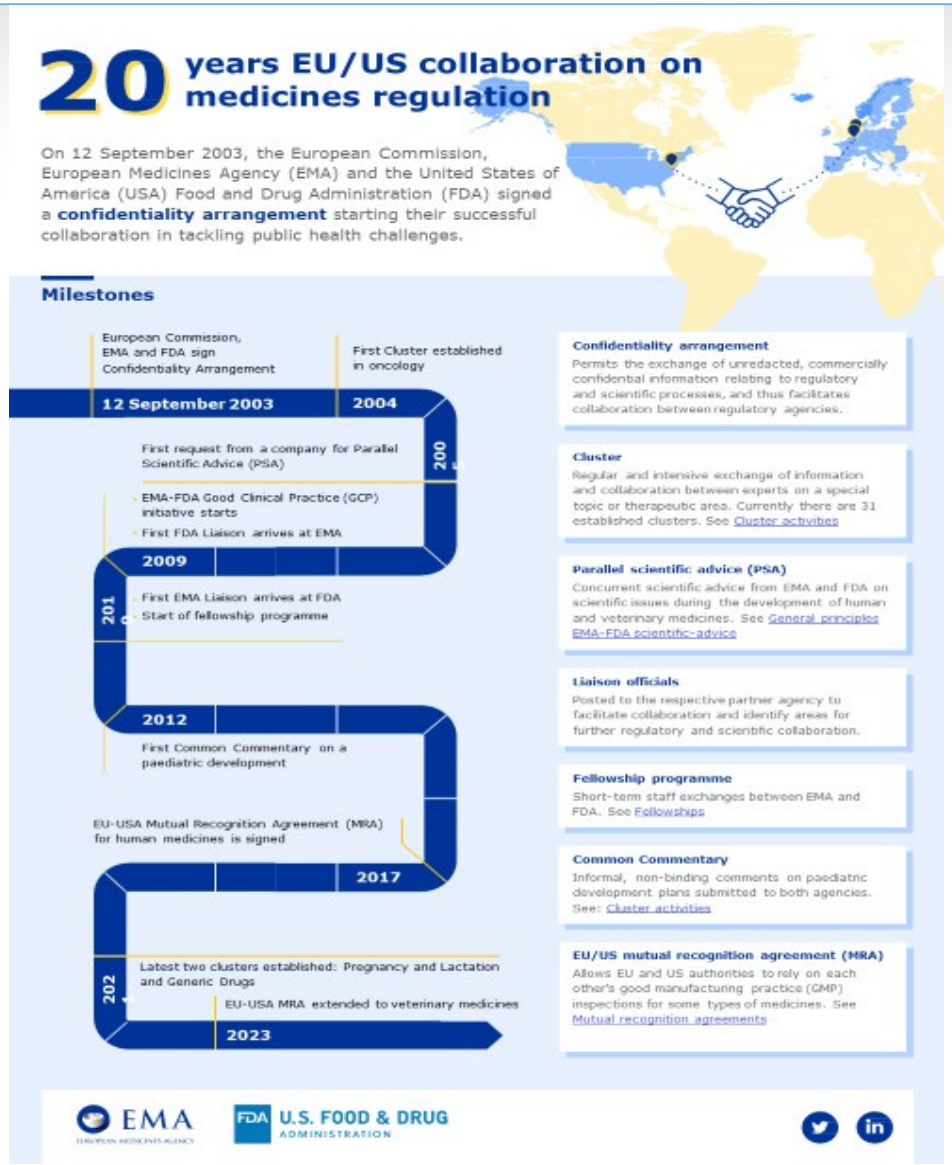
Foundational Collaborations with the EMA

- **Clusters**
  - Groups formed around topical areas of interest for regular discussion and information exchange
- **Parallel Scientific Advice (PSA)**
  - A mechanism where EMA and FDA concurrently exchange their views on scientific issues regarding product development with the sponsor
- **Fellowships***
  - Two-week intensive exchange of EMA/FDA personnel on a specific topic

Ad Hoc Collaborations

- Over half of the collaborative activities between FDA and EMA are ad hoc
- Product exchanges and teleconferences on specific review and safety issues
- Follow-up discussions on outcomes of GMP / GCP inspections
- Discussion/development/comments on a specific guideline
- Observers at scientific meetings
- Participation in each other's trainings
- Advanced warning and discussion on key public communications.
- Example: During COVID-19, EMA and FDA held multiple ad-hoc fora to discuss clinical trials protocols, scientific evidence for regulatory decisions, development and updates on guidance



Parallel Scientific Advice (PSA)

➢ Parallel Scientific Advice

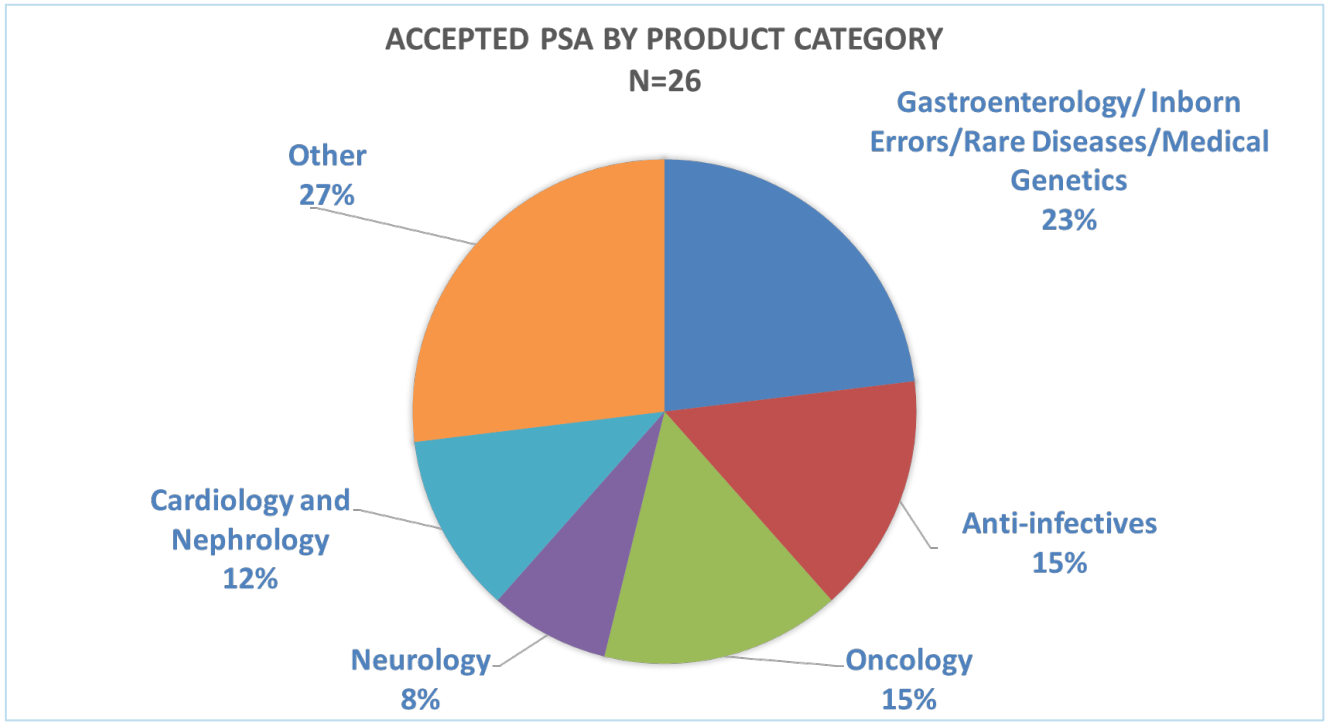
- A mechanism where EMA and FDA concurrently exchange their views on scientific issues with the sponsor
- Formal process at the request of the sponsor

➢ Goals and Results

- Increase dialogue early in product lifecycle
- Deepen understanding of regulatory decisions
- Optimize development
- Support global development plans
- Avoid unnecessary testing

➢ Additional Information

- https://pubmed.ncbi.nlm.nih.gov/36871110/
- https://www.youtube.com/watch?v=Oq0zUVyF1Tc



EMA – FDA Clusters

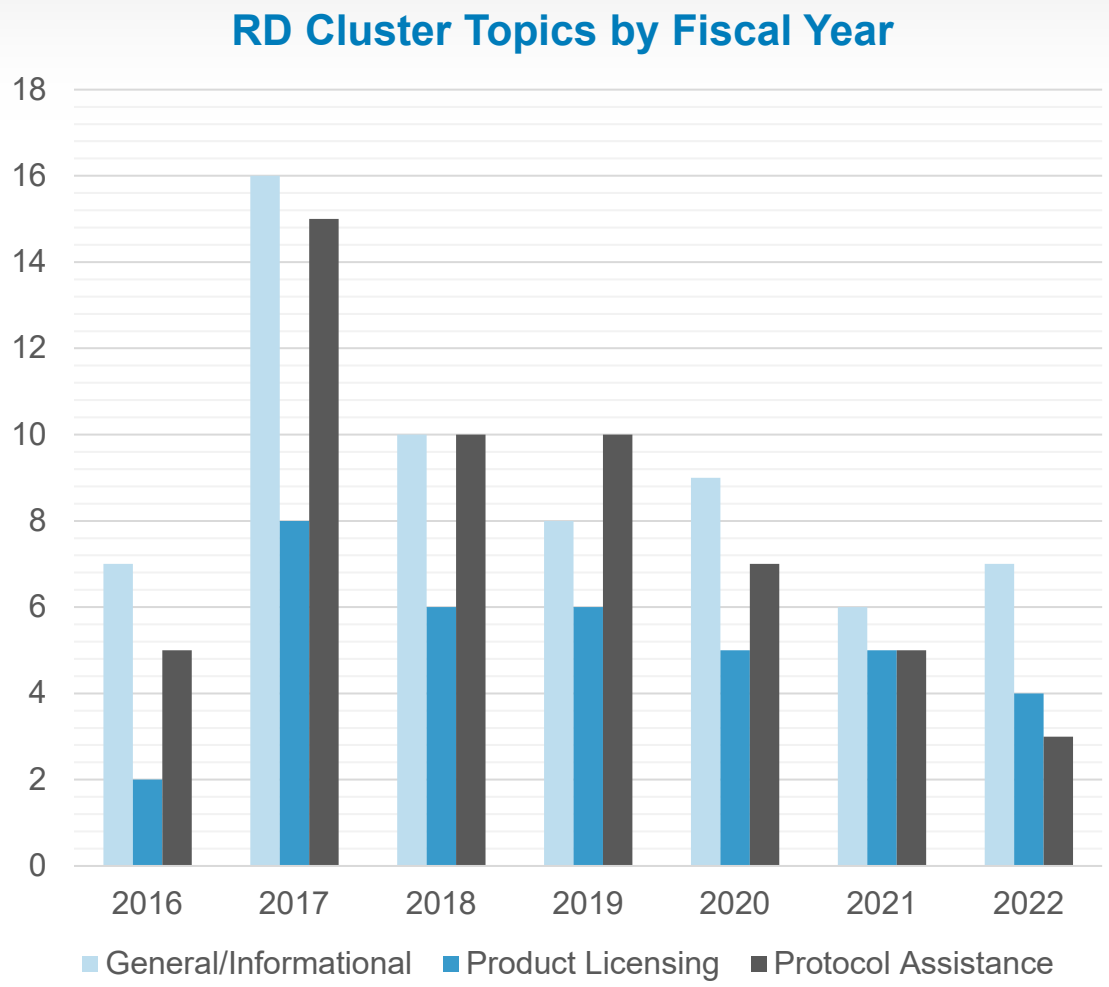
- Groups formed around topical areas of interest
  - Current **31** FDA-EMA Clusters
  - Regular cadence of meetings to facilitate timely information exchange
  - Discussion of ongoing applications/procedures; Joint workshops and publications; Guidelines
- Initially formed by FDA and EMA, but may expand to other regulators, at the agreement of the two agencies
- Clusters of relevance to rare diseases include Rare Disease Cluster, Advanced-Therapy Medical Products Cluster, Blood Cluster, Pediatric Cluster, Oncology-Haematology Medicinal Products Cluster, Orphan Medicinal Products Cluster, Patient Engagement Cluster, Real World Evidence Cluster

International Rare Diseases Cluster Objectives

- The International Rare Diseases Cluster is expected to fulfill four objectives:

1. Achieve a common understanding of each Agency's regulatory approaches to rare diseases drug development based on internal policies, guidance documents and regulations.
2. Provide a forum for discussion of candidate drugs and drug classes for the treatment of rare diseases including issues such as trial end points, safety populations, statistical approaches to rare disease populations, flexibility, methodologies for post marketing issues pre-clinical evidence to support development programs.
3. Offer a confidential forum to share scientific evaluations of rare disease drug development.
4. Address long term safety issues and ensure a global safety net for drugs developed to treat rare diseases through confidential sharing of reports.

Summary of Cluster Meeting Topics 2016-2022



- 150 Topics discussed (9/2016 – 9/2022)
  - Protocol Assistance (N=53) – (e.g., elements of trial design in the IND phase)
  - Product Licensing (N=34) – (e.g., marketing applications)
  - Informational Presentations (N=63) – (e.g., guidances, initiatives, etc.)

Discussion Cluster for Advanced Therapy Medicinal Products (ATMP)

- Established: 2008
- Meeting frequency: four to five times a year by teleconference
- Multilateral-FDA, EMA and others (e.g., Health Canada, Japan PMDA)
- Objective: to develop a common understanding of each Agency's regulatory approaches for advanced-therapy medicinal products (ATMPs).

Objective of the ATMP Cluster

- Goals: Information sharing, convergence of regulatory approaches when appropriate
- Products Under Discussion:
  - Cell-based products
  - Gene Therapy Products
  - Tissue Engineered Products
  - Xenotransplantation Products
- Topics Discussed:
  - Guidance/guidelines under development
  - Testing requirements for specific products
  - Pre-approval and Post-approval requirements
  - Adverse Events
  - Clinical endpoints
  - Workshops
  - New indications for approved products
- The ATMP cluster is a product-specific cluster. Discussions often include members of other clusters.

International Pediatric Cluster Objectives

- The International Pediatric Cluster is expected to fulfill the following objectives:[1]
  1. **Facilitate regular exchange of information** related to scientific and ethical issues on pediatric product development submitted according to EU/US legislation to avoid exposing children to unnecessary or duplicative trials
  2. **Aim at global pediatric development** in line with the pediatric legislation and regulations in the EU and US
  3. **Understand the scientific rationale** when differences in opinion exist
  4. **Discuss post-marketing pediatric requirements** and issues, including risk management and plans for long term safety monitoring
  5. **Discuss general topics** of regulatory and scientific interest to the participating agencies
  6. **Inform the participants** of planned scientific meetings or workshops related to pediatric matters with the possibility of attending the meetings

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Health Canada Santé Canada

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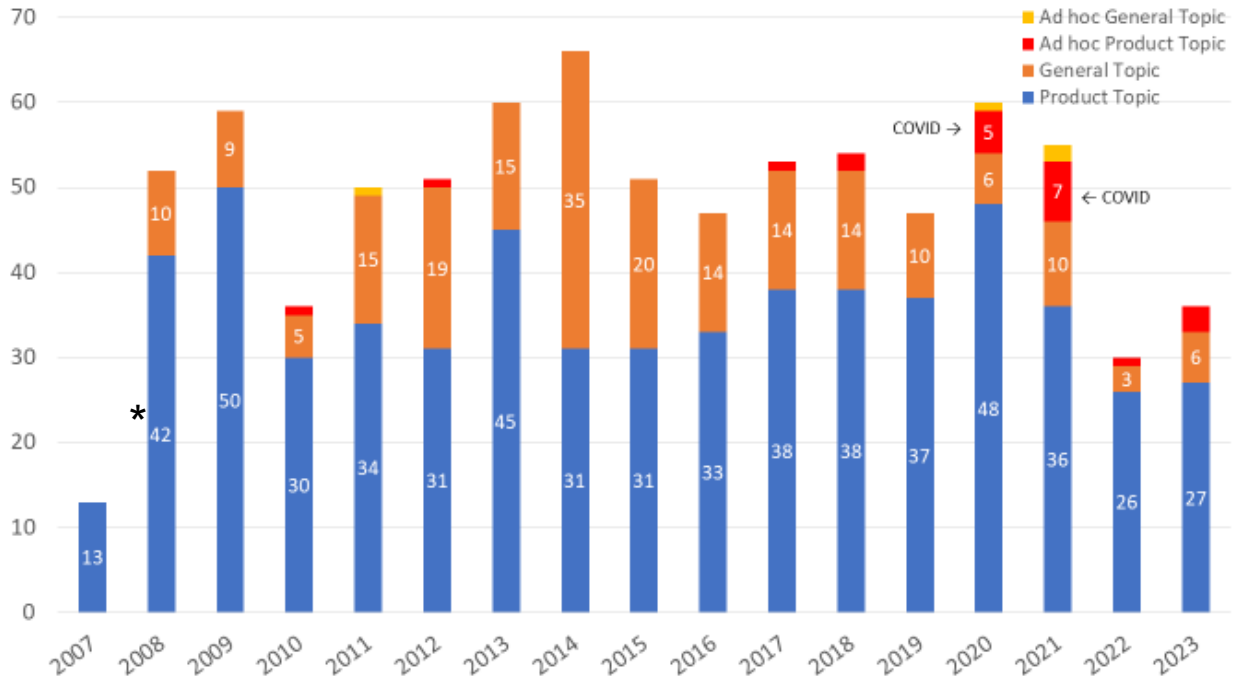
Pharmaceuticals and Medical Devices Agency

Australian Government
Department of Health
Therapeutic Goods Administration

[1]Source: Terms of Reference for the Pediatric Medicinal products cluster June 2007, updated April 2023

Summary of Pediatric Cluster Meetings, Topics, and Issues Discussed

Pediatric Cluster Topics Sept 2007- Sept 2023 N=820



*Partial year since Peds Cluster established in July 2007

- Established in 2007
- From 2007 through September 2023:
  - 206 t-cons
  - 611 product topics
  - 209 general topics
- Most frequently discussed product issues through September 2023:
  - Scope of pediatric development / pediatric development plan
  - Safety
  - Types of clinical studies
  - Study design
  - Study population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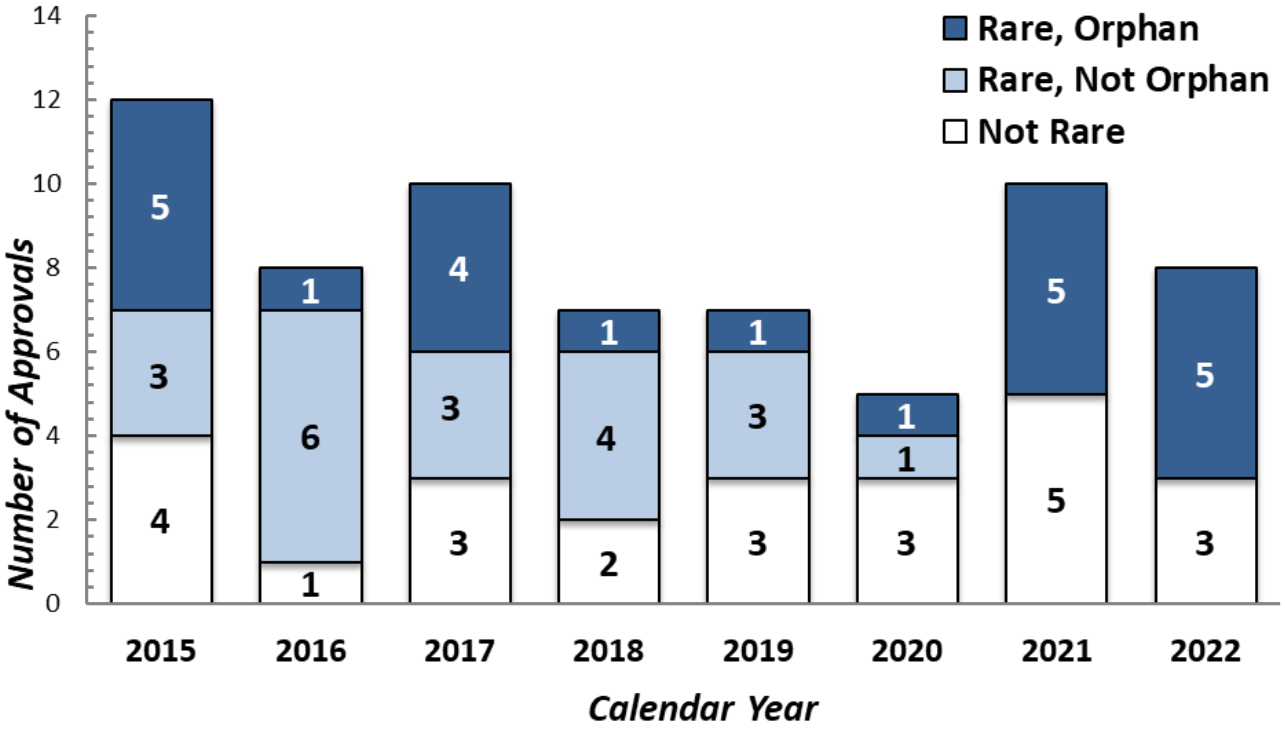
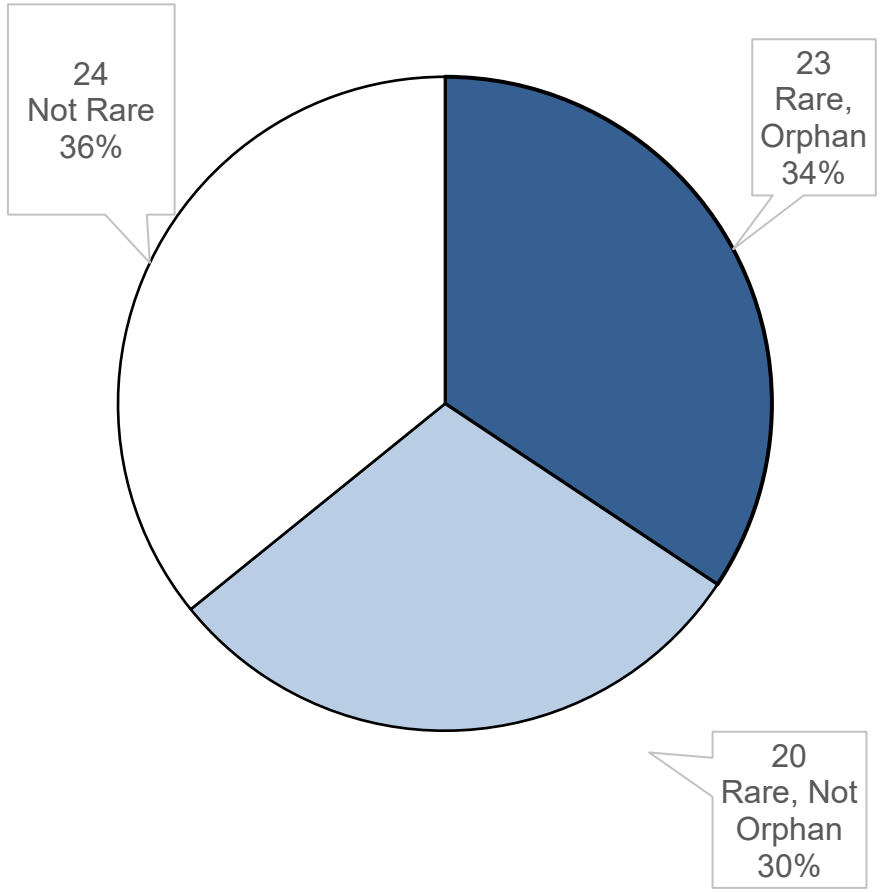
Appendix

CBER Novel Biologic Approvals for use of Rare Disease 2015-2022



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

67 Approvals



FDA Approval Standards for New Drugs and Biological Products

Kevin Fain, JD, MPH, DrPH
Senior Policy Advisor
Office of New Drug Policy
Office of New Drugs
Center for Drug Evaluation and Research

Outline

- Approval Standard for New Drugs and Biological Products
- Effectiveness Standard
  - Substantial Evidence Requirement
- Safety Standard
- Benefit-Risk Assessment for New Drugs and Biological Products: Balancing Effectiveness and Safety

Approval Standard for New Drugs and Biologic Products

- Federal Food, Drug, and Cosmetic Act (FDC Act), and FDA regulations, set forth the relevant standards for approval of a new drug under a new drug application (NDA).
- Public Health Service Act (PHS Act), and FDA regulations, set forth the relevant standards for approval of a biological product under a biologics license application (BLA).
- For a new drug or biological product to be approved for marketing in the United States, FDA generally must determine that the drug is **safe** and **effective** for the intended use (e.g., section 505(d) of the FDC Act; section 351(a) of PHS Act; 21 CFR 314.125(b)).
  - Under the PHS Act, licenses for biologics have been issued only upon a showing that the products are "safe, pure, and potent." Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)).
  - This approval standard applies to all new drugs and biological products, including drugs and biological products intended to treat rare diseases.

Demonstrating Effectiveness

- The demonstration of effectiveness under this standard requires **substantial evidence** that the drug will have its intended effect. (section 505(d)(5) of the FDC Act; section 351(a) of PHS Act; 21 CFR 314.125(b)(5))
  - FDA has generally considered substantial evidence of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act.
- Substantial evidence is defined in the FDC Act and FDA regulations:
  - "[E]vidence consisting of **adequate and well-controlled** investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved…." (Section 505(d); 21 CFR 314.125(b)(5))
  - "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." (Section 505(d))
- FDA regulations and guidance address the **quality** and **quantity** of such investigations.

Adequate and Well-Controlled Investigations: Quality

- Characteristics of adequate and well-controlled investigations are described in FDA regulations (21 CFR 314.126), including:
  - Choice of control
  - Method of patient assignment to treatment (e.g., randomization)
  - Adequate measures to minimize bias (e.g., blinding)
  - Well-defined and reliable assessment of individuals' response (efficacy endpoint)
  - Adequate analysis of investigation's results to assess the drug's effects (i.e., statistical methods)

Adequate and Well-Controlled Investigations: Quality

- Randomized, double-blinded, concurrently controlled superiority trials are usually regarded as the most rigorous design.
- But other trial designs may satisfy the requirement for “adequate and well-controlled” investigations, depending on the specific circumstances and provided that they are scientifically sound.
- FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Dec 2019) discusses select trial designs in more detail.[1]

[1] The draft guidance, when finalized, will represent FDA’s current thinking on this topic.

Adequate and Well-Controlled Investigations: Quality

- Trial Endpoints
  - Methods of assessment of subjects' response are well-defined and reliable. (21 CFR 314.126)
  - Such a method of assessment can be a **clinical endpoint** or, where appropriate, a **surrogate endpoint**.[1]
  - The effect shown in the adequate and well-controlled clinical investigations must be, in FDA's judgment, **clinically meaningful**.[1]
- Standard (Traditional) Approval: Clinical endpoint OR surrogate endpoint known to predict clinical benefit ("validated" surrogate endpoint)
- Accelerated Approval: Surrogate endpoint is "reasonably likely" to predict clinical benefit

[1] FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. (Dec 2019)

Adequate and Well-Controlled Investigations: Quantity

Number of studies to establish substantial evidence of effectiveness:[1,2]

- 2 adequate and well-controlled clinical investigations
- 1 adequate and well-controlled **large multicenter trial** that can be considered, both scientifically and legally, to be multiple trials
- 1 adequate and well-controlled clinical investigation plus **confirmatory evidence** if FDA determines it is appropriate based on relevant science

[1] FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. (Dec 2019)

[2] FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence. (Sept 2023)

Adequate and Well-Controlled Investigations: Quantity

- FDA Draft Guidance on Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence published September 2023[1]
- Confirmatory evidence (CE) is defined as data drawn from one or more sources to substantiate results of one adequate and well-controlled (A&WC) clinical investigation.
- Draft Guidance provides a framework for how to consider the approach for 1 A&WC clinical investigation + CE:
  - A highly persuasive A&WC clinical investigation might be supported by a lesser quantity of CE, while a less-persuasive A&WC clinical investigation may require a greater quantity of compelling CE.
  - The clinical context and scientific rational are important when considering whether a 1 AWC clinical investigation + CE approach is appropriate.

[1] FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence. (Sept 2023)

Adequate and Well-Controlled Investigations: Quantity

Categories of Confirmatory Evidence:[1]

- Clinical Evidence from a Related Indication
- Mechanistic or Pharmacodynamic Evidence
- Evidence from a Relevant Animal Model
- Evidence from Other Members of the Same Pharmacological Class
- Natural History Evidence
- Real-World Data/Evidence
- Evidence from Expanded Access Use of an Investigational Drug

Additional information is provided in the FDA Draft Guidance on Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (September 2023).[1]

[1] FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence. (Sept 2023)

Substantial Evidence of Effectiveness: Other Considerations

- Some study designs (such as placebo concurrent control) provide more certainty than others (such as external controls).
  - However, study designs that produce less certainty may be relied upon in some circumstances when a better design is not feasible or ethical.
  - This may be the case for life-threatening and severely debilitating diseases with an unmet medical need, or for certain rare diseases.
- In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug.
- But the degree of certainty supporting such a conclusion may differ, depending on the clinical circumstances (e.g., severity and rarity of the disease and unmet medical need).[1]
- Application of flexibility: "While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus, FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards." (21 CFR 314.105(c))

[1] FDA draft guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. (Dec 2019)

Demonstrating Safety

- The burden of establishing that a drug is safe lies with the applicant.
- The applicant generally must provide evidence from “adequate tests by all methods reasonably applicable to show whether the drug is safe for use” under the proposed conditions of use. (Section 505(d)(1) of the FDC Act; 21 CFR 314.125(b)(2); see also section 351(a) of PHS Act).
- Among other reasons, FDA will deny approval if the results of the tests do not show that the drug is safe for use under such conditions. (Section 505(d)(2) of the FDC Act; 21 CFR 314.125(b)(3) see also section 351(a) of PHS Act)

Benefit-Risk Assessment

- Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks.[1]
- Benefit-risk assessment is integrated into FDA's regulatory review of marketing applications for new drugs.
- Section 505(d) of the FDC Act requires FDA to "implement a structured risk-benefit assessment framework in the new drug approval process" and provides that this requirement does not alter the statutory criteria for evaluating an application for marketing approval of a drug.
- FDA uses **scientific assessment** and **regulatory judgment** to determine whether the drug's benefits outweigh the risks, and whether additional measures are needed and able to address or mitigate this uncertainty.[1]

[1] FDA final guidance on Benefit-Risk Assessment for New Drug and Biological Products (Oct 2023)

Benefit-Risk Assessment

FDA's benefit-risk assessment comprises a case-specific, multi-disciplinary assessment of science and medicine, which considers:[1]

- Therapeutic context in which the drug will be used, including:
  - Nature and severity of the condition
  - Degree that patients' needs are met by currently available treatments.
- Strengths and limitations of evidence for benefits and risks
- Benefits, including:
  - Nature of the effect (e.g., survival, reduction of serious outcomes, reduction of symptoms)
  - Effect size and associated uncertainty, including clinical importance
- Risks, including:
  - Severity of adverse event, likelihood of occurrence, reversibility
  - Effect size and associated uncertainty
- FDA's regulatory options (such as requirements for additional premarket or postmarket studies, labeling content, other risk mitigation strategies)

[1] FDA final guidance on Benefit-Risk Assessment for New Drug and Biological Products (Oct 2023)

Typical Process for Approval to Market a New Drug or Biologic Product

- Applicant pursues drug development program through regulatory steps, including the submission of an Investigational New Drug (IND) application, pursuant to 21 CFR Part 312, to conduct human clinical trials.
- Applicant can meet and correspond with FDA at various points in the development program, including about clinical trials (e.g., “end-of-phase 2” meeting before major commitments of effort and resources to specific phase 3 trials are made).[1]
- Sponsor submits new drug application (NDA) or biologics license application (BLA), as applicable, pursuant to relevant statutory and regulatory provisions for FDA’s approval to market the drug.
- If the sponsor includes the information required by statute and regulations for an application, FDA then assesses the submitted evidence to determine if statutory and regulatory standards are satisfied for approval.
- Applicant can supplement information through amendments to the NDA or BLA.[2]

[1] 21 CFR 312.47(b). [2] e.g., 21 CFR 314.60.

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FDA Expedited Programs Reference Slides

Serious Conditions

- A **serious disease or condition** is defined as:
  - **A disease or condition associated with morbidity that has substantial impact on day-to-day functioning**
- Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent
- Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one

Guidance to Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, Final May 2014 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

Available Therapy

- FDA considers **available therapy (AT)** as a therapy that:
  - Is approved or licensed in the United States for the same indication being considered for the new drug and
  - Is relevant to the current U.S. standard of care (SOC) for the indication
- Determination focuses on treatment options that reflect the current SOC for:
  - The specific indication for which a product is being developed
  - The disease stage for the specific indication
- When determining whether a drug granted accelerated approval (AA) is available therapy:
  - **Would not be AT** if the drug is granted AA based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies
  - **Would be AT** if the drug is granted AA because of restricted distribution and the study population for the new drug under development is eligible to receive the approved drug under the restricted distribution program

Guidance to Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, Final May 2014 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

Unmet Medical Need

- An unmet medical need is a condition whose treatment or diagnosis is **not addressed adequately by AT**
- An unmet medical need includes an **immediate need for a defined population** (i.e., to treat a serious condition with no or limited treatment) or a **longer-term need for society** (e.g., to address the development of resistance to antibacterial drugs)
- If there is no available therapy for a serious condition, there is an unmet medical need

Guidance to Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, Final May 2014 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

Unmet Medical Need Continued

- When AT **does** exist for a condition, a new treatment **generally would be** considered to address an unmet medical need if the treatment:
  - Has an effect on a serious outcome of the condition not known to be influenced by AT(e.g., progressive disability or disease progression)
  - Has an improved effect on a serious outcome(s) of the condition compared with AT(e.g., superiority of the new drug to AT)
  - Has an effect on a serious outcome of the condition in patients who are unable to tolerate or failed to respond to AT
  - Can be used effectively with other critical agents that cannot be combined with AT
- If treatment provides efficacy comparable to AT:
  - While avoiding or decreasing serious toxicity associated with AT, or reducing the potential for drug interactions
  - Or has a documented benefit, such as improved compliance, that is expected to lead to an improvement in serious outcomes
- If treatment addresses an emerging or anticipated public health need, such as a drug shortage

Guidance to Industry: Expedited Programs for Serious Conditions-Drugs and Biologics, Final May 2014 (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf)

Breakthrough Therapy Designation: Orphan Diseases *or* Available Therapy

Center for Drug Evaluation & Research (CDER) decisions to grant or deny breakthrough therapy designation requests (n=240) for non-oncology drugs/biological products: 1 Jan 2017 thru 31 Dec 2019

BTD decisions & orphan designation of drug:

Category; n (%)	Granted	Denied
Orphan; n=90 (42%)	47 (52%)	43 (48%)
Not orphan; n=150 (58%)	46 (31%)	104 (69%)
Total; N=240	93	147

BTD decisions & availability of FDA-approved therapy:

Category; n (%)	Granted	Denied
No therapy; n=133 (55%)	63 (47%)	70 (53%)
Therapy available; n=107 (45%)	30 (28%)	77 (72%)
Total; N=240	93	147

Analyses by Atasi Poddar, Miranda Raggio, John Concato (CDER)


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