U.S. FOOD & DRUG ADMINISTRATION

Accelerating Rare disease Cures (ARC) Program

YEAR TWO: Annual Report

Driving Innovation through Scientific and Regulatory Advancement

October 2024

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Message from the Director of the Center for Drug Evaluation and Research

Since its launch in May of 2022, Food and Drug Administration's (FDA) Center for Drug Evaluation and Research's (CDER) Accelerating Rare disease Cures (ARC) Program has become a key resource for the rare disease community and a driver of innovation in rare disease drug treatments. The ARC Program remains dedicated to driving scientific and regulatory innovation and engagement while closing the gap between the challenges of developing drugs for rare diseases and the urgent need for treatment options for patients.

Dr. Patrizia Cavazzoni

Over the past year, the ARC Program has concentrated on initiatives to accelerate and enhance the development of drugs for rare diseases. In June 2023, ARC was excited to partner with the Center for Biologics Evaluation and Research (CBER) to launch the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, which offers selected participants enhanced communication from FDA staff to address program-specific development issues. In addition to the START Pilot Program, ARC has sought to address the unique needs of drug sponsors in developing clinical trials for rare disease drugs by launching and expanding the reach of ARC's Translational Science Team (TST), a unit of subject matter experts and senior leaders focused on supporting new drug application review teams across CDER.

The ARC Program also announced the publication of a public report and an informational video developed under the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) initiative. Furthermore, enhancements to ARC's website gave patients and drug developers greater access to critical resources and updates regarding rare disease activities.

ARC has continued to prioritize patients by hosting listening sessions and patient-focused drug development meetings that allowed patients and patient advocacy groups to inform and enhance innovative approaches to rare disease drug development. Further, ARC engaged academics and drug developers to ensure their expertise and unique perspectives are leveraged in the innovation and development of rare disease therapies. Additionally, you will discover how CDER is using innovative approaches to spur the development of safe and effective rare disease therapies.

Keeping the momentum, we are looking forward to the establishment of a rare disease collaborative hub space in the coming year. The Rare Disease Innovation Hub (the Hub) will leverage the activities across CDER's and CBER's rare disease programs, enhancing existing cross-center collaborations. We are excited about the potential benefits this intercenter engagement will bring to the rare disease community.

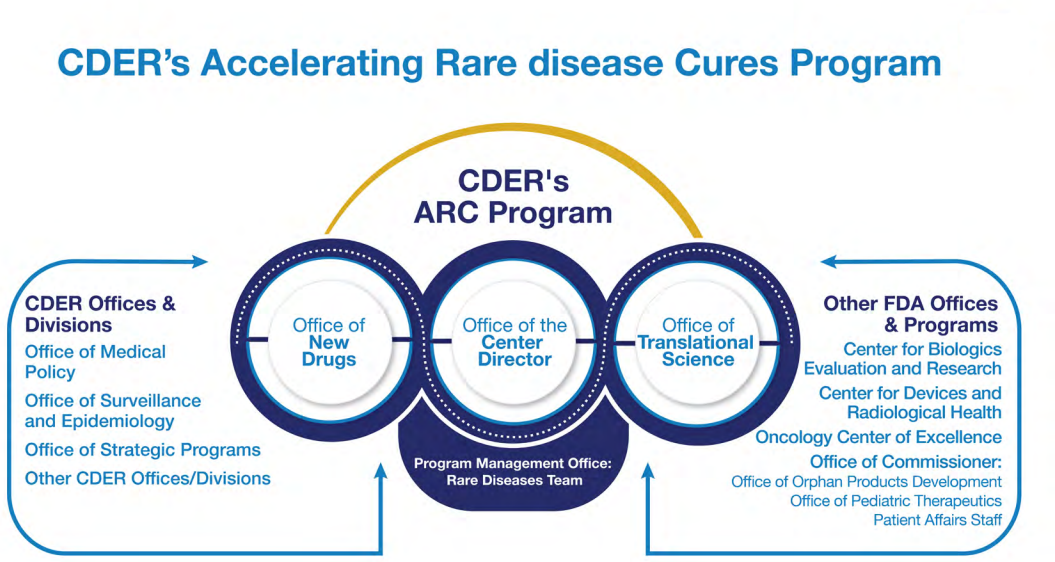
The ARC Program, supported by a dedicated team, CDER's Rare Diseases Team (RDT), continues to inspire CDER by driving change through empathy, intelligence, and passion. I am proud of the significant initiatives we have undertaken over the past year and look forward to what we all can accomplish together in advancing rare disease therapies that will benefit the rare disease community.

About the ARC Program

A rare disease is any disease that affects fewer than 200,000 people in the U.S. There are approximately 25 to 30 million Americans living with a rare disease (about 1 in 10 people). Drug development for the approximately 10,000 rare diseases and conditions can be complex for many reasons, such as:

- There can be challenges with using well-established trial designs.
- Endpoint selection to measure drug efficacy can be complicated if there is a limited understanding of the natural history of the disease.
- Small patient populations can make it difficult to perform and interpret rare disease clinical trials.

For these and other reasons, many rare diseases have few or no available treatments for patients who suffer from them. ARC strives to increase the number of safe and effective rare disease drugs by promoting innovative scientific design, providing a deeper understanding of regulatory policies, and engaging in dialogue with rare disease patients and patient advocacy groups.



The ARC Program is a CDER-wide effort led by the Office of New Drugs (OND), in close collaboration with the Office of the Center Director (OCD), the Office of Translational Sciences (OTS), and other CDER offices. ARC also brings together other FDA Offices and programs, such as CBER, the Center for Devices and Radiological Health (CDRH), the Oncology Center of Excellence (OCE), and the Office of the Commissioner, underscoring FDA's strong commitment to advancing treatment options for rare diseases and conditions. The ARC Program's management and operations are supported by CDER's RDT. Coordination and consistency for rare disease treatments is critical to ARC's endeavors. In addition

to leading development of cross-cutting rare disease guidances and promoting and educating on shared policies and practices across the center, the RDT works closely across FDA's rare disease community to detail the agency's activities dedicated to the development and review of drugs and biologics for rare diseases. The ARC Program continues to focus on strengthening internal and external partnerships and engaging experts to help identify solutions for the challenges in rare disease drug development. The following sections take a more comprehensive look in to some of these activities and the significant milestones achieved over the past year.

Our Vision

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

Our Mission

CDER's ARC Program drives scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

Year At-A-Glance

Building on its successful launch in 2022, close collaboration with CDER offices and across FDA enabled the ARC Program to support various activities to advance rare disease drug development.

Over the past year, achievements included:

15

Patient Listening Sessions on Rare Diseases:

12 held by the Office of the Commissioner Patient Affairs Staff (PAS) with participation from CDER staff, and **3** organized by Professional Affairs and Stakeholder Engagement (PASE)

29

Rare Disease New Drug Approvals

32,358

CDER Rare Disease News Subscribers

40+

public speaking engagements featuring the ARC Program

3

ARC Quarterly Newsletters

13

externally-led Patient-Focused Drug Development Meetings on Rare Diseases supported by CDER staff

1M+

1,047,976 impressions (views) across **103** social media posts

Outreach and Education

ARC's outreach and education initiatives focus on engagement with the rare disease community to leverage expertise and innovation in the rare diseases space. Input from patients living with rare diseases is crucial throughout the drug development process. FDA staff undertook several initiatives to deepen the understanding of the regulatory framework while other initiatives aimed to provide more accessible information about CDER rare disease news and initiatives to the rare disease community.

Patient-Focused Initiatives

FDA's CDER Patient-Focused Drug Development (PFDD) Program strives to more systematically obtain the patient perspective on specific diseases and their treatments throughout drug development through efforts such as the PFDD Guidance Series, public meetings such as the FDA-Duke Margolis Meeting, Advancing the Development of Therapeutics Through Rare Disease Patient Community Engagement that was held in December of 2023, and PFDD meetings. The event focused on how to best understand patients' experiences living with a rare disease and how to incorporate those experiences and priorities throughout the drug development process.

PFDD meetings give FDA and other key interested parties (such as medical product developers, health care providers, and federal partners) an important opportunity to hear directly from patients, their families, caregivers, and patient advocates about the symptoms that matter most to them, the impact the disease has on patients' daily lives, and patients' experiences with currently available treatments. This input can provide critical information to medical product developers throughout the drug development lifecycle, including as they identify targets for therapies, develop or select clinical trial endpoints (endpoints are measurements of efficacy from a clinical trial), and design clinical trials. The meetings can also help provide important information for FDA when meeting with sponsors, and they may provide important therapeutic context during ARC's review of a marketing application. CDER staff attended and supported the conduct of **17 externally-led PFDD meetings** from October 2023-September 2024 (FY24). Of these, 13 meetings were focused on rare conditions.

Patient listening sessions (PLS) are another way for the patient (and advocacy community) to share their experiences and perspectives about their condition(s). These sessions are small, informal, non-regulatory, non-public teleconference meetings that allow participants to connect with FDA staff to share their experiences, perspectives, and needs related to their condition. During FY24, Patient Affairs Staff (PAS) from FDA's **Office of the Commissioner supported 12 listening sessions** for patients with rare diseases. Additionally, CDER's Professional Affairs and Stakeholder Engagement (PASE) Staff supported three listening sessions, covering rare diseases such as Prader Willi syndrome, atypical hemolytic uremic syndrome, and epidermolysis bullosa.

While patients with rare diseases and their families have extensive direct experience living with their disease and available drug treatments, CDER recognizes that they often have more limited information on the processes that are involved in developing new drugs, as well as the evidence needed to demonstrate their effectiveness. In late summer 2022, CDER initiated discussions with the National Organization for Rare Disorders (NORD) to develop some advanced tools and related training for patients with rare diseases and their families. The goal of this new education series is to provide patients and families with a deeper knowledge of the drug development and regulatory process. The information will support their ability to play a more active role in the drug development and regulatory process as well as to promote the most effective drug development programs for their disease areas. NORD announced the first portion of the series titled, "Rare Disease Drug Development: What Patients and Advocates Need to Know" in October 2023 and have recently announced the availability of additional modules. The education series is available free of charge in both English and Spanish. It can be accessed through the NORD website.

Learning and Education to ADvance and Empower Rare Disease Drug Developers (LEADER 3D)

CDER is pleased to announce the publication of new educational materials developed under the ARC Program's Learning and Education to ADvance and Empower Rare Disease Drug Developers (LEADER 3D) initiative. As part of this initiative, CDER'S RDT, in partner with an independent third-party contractor, engaged with members of the rare disease drug development community who design and conduct rare disease drug development programs, to identify regulatory topics that could benefit from new or expanded educational materials. The RDT **used the community's valuable feedback to create educational materials** that provide fundamental information to aid drug developers in navigating the challenges inherent to rare disease drug development and illustrate relevant regulatory considerations for rare disease drugs and biologics regulated by CDER.

The newly published materials include:

- A public report to encourage innovation and mitigate challenges associated with rare disease drug development. CDER conducted interviews with the rare disease drug development community and performed a review of public docket comments to identify educational opportunities across topics in rare disease drug development. Published in early 2024, the LEADER 3D public report summarizes the findings from the analysis of these interactions and provides recommendations to continue efforts for expanded outreach and education to the rare disease drug development community.
- An animated video on Challenges, Strategies, and Regulatory Considerations for the Design of Rare Disease Clinical Trials, which covers foundational aspects of planning, conducting, and analyzing rare disease clinical trials.

Based on input from the rare disease community, multidisciplinary subject matter experts at CDER collaborated to develop these initial materials in support of the CDER ARC Program's objective to engage with the community to accelerate the availability of drug and biologic products for patients with rare diseases.

Other enhancements to the ARC webpage resulting from feedback received [for LEADER 3D] from the community include:

- A list of guidance documents relevant to rare disease drug development organized by topic
- A link to relevant funding opportunities for rare disease drug development community

ARC Quarterly Newsletter

As part of the ARC Program's ongoing commitment to foster communication among the rare disease community, ARC distributes the "CDER Rare Disease News." This quarterly newsletter updates subscribers on program developments, new drug approvals, and highlights relevant conferences, partnerships, or initiatives of interest to the rare disease community. Since launching, the number of readers continues to grow – surpassing ARC's 2024 goal with **32,358 subscribers**. As readership expands in coming years, ARC hopes that the newsletter will act as a powerful virtual tool to enhance collaboration among the rare disease community.

To subscribe to this newsletter, please visit CDER Rare Disease News.

ARC Online Presence

A valuable resource, ARC's website has continued to provide important tools for rare disease patients and drug developers alike. The site features current guidance documentation on the design and conduct of rare disease clinical trials, upcoming and recent rare disease events, policy and program initiative highlights, funding opportunities, and other helpful rare disease resources. From January to June 2024, the ARC Program website logged **nearly 10,000 views** with 6,312 unique users, and an engagement rate, which demonstrates how actively people interact with the site's content, of 80%. The Guidance Documents For Rare Diseases Drug Development webpage captured roughly 4,000 views with an engagement rate of 76%.

The ARC Program also continued to support the "Original Rare Disease Application Approval" and "Novel Rare Disease Drugs Approval" filters in CDER's Drugs and Biologics Dashboard hosted on FDA-TRACK. FDA-TRACK is the agency-wide performance management program that reports on performance measures and key projects for various FDA centers and programs. Visitors can toggle-view the history of CDER's cumulative drug approvals to view those which were approved for the treatment of rare diseases. This information within FDA-TRACK provides a more accessible view to the rare disease community about the development and approval of safe and effective drugs to treat rare diseases.

In August 2024, the editorial *9 Things to Know about CDER's Efforts on Rare Diseases* explored CDER's efforts to accelerate the development of safe and effective drugs to treat rare diseases and conditions.

In September 2023, the CDER Social Media team collaborated with ARC to strategically launch a content calendar highlighting rare diseases on social media platforms. Fundamental to the mission of FDA is to engage patients and caregivers

– to understand their unique perspectives and experiences and keep them front of mind as the agency reviews medical products for rare disease patients. Thus, the goal for this collaboration was to significantly amplify the agency's outreach and engagement concerning rare diseases. By expanding FDA's rare disease focused presence beyond X (formerly Twitter) to include Facebook and LinkedIn, ARC has reached a broader audience, sharing prompt updates on rare disease approvals, meetings, and guidance documents, and providing the external rare disease community with knowledge about opportunities to engage directly with the FDA. This comprehensive approach has strengthened ARC's connections with the rare disease community, ensuring that vital information and resources are accessible to the American public through several channels.

1M+

1,047,976 impressions (views) across 103 social media posts

Conferences, Workshops, and External Speaking Engagements

Conferences, workshops, and meetings focused on rare disease drug development serve as key platforms where communities of rare disease stakeholders united to exchange experiences, insights, challenges, and discuss future innovations. Since external outreach remains central to the ARC Program, FDA staff have participated in over **40 public speaking engagements** over the last year as presenters, panelists, and audience members to amplify CDER rare disease initiatives, and listen to the efforts and experiences of other participants, including rare disease patients and drug developers.

ARC staff and programs were featured at FDA's Rare Disease Day 2024, a virtual public meeting themed, "Dedicated to patients and providers." ARC staff co-moderated a panel that highlighted the legal frameworks governing the use of investigational drugs, biological products, and devices in FDA-regulated research and the standards governing the review and marketing authorization of such products. During the panel discussion of the day, "FDA initiatives to advance medical product development for rare diseases," CDER Rare Diseases Team Staff provided an update on CDER engagement initiatives for rare diseases.

ARC has made information, recordings, and meeting materials available on its webpage for the following events in which it participated this past year:

- Natural History Studies and Registries in the Development of Rare Disease Treatments: May 13, 2024
- Advancing the Use of Complex Innovative Designs in Clinical Trials: From Pilot to Practice: March 5, 2024
- Public Meeting on Advancing the Development of Therapeutics Through Rare Disease Patient Community Engagement: December 14, 2023
- FDA CDER and CBER & Duke-Margolis Center for Health Policy | Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development: June 7-8, 2023

Scientific and Regulatory Initiatives

The ARC Program supports various scientific and regulatory initiatives intended to provide direction and to drive the development of various supporting tools to promote rare disease drug development. Activities include strengthening platforms that facilitate natural history studies for rare diseases; developing, testing, and validating methodologies to construct novel endpoints; expanding the utilization of drug/disease modeling; establishing efficient approaches to dose selection for drugs for small population diseases; and expanding efforts in translational medicine approaches for individual rare disease programs. By promoting innovative scientific design and providing a deeper understanding of regulatory policies, ARC strives to accelerate the availability of treatments for patients with rare diseases.

Following another productive year of reviews and approvals for rare disease therapies, CDER's Office of New Drugs (OND) and Office of Translational Sciences (OTS) (Office of Biostatistics (OB) and Office of Clinical Pharmacology (OCP)) have contributed to and led multiple scientific and regulatory initiatives to advance the complex and multi-disciplinary considerations of rare disease drug development.

By promoting innovative scientific design and providing a deeper understanding of regulatory policies, ARC strives to accelerate the availability of treatments for patients with rare diseases.

Regulatory Science Research

Over the past year, FDA's CDER RDT supported and led research to advance rare disease drug development, inform product review, and improve policy related to rare disease therapeutics. The RDT engaged in internal (e.g., research projects for fellows and interns mentored by RDT and external (e.g., through research contracts) regulatory science projects that supported policy development. The RDT's research sought to utilize regulatory science to identify broader challenges and potential solutions that could inform rare disease drug development across therapeutic areas. Many active areas of regulatory science research in the last year are described below:

- **Efficacy.** Many rare disease novel drug applications utilize one (1) adequate and well-controlled trial plus confirmatory evidence (CE) of effectiveness to meet FDA's requirement for demonstrating substantial evidence of effectiveness. To understand how CE of effectiveness is used to support rare disease drug approval, ongoing research by the RDT has categorized CE in approved new molecular entity (NME) new drug applications (NDAs) and original biologics license applications (BLAs) in the CDER. These results will build a foundation for future regulatory research that can contribute to better transparency, understanding, and communication of CE used in rare disease drug development. In addition, insight from this analysis may facilitate FDA's review of CE data in rare disease drug development programs.
- **Endpoint Biomarkers.** Biomarkers that can predict clinical benefit are often used as efficacy endpoints, and they are especially beneficial for rare disease drug development. Ongoing research by RDT has examined biomarkers that supported the approval of novel drugs for non-oncologic rare diseases in the U.S. over a decade.
- **Patient Input.** Patient experience data is useful when designing clinical trials as this information may increase the likelihood that drugs developed for rare disease patients will address their most critical unmet needs. Drug developers and FDA use various sources of patient/caregiver experience data including patient-focused drug development (PFDD) and patient listening session (PLS) meetings to help inform the design and assessment of clinical trials. RDT's regulatory research on the alignment of approved rare disease

trial design, clinical endpoints, and drug characteristics (e.g., route of administration) with patient input may provide a better understanding of whether and how the needs of patients and caregivers are currently being considered during drug development and regulatory review.

- **Nonclinical Models.** Depending on scientific and therapeutic context, data from nonclinical models can sometimes be evaluated to provide mechanistic insight into drug effectiveness to inform regulatory review of new drug applications. Use of nonclinical models may be helpful in challenging rare disease drug development programs, where small patient populations, disease heterogeneity, and slow or variable disease progression may complicate clinical study design and analysis. RDT's regulatory research assessed nonclinical models that FDA has accepted as high-quality efficacy data supporting approvals for rare disease therapeutics. This research may inform review of applications utilizing these approaches in future drug development programs for rare diseases.

Innovative Statistical Methodologies

The Office of Biostatistics (OB) is recognized for excellence in the application and communication of statistical science in drug regulation and development. Over the past year, OB members have worked on the following projects to address challenges specific to rare disease drug development:

- Project 1. OB evaluated the potential benefits and risks of using the **win-ratio test method**. OB continues to summarize the existing literature and examine potential gaps. As a result, OB members published a paper entitled "Statistical power consideration in the use of win-ratio in cardiovascular outcome trials" in 2023.
- Project 2. OB compared different methods utilizing **Bayesian borrowing approaches**. The project also examined the required sample size and power to assist in trial design for rare disease clinical trials. OB members are capturing outcomes in a forthcoming manuscript and presentations.
- Project 3. OB focused on creating best practice guidelines for constructing **multi-component endpoints**. While still a challenge to construct and interpret, these guidelines may offer improved statistical power in rare diseases. The OB members completed a literature review and are finalizing plans to analyze the in-house data.
- Project 4. OB reviewed and developed innovative methods to precisely **estimate treatment effects** in small subset of patients when relying on generalization (conclusions based on limited information).
- Project 5. OB developed and evaluated **a new global test** using simulations

to allow for different (or multiple) primary endpoints among different subsets of patients, depending on clinical manifestations. Because treatments for rare diseases may impact multiple organs, resulting in a greater combined effect than on any single organ, testing could benefit from considering multiple endpoints. And yet, traditional global tests tend to use the same endpoints for all patients. The OB members have written a manuscript.

- Project 6. OB members established a formal research collaboration agreement and investigated the benefits of using **Targeted Maximum Likelihood Estimation (TMLE)** when the outcome is bounded (has a limit).
- Project 7. OB sought to develop a **best practices** document for statistical reviewers on the evaluation of surrogate endpoints **in rare disease clinical trials**. The team has completed and summarized the literature review of methods and regulations. They are currently reviewing examples from across divisions and drafting the best practices document.

Rare Disease Drug Development Design (RD4)

To foster deep collaboration and connect a variety of expertise and experience across divisions, offices, and centers, the RD4 Workgroup was empaneled in fall 2023 to address a key issue common to rare disease drug trials–trial design.

A co-led effort between CDER OND and OB, the workgroup leveraged subject matter experts from Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (ORPURM)/Division of Rare Diseases, Pediatrics, Urologic and Medical Genetics (DRDMG), Office of Neuroscience (ON), Office of New Drug Policy (ONDP), as well as CBER Office of Biostatistics and Pharmacovigilance (OBPV), and external academic experts to **identify ways to improve trial design and analysis** so that trials would be more likely to provide interpretable data clearly showing a product's efficacy or lack of efficacy.

RD4 has worked to address archetypical problems in rare disease trial analysis and design. By purposefully engaging experts in research discussions, case

study simulations, and active clinical review team development programs, RD4 has focused on developing design tools to facilitate assessment and application of innovative methodologies to address trial design challenges common in small populations trial design.

Clinical Pharmacology and Translational Medicine

The discipline of clinical pharmacology is uniquely poised to provide the necessary biological, mechanistic, and clinical connections to enable drug development for rare diseases with substantial unmet medical needs. By thoroughly characterizing the clinical pharmacology of new drugs, developers can more effectively identify appropriate dosages, select patients more likely to benefit while experiencing fewer risks, and tailor drug use based on concomitant medications and comorbidities.

In the past year, the Office of Clinical Pharmacology (OCP) engaged in several activities that aimed to advance science for the benefit of patients with rare diseases and bolster patient-centered engagement. Beyond working with pharmaceutical companies and other stakeholders on specific drug development programs, select accomplishments include the following:

- **CDER launched the Quantitative Medicine Center of Excellence** (QM CoE) with leadership from OCP. Innovative approaches relying on nonclinical models and quantitative methodologies have become a major focus of OCP because of their potential to facilitate the development of new treatments, particularly when it comes to optimizing the dosage and establishing evidence of effectiveness.
- OCP published a variety of articles in the peer-reviewed literature on topics related to FDA's regulatory review of specific marketing applications, use of novel modeling approaches such as quantitative systems pharmacology, considerations for individualized oligonucleotide therapies, practices for selecting and optimizing dosages for biological enzyme replacement therapy and for first-in-human clinical trials for enzyme replacement therapies, and dosing strategies for pediatric drug products.
- OCP presented information on state-of-the-art clinical pharmacology approaches in drug development at a variety of national conferences. Topics included general aspects of a comprehensive clinical pharmacology program for rare diseases, validation of a biomarker as a surrogate endpoint to support accelerated approval, biomarker studies in neurodegenerative and other rare diseases, and data beyond clinical trials that can support regulatory decision-making.
- OCP held a session focused on rare diseases at a workshop titled Clinical Pharmacology Guidances – Advancing Drug Development and Regulatory

Assessment. This workshop and a related docket will help OCP identify emerging scientific topics that might benefit from the development of scientific research and recommendations.

- OCP continued and initiated numerous regulatory science initiatives that aspire to 1) support the development and application of biomarkers in specific diseases or drug development contexts, 2) define best practices for developing specific therapeutic modalities/drug classes through examination of the drug development landscape, 3) advance the use of novel translational tools to meet the substantial evidence standard, and 4) define approaches to optimize patient selection and dosing to manage population heterogeneity. For example, OCP has a collaboration with the University of Pennsylvania to evaluate the value of multiple "–omic" measures to support the characterization of rare disease mechanisms.
- OCP continued activities under its Rare Disease Scientific Interest Group (RaD-SIG) to facilitate communication among clinical pharmacologists working on different rare diseases, and to create a venue for external experts to educate OCP's staff. OCP invited several speakers to share knowledge on topics such as Single Subject clinical trials (N-of-1) trials, clinical trial designs, gene therapies, community engagement for clinical research, use of alternative cell models to inform drug development, and data analytics platforms. OCP launched an internal web resource for staff to find information on research projects, presentations, application review cases, and other resources that can be used to support regulatory review of rare disease drug development programs.

Rare Disease Endpoint Advancement (RDEA) Pilot Program

The Rare Disease Endpoint Advancement (RDEA) Pilot Program fulfills a performance goal under the FDA User Fee Reauthorization Act of 2022. This is in accordance with the Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027 letter (PDUFA VII letter), and a requirement under section 3208 of the Food and Drug Omnibus Reform Act of 2022 (FDORA).

A joint program between CDER and CBER, the RDEA Pilot Program supports novel endpoint efficacy development for sponsors with an active Investigational New Drug (IND) or pre-IND for a rare disease. The RDEA Pilot Program also supports sponsors who do not yet have an active development program but have, or are initiating, a rare disease natural history study where the proposed endpoint is intended to be studied. Sponsors whose RDEA proposals

are admitted into the RDEA Pilot Program will have increased opportunity to interact with interdisciplinary FDA experts in endpoint development, as well as the associated clinical review division, in a series of up to four focused meetings to discuss their proposed novel endpoint.

The RDEA Pilot Program is designed to:

- Provide 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, including prior to FDA's approval for a drug studied in the trial.
- **Develop FDA staff capacity to enable and facilitate** the development and use of novel endpoints to evaluate the efficacy of rare disease therapies.

In preparation for receiving RDEA proposals, FDA enhanced the RDEA Pilot Program website by adding pages for the following Program topics:

- Submissions Deadlines and Process
- Content and Format of the RDEA Proposal
- RDEA Pilot Program Disclosure Agreement
- Content and Format of the RDEA Meeting Request and Package

ARC will work to share Pilot Program learnings to the internal and external rare disease drug development community.

FDA began accepting proposals on a quarterly basis for admission into the RDEA Pilot Program on July 1, 2023. The quarterly deadlines for submitting RDEA proposals are March 31, June 30, September 30, and December 31. The last quarterly deadline for submitting an RDEA Pilot proposal will be June 30, 2027. To date, FDA has received ten RDEA proposals and admitted two RDEA proposals (1 CDER; 1 CBER) to the RDEA Pilot Program.

RDEA Program team members also have presented the RDEA Pilot Program to the external rare disease community at numerous conferences. While the RDEA Pilot Program is not directly under the ARC Program, ARC will work to share Pilot Program learnings to the internal and external rare disease drug development community.

PDUFA VII and FDORA also include a performance goal and requirement, respectively, for the conduct of up to three RDEA public workshops to discuss various topics relevant to the development of endpoints for rare diseases. The first workshop, entitled "Rare Disease Endpoint Advancement Pilot Program Workshop: Novel Endpoints for Rare Disease Drug Development," took place on June 7 – 8, 2023.

Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis (ALS) (Act for ALS)

In March 2024 in conjunction with and at FDA headquarters, the Critical Path Institute's Rare and Orphan Disease Program (CP-RND) hosted the "Rare Neurodegenerative Disease Efforts under the ACT for ALS" hybrid event. During this event members had an in-depth discussion on how the Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis (Act for ALS) affects those living with neurodegenerative diseases. Presentations included FDA's Office of Orphan Products Development (OOPD) mission and accomplishments, CP-RND's efforts including establishing the Scientific Public Private Partnership and Consortia (PPP) with FDA and National institute of Health (NIH) aimed at advancing research in ALS and other rare neurodegenerative diseases (RNDs) and advancing therapies for those living with RNDs.

The Accelerating Medicines Partnership in Amyotrophic Lateral Sclerosis (AMP ALS) was launched in May 2024 in collaboration with the Foundation for the NIH. , The AMP ALS brings together resources and expertise from NIH, FDA, and Critical Path Institute, with advocacy organizations in the rare disease community, including people with lived experience in ALS, academia, and life science companies. This expansion of the FDA-NIH public-private partnership under Act for ALS will advance knowledge of and accelerate drug development for those affected by ALS by collecting and centralizing current and future ALS datasets in an openly accessible knowledge portal. Researchers can focus on identifying and validating biomarkers and therapeutic targets specific to ALS, as the centralization of data will provide rapid access to clinical outcome assessments, including those direct from the patients.

Support for Clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program

In a Federal Register Notice published on October 2, 2023, the CBER Office of Therapeutic Products (OTP) and CDER OND announced the opportunity for a limited number of development programs to participate in the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, with the goal of further accelerating the pace of development of novel drug and biological products that are intended to address an unmet medical need as a treatment for a rare disease.

The START Pilot Program is designed to:

- Be **issue-oriented** such that sponsors of selected development programs will have enhanced communications with FDA to address specific issues for individual products.
- Be **milestone-driven**, and participation in the START Pilot will be considered concluded when the development program has reached a significant regulatory milestone such as initiation of the pivotal clinical study stage or the pre- Biologics License Application (BLA) or pre- New Drug Application (NDA) meeting stage.

Selected participants will be able to interact with FDA through enhanced communication mechanisms to provide a mechanism for addressing product-specific development issues, including but not limited to clinical study design, choice of control group, fine-tuning the choice of patient population, leveraging nonclinical information, or product characterization. These enhanced communications are intended to augment currently available formal meeting procedures between FDA and sponsors relating to the development and review of drug or biological products, to facilitate program development, and to help generate high quality and reliable data intended to support a BLA or NDA.

Selected participants will be able to interact with FDA through enhanced communication mechanisms to provide a mechanism for addressing product-specific development issues

CDER participants in the START Pilot also will have access to other CDER and CBER programs as well as CDER-specific unique programs and initiatives based on the specific development needs of the individual products such as:

- Advancing Real-World Evidence Program (RWE),
- CDER Center for Clinical Trial Innovation (C3TI),
- CDER Quantitative Medicine Center of Excellence (QM CoE),
- CDER's Rare Disease Drug Development Design (RD4) Workgroup,
- CDER's Translational Science Team (TST),
- Complex Innovative trial Design (CID),

- Model-Informed Drug Development (MIDD) Paired Meeting Program, and
- Rare Disease Endpoint Advancement (RDEA) Pilot Program.

The ARC Program supports the START Pilot Program by fostering communication between review teams and other relevant existing Programs and initiatives to leverage FDA expertise. ARC will work to connect review teams and CDER START Pilot participants with ongoing Programs and initiatives to provide thoughtful and holistic advice and consideration to address sponsor needs and facilitate development of selected development programs.

FDA accepted requests to participate in the START Pilot Program from January 2 through March 1, 2024. In that time, the agency received approximately 30 requests to participate, with CDER addressing 13 of those requests.

CDER considered development programs for novel drugs intended to treat rare neurodegenerative conditions (including those of rare genetic metabolic etiology). The following three (3) development programs were selected by CDER to participate in the START Pilot:

SPONSOR	PRODUCT	TARGETED DISEASE
Larimar Therapeutics	Nomlabofusp	Friedreich's ataxia
Calico Life Sciences	ABBV-CLS-7262	Vanishing White Matter disease
Denali Therapeutics	DNL126	Mucopolysaccharidosis Type IIIA (Sanfilippo syndrome)

Supported by ARC and managed by CDER's RDT, START Pilot Program preparations began in fall 2023. Since then, RDT has empaneled and led a focused interdisciplinary team of CDER experts to develop operational processes to implement this exciting initiative. In addition, RDT collaborated with CBER to align operational processes to implement the START Pilot Program.

ARC is excited to engage the rare disease community to advance the development of the selected START Pilot participants and will work to synthesize learnings from this Pilot to strengthen connections and broaden rare disease networks to drive future drug development.

Translational Science Team (TST)

ARC created the Translational Science Team (TST), a multi-disciplinary unit supporting rare disease drug application review teams across CDER by providing focused expertise to help guide the development of and to support regulatory evaluation of and, where appropriate, acceptance of novel surrogate biomarkers

and confirmatory evidence that can be an essential component of the package of evidence for rare disease drug applications. Since such applications require a deep understanding of disease biology and pharmacology, as well as substantive analysis of preclinical and early clinical data, the subject matter experts collaborated with review teams to evaluate submissions on surrogates or confirmatory evidence by companies. The TST includes experts from the OCP Division of Applied Regulatory Science (DARS) and Division of Translational and Precision Medicine (DTPM), OND Divisions of Pharmacology/Toxicology, OND Office of Drug Evaluation Science, and staff from the ARC Program on the RDT.

Early in development the TST can provide input to the clinical team that can be provided to companies to enhance the evidence in support of the surrogate or confirmatory evidence. Later in development, or during NDA/BLA review, the TST's evaluation provides important perspective and advice to the clinical team regarding the sufficiency of evidence for acceptance of the surrogate or the robustness of the proposed confirmatory evidence. A TST review can aid in improving submission quality and charting a regulatory path forward for complex and challenging rare disease drug development programs by providing detailed feedback on the development of translational approaches.

The **TST functions by working in collaboration with CDER review teams**, helping to facilitate a detailed evaluation of proposed surrogate endpoints and/or confirmatory evidence packages. The TST is available to provide advice to review teams on key regulatory drug development decisions across the continuum of drug development that involve translational science issues, particularly in the rare disease space, with an eye toward translating this input into clear, pragmatic advice to sponsors.

After executing an awareness campaign to ensure personnel across CDER had knowledge of the available support, the TST now has completed consults from multiple OND Offices.

With an eye on continuous improvement, TST has implemented knowledge management tools and held an internal Translational Science Workshop to identify additional needs and inform future translational science initiatives, education, and guidance to share with FDA staff as well as the larger rare disease community.

Message from the Associate Director for Rare Diseases

ARC's Future Look

Dr. Kerry Jo Lee

As noted throughout this annual report, the ARC Program remains committed to accelerating safe and effective treatments for rare diseases. With great intention, ARC has and will continue to balance the needs of building strong foundations in regulatory science, education, and engagement to support the rare disease community while exploring continuous improvement and innovation in understanding and developing safe and effective drug therapies for rare diseases.

This year, ARC has made strides in the scientific and regulatory aspects of rare disease drug development. The ARC Program has expanded efforts in translational medicine approaches for individual rare diseases and contributed to the clinical and regulatory knowledge that is needed to make informed decisions for rare disease drug development. ARC has also strengthened and initiated work that focuses on bolstering the use and development of frameworks to support innovative statistical designs.

As we progress through the end of 2024 and into 2025, ARC will maintain its commitment to engagement and collaboration. ARC will continue our commitment to open and ongoing dialogue to hear what is important from the rare disease community to educational materials and workshops through the LEADER 3D initiative, such as our recent workshop entitled *Natural History Studies and Registries in the Development of Rare Disease Treatments* that was held in conjunction with the Reagan-Udall Foundation for the FDA and the National Institutes of Health's Division of Rare Diseases Research Innovation within the National Center for Advancing Translational Sciences. These and other efforts such as the organization of guidances relevant to rare disease drug development organized by topic can all be found on the ARC webpage and are the direct result of feedback from the rare disease community. CDER leads for patient engagement have made considerable progress through PFDD's complimentary Program with NORD and their continued efforts to learn about the rare disease patient experience through patient-focused drug development meetings and patient listening sessions.

Having built a strong foundation, CDER's ARC Program is enthusiastic about the upcoming year as one to continue to strengthen collaboration to accomplish even more progress in rare disease drug development. ARC will continue to enable CDER to innovate and move forward in order to improve outcomes and options for the rare disease community. Successful drug development is grounded in our ability to work together to harness the strength of scientific advancement combined with early planning and partnership with FDA for regulatory considerations. Understanding that it takes all of us working together to truly move the needle in rare disease drug development, this approach aims to accelerate the path to bringing safe and effective rare disease drugs to patients.

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Glossary of Terms

Act for ALS	Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis
ALS	Amyotrophic Lateral Sclerosis
AMP ALS	Accelerating Medicines Partnership in Amyotrophic Lateral Sclerosis
ARC	Accelerating Rare disease Cures Program
BLA	Biologics License Application
C3TI	CDER Center for Clinical Trial Innovation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CE	Confirmatory Evidence
CID	Complex Innovative trial Design
CP-RND	Critical Path Institute's Rare and Orphan Disease Program
DARS	Division of Applied Regulatory Science
DRDMG	Division of Rare Diseases, Pediatrics, Urologic and Medical Genetics
DTPM	Division of Translational and Precision Medicine
FDA	Food and Drug Administration
FDORA	Food and Drug Omnibus Reform Act of 2022
IND	Investigational New Drug
LEADER 3D	Learning and Education to Advance and Empower Rare Disease Drug Developers
MIDD	Model-Informed Drug Development
NDA	New Drug Application
NIH	National Institute of Health
NORD	National Organization for Rare Disorders
OB	Office of Biostatistics
OBPV	Office of Biostatistics and Pharmacovigilance
OCD	Office of the Center Director
OCE	Oncology Center of Excellence
OCP	Office of Clinical Pharmacology
OCPAS	Office of the Commissioner Patient Affairs Staff
ON	Office of Neuroscience
OND	Office of New Drugs
ONDP	Office of Neuroscience Policy
OOPD	Orphan Products Development
ORPURM	Office of Rare Diseases, Pediatrics, Urologic and Medical Genetics
OTP	CBER Office of Therapeutic Products
OTS	Office of Translational Science
PASE	Professional Affairs and Stakeholder Engagement
PDUFA	Prescription Drug User Fee Act
PDUFA VII letter	Reauthorization Performance Goals and Procedures Prescription Drug User Fee Act
PFDD	Patient-Focused Drug Development Program
PPP	Scientific Public Private Partnership and Consortia
QM CoE	Quantitative Medicine Center of Excellence
RaD-SIG	Rare Disease Scientific Interest Group
RD4	Rare Disease Drug Development Design
RDEA	Rare Disease Endpoint Advancement
RDT	Rare Diseases Team
RWE	Advancing real-World Evidence Program
START	Support for clinical Trials Advancing Rare disease Therapeutics Pilot Program
The Hub	The Rare Disease Innovation Hub
TMLE	Targeted Maximum Likelihood Estimation
TST	Translational Science Team

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Accelerating Rare disease Cures Program

Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993