U.S. FOOD & DRUG ADMINISTRATION

Accelerating Rare Disease Cures (ARC) Program

YEAR THREE:

Annual Report

Resilience in Rare Disease Drug Development through Innovation and Partnerships

December 2025

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

As I step into my new role as Director of the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), I am deeply impressed by the transformative impact of the Accelerating Rare disease Cures (ARC) Program since its launch in May 2022. The program exemplifies CDER's commitment to addressing one of the most challenging areas in drug development—accelerating the availability of treatments for patients with rare diseases and high unmet medical need.

Dr. Richard Padzur

Throughout this past year, the ARC Program has demonstrated remarkable resilience, perseverance, and innovation in advancing rare disease drug development. The continued success of the Support for Clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, developed in partnership with the Center for Biologics Evaluation and Research (CBER), provides an invaluable enhanced communication pathway for sponsors navigating complex development challenges. The START program has been so successful, we are looking to broaden it throughout FDA. The expansion of ARC's Translational Science Team (TST) has further strengthened our ability to provide specialized and consistent expertise across CDER's review teams.

Building on my extensive experience in oncology drug development and regulatory science, including my leadership of the FDA's Oncology Center of Excellence, I am particularly energized by ARC's patient-centered approach. The program's commitment to hosting listening sessions and patient-focused drug development meetings ensures that patient voices remain at the center of our regulatory planning for rare disease therapeutic development. These engagements, combined with our continued collaboration with academics and industry partners, create a robust ecosystem for innovation.

Looking ahead, I am excited about the continued evolution of ARC's collaborations across the agency through the Rare Disease Innovation Hub (RDIH or the Hub), which was formally launched in October 2024. The Hub's Strategic Agenda will focus on advancing regulatory science, strengthening inter-center alignment, and creating more accessible pathways for external partners to engage with FDA.

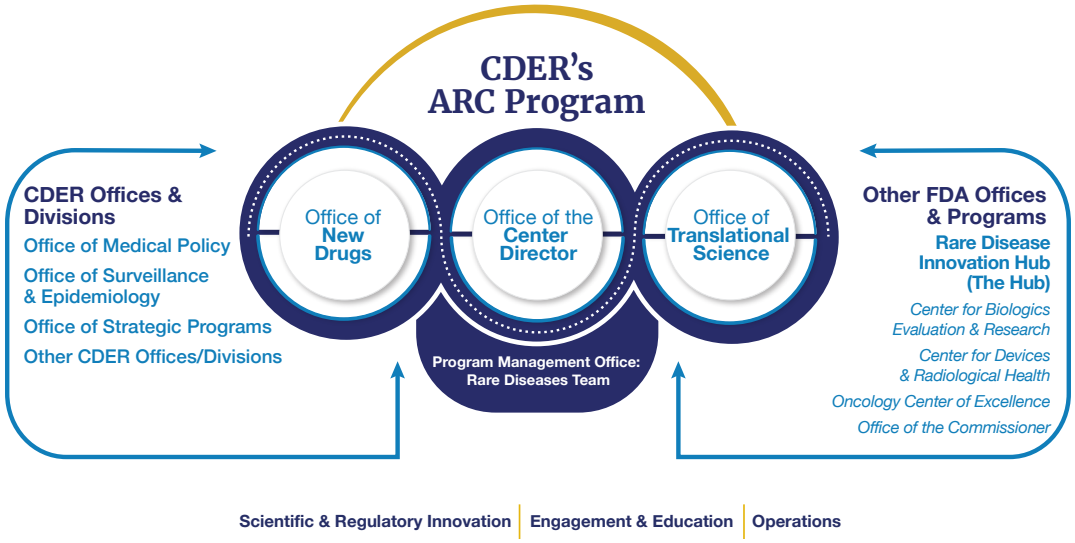
The dedication of CDER's Rare Diseases Team (RDT), ARC's dedicated leadership throughout the Office of New Drugs and Office of Translational Sciences, and the entire ARC Program continues to inspire me. Their work embodies the scientific rigor, regulatory excellence, and compassionate mission that defines our center. As we move forward, I am committed to supporting and expanding these efforts to help ensure that patients with rare diseases have access to safe, effective, and innovative therapies.

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, including the following:

- Small populations can make it difficult to perform and interpret rare disease clinical trials.
- Endpoint and biomarker selection to measure drug efficacy can be complicated if there is a limited understanding of the natural history of the disease.
- An absence of regulatory precedent for drug development.

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 Centers, 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 guidance documents and promoting and educating on shared policies and practices across the center, the RDT works closely with FDA's RDIH to promote the agency's activities dedicated to the development and review of drugs and biologics for rare diseases.

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

Close collaboration with CDER offices across FDA enabled the ARC Program to support various activities to advance rare disease drug development.

Achievements in this annual cycle include:

10

Patient Listening Sessions on Rare Diseases held by the Office of the Commissioner Public Engagement Staff

26

Rare Disease New Drug Approvals (in calendar year 2024)

45,000+

CDER Rare Disease News Subscribers

30+

Public speaking engagements featuring the ARC Program

3

ARC Quarterly Newsletters

10

Externally-led Patient-Focused Drug Development Meetings on Rare Diseases supported by CDER Staff

1M+

Total posts
1,444,628 impressions (views) across 121 social media posts

Engagement and Education

ARC's engagement and education initiatives focus on outreach with the rare disease drug development community to leverage expertise and innovation in the rare diseases space. FDA staff undertook several initiatives to make the regulatory landscape more accessible and understandable for the rare disease community. Other initiatives aimed to deliver timely information about CDER rare disease news and activities.

Rare Disease Innovation Hub

FDA announced The Rare Disease Innovation Hub (RDIH or the Hub) in July 2024 and formally launched it in October 2024. The Hub was created to serve as a point of collaboration and connectivity between CBER and CDER with the goal of improving outcomes for rare disease patients. Led by the Directors of CBER and CDER as co-chairs, with joint project management by CDER's ARC/RDT and CBER's Rare Disease Program, the Hub enhances collaboration across FDA to address common scientific, clinical, and policy issues related to rare disease medical product development. The Hub also promotes consistency across offices and Centers while particularly focusing on challenges within smaller populations where natural history is variable and not fully understood.

Patient-Focused Initiatives

Input from patients living with rare diseases and their caregivers is important throughout the drug development process. FDA's CDER Patient-Focused Drug Development (PFDD) Program supports the incorporation of the patient perspective throughout drug development through efforts such as the PFDD Guidance Series, public meetings such as the "Patient-Focused Drug Development: Workshop to Discuss Methodologic and Other Challenges Related to Patient Experience Data" held on December 13, 2024, and ongoing PFDD meetings. The December workshop explored the different types of patient experience data and how FDA utilizes such data for regulatory decision-making, along with considerations for submitting patient experience data to FDA. In addition, this workshop featured presentations and panel discussions with experts on selected methodologies and the challenges and opportunities they present.

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 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. These meetings also provide FDA with important information for sponsor interactions and may also offer valuable therapeutic context during the regulatory review process. CDER staff attended and supported the conduct of 10 externally led PFDD meetings focused on rare conditions from July 2024 - July 2025.

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. From July

2024 to July 2025, Public Engagement Staff (PES) from FDA's OC supported 10 listening sessions for patients with rare diseases.

CDER recognizes that, while patients with rare diseases and their families and caregivers have extremely valuable information to share about their experiences living with their conditions, they may have more limited information on the processes that are involved in developing new drugs, as well as the evidence needed to demonstrate the drugs' safety and effectiveness for regulatory decision-making. Therefore, in 2022, CDER initiated discussions with the National Organization for Rare Disorders (NORD) to develop training materials for patients with rare diseases and their families/caregivers. These materials support their ability to play a more active role in the drug development process and help them support the most effective drug development programs for their disease areas. NORD completed content and launched the final version of a course entitled, "Rare Disease Drug Development: What Patients and Advocates Need to Know" in September 2024. This course is available free of charge in both English and Spanish and 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.

All educational materials were developed with the assistance of agency subject matter experts and reside on a newly developed webpage dedicated to LEADER 3D information and educational materials. The newly published materials include:

- An animated video on Challenges, Strategies, and Regulatory Considerations for the Design of Rare Disease Clinical Trials, published in October 2024, which covers foundational aspects of planning, conducting, and analyzing rare disease clinical trials.
- An animated video on Understanding Endpoints in Rare Disease Drug Development, published in March 2025, which covers important considerations for selecting endpoints when designing clinical trials to support rare disease drug development.
- An animated video on Considerations for Collecting and Using Natural History Data that are Fit for Use in the Regulatory Setting, published in March 2025, which covers important considerations in leveraging natural history data to support regulatory decision making.
- Six case studies accompanied by a user guide, published in March and April 2025, that include the following topics:

  - **Odevixibat:** Developing Novel Clinical Outcome Assessment Instruments for Use in the Demonstration of Substantial Evidence of Effectiveness for a Rare Disease
  - **Vutrisiran:** Use of an Externally Controlled Trial and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness
  - **Toferson:** Use of a Surrogate Endpoint to Demonstrate Substantial Evidence of Effectiveness for an Accelerated Approval
  - **Avalglucosidase alfa-ngpt and Seladelpar:** Use of Biomarkers as Surrogate Endpoints for Approval
  - **Fosdenopterin:** Use of a Single Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness for a Rare Disease
  - **Olipudase alfa-rpcp:** A Clinical Dose Escalation Strategy for a Rare Disease Drug Program

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." These updates include a quarterly newsletter and provide subscribers with highlights on program developments, new drug approvals, and relevant conferences, partnerships, and initiatives of interest to the rare disease community. Since launching, the number of readers continues to grow – surpassing **45,000 subscribers**. As readership expands in coming years, ARC hopes that the newsletter will act as a powerful virtual tool to enhance collaboration and foster dialogue among the rare disease community.

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

ARC Online Presence

The ARC website continues to serve as an essential center for rare disease patients and drug developers, offering comprehensive resources and tools to support the rare disease community. The site provides access to current guidance documentation for rare disease clinical trial design and conduct, information on upcoming and recent rare disease events, highlights of key policy and program initiatives, funding opportunities, and additional valuable resources for the rare disease drug development community.

Website Performance Metrics (July 2024 to July 2025):

- The ARC Program website demonstrated significant growth in user engagement, logging 23,288 total views across 20,414 sessions from 15,706 users, including 5,084 new users. This represents substantial growth compared to the first half of 2024, with total views increasing by more than 130% and unique users growing by nearly 150%.
- The Guidance Documents For Rare Diseases Drug Development webpage captured 11,235 views with an engagement rate of 73.0%, representing a significant increase of over 180% in views compared to the previous period.

The ARC Program continues 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.

Fundamental to the FDA's mission is engaging 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.

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.

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Conferences, Workshops, and External Speaking Engagements

Conferences, workshops, and meetings dedicated to rare disease drug development provide vital forums where diverse stakeholders convene to share experiences, insights, and challenges while exploring future innovations in the field. Recognizing that external outreach is fundamental to the ARC Program's mission, FDA staff actively engaged in more than **30 public speaking engagements** over the last year as presenters, panelists, and attendees. These engagements served dual purposes: amplifying CDER's rare disease initiatives while providing valuable opportunities for FDA staff to learn directly from the experiences and perspectives of rare disease patients, caregivers, advocacy organizations, and drug developers. Through this collaborative dialogue, the ARC Program strengthened its understanding of community needs while sharing regulatory insights that support ongoing rare disease drug development efforts.

ARC has made information, recordings, and meeting materials available on its webpage which include:

- Opportunities to Improve Dose-Finding and Optimization for Rare Disease Drug Development: October 29, 2024
- Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub: October 16, 2024

Scientific and Regulatory Innovation

The ARC Program supports a comprehensive approach to scientific and regulatory innovation, driving development of essential tools and frameworks that empower drug developers to more effectively bring life-changing treatments to rare disease patients. ARC's activities include:

- Enhancing platforms that facilitate natural history studies.
- The development, testing, and validation of methodologies for creating novel endpoints that better capture meaningful change, ensuring that clinical trials measure what truly matters to those living with rare diseases.
- Expanding the strategic use of drug and disease modeling to more accurately predict treatment responses.
- Establishing efficient approaches to dose selection and supporting the use of fit-for-purpose statistical analyses for small patient populations where traditional methods may fall short.
- Advancing translational medicine approaches that bridge the gap between laboratory discoveries and clinical applications for individual rare disease programs.

By fostering both a deeper understanding of regulatory policies and the use of innovative scientific methodologies, the ARC Program strives to accelerate the availability of safe and effective treatments for patients with rare diseases.

Following another productive year of reviews and approvals for rare disease therapies, CDER's OND and OTS (which includes the 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 involved in rare disease drug development.

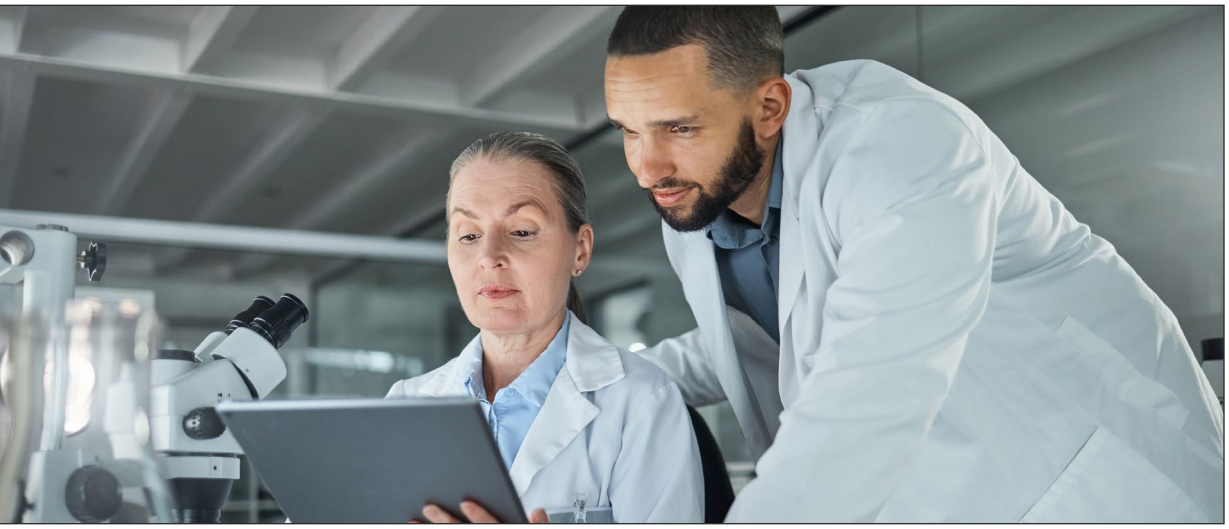
Regulatory Science Research

FDA's CDER RDT continues to support and lead 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. 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 is used to support rare disease drug approval, research by the RDT has categorized CE in approved new molecular entity (NME) new drug applications (NDAs), and original biologics license applications (BLAs) in CDER. This work was recently published in *Clinical Pharmacology and Therapeutics*.
- **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. This work was recently published in the journal *Clinical Trials*.

- **Extramural Research.** ARC's RDT supports external regulatory science projects through ARC-funded Broad Agency Announcement (BAA) research contracts. The research contracts aim to develop novel tools, inform regulatory review, and advance rare disease drug development by developing innovative methods and tools to be used in rare disease drug development. ARC currently funds two BAA research contracts:
  - **Seamless Design for Multicomponent Endpoints for Drug Development in Rare Diseases conducted by the University of Michigan.** This project, conducted with the University of Michigan Department of Biostatistics, aims to assist statisticians working on clinical trial design and analyses to support drug registration in rare diseases using small samples. It will utilize multicomponent endpoints, interim analyses, and Bayesian joint modeling to improve trial efficiency and robustness.
  - **Advancement of drug development tools for Autosomal Dominant Tubulointerstitial Kidney Disease** (ADTKD). This project, conducted by Wake Forest University and the Critical Path Institute, aims to leverage the patient level ADTKD registry at Wake Forest School of Medicine in order to ingest, curate, and map the clinical phenotyping data followed by the development of estimated glomerular filtration rate (eGFR) disease progression models that incorporate retrospective and prospective baseline and longitudinal fluid and imaging biomarker covariate measurements of interest.

Innovative Statistical Methodologies



Over the past year, OB in CDER has worked on the following projects to address challenges specific to rare disease drug development:

Project 1: OB produced a best practice document to assist statistical reviewers in providing advice on the design and analysis of trials conducted to develop drugs for rare diseases. It includes discussion of non-traditional study designs and other innovative approaches. Because of rapid developments and the need to provide the most up-to-date advice, the document will be updated as the field develops and advances.

Project 2: OB is initiating a Rare Disease Scoping Meeting, offering an opportunity for statistical reviewers to seek advice on challenging current reviews of drug for rare diseases. In the initial stage of implementing these meetings, all new (original) protocols for rare diseases involving very small population sizes (a disease with a prevalence of less than 1,000) are expected to be brought for discussion, as well as studies with novel designs. The focus on new protocols promotes efficient and informative studies.

Project 3: As part of the Real-World Evidence (RWE) Scientific Working Group of the American Statistical Association Biopharmaceutical Section, OB staff have published "Challenges and Possible Strategies to Address Them in Rare Disease Drug Development: A Statistical Perspective" and "Use of Real-World Data and Real-World Evidence in Rare Disease Drug Development: A Statistical Perspective" in *Clinical Pharmacology & Therapeutics*.

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 to address key issues in the design and analysis of trials for rare diseases.

This workgroup, jointly led by CDER OND and OB, leveraged subject matter experts from the Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (ORPURM) /Division of Rare Diseases, Pediatrics, Urologic and Medical Genetics (DRDMG), Office of Neuroscience (ON), OB, 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 for regulatory decisions on safety and effectiveness.

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 and analysis challenges common in small populations.

RD4 has explored several innovative approaches including Proportional Odds Model, Ordinal Markov Modeling, and Longitudinal Data Analysis Approaches and factors *(e.g., heterogeneity of clinical findings, disease status and courses)* to consider in study design.

In year three of ARC, RD4 began a pilot consult service to provide review teams with expert advice in the design and analysis of rare disease clinical trials.

Clinical Pharmacology and Translational Medicine

Translational studies and clinical pharmacology assessments that bridge aboratory investigations and clinical care are critical to support drug efficacy and safety evaluations, identify what dosages should be evaluated in trials and approved for clinical use, and individualize therapy based on patient-specific factors.

Over the past year, efforts in the area of translational and clinical pharmacology aimed to promote generation of high-quality data in drug development programs and advance integration of novel technologies. In addition to working with pharmaceutical companies and other stakeholders on specific drug development programs, select accomplishments include the following:

- FDA, in collaboration with Duke-Margolis Institute for Health Policy, hosted a workshop on dose finding and optimization for drugs to treat rare diseases. The workshop brought together patients, scientists, and clinicians with a broad range of expertise to share experiences and ideas to overcome challenges related to dose finding and optimization in small patient populations. Discussions highlighted patient and caregiver challenges in participating in clinical trials, novel approaches to inform dose finding and optimization, and use of different novel data sources.
- Advancing regulatory science projects that improve the development and regulatory evaluation of drugs to treat rare diseases. Research projects focus on using clinical pharmacology and translational science approaches, such as:

- Advancing the use of biomarkers in specific diseases (e.g., GM1 and GM2 Gangliosidosis and Niemann-Pick Disease Type C),
- Characterizing trends and best practices for drug development (e.g., first-in-human trials of oligonucleotide therapeutics and enzyme replacement therapies; confirmatory evidence; pediatrics),
- Application of novel quantitative methods (e.g., artificial intelligence/machine learning in sickle cell disease), and
- Evaluation of new approach methods for predicting patient response (use of microphysiological systems to predict response to novel sarcomere modulators; in vitro approaches to characterize rare enzyme variant effects on drug exposure).

- Experts communicated FDA perspectives to rare disease stakeholders on a variety of topics through publications in scientific journals and speaking at national conferences. Some key publications focused on dose optimization and general drug development considerations. Presentations were on topics such as biomarker development (including surrogate endpoints), quantitative approaches in regulatory decisions, newer drug modalities such as oligonucleotides, use of real-world evidence, new approach methods for nonclinical testing, demonstrating substantial evidence of effectiveness, pediatric drug development, and using patient centric and model-informed approaches for dose selection and optimization in rare diseases.

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 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.

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 approximately 20 RDEA proposals and admitted five (3 CDER; 2 CBER) into the RDEA Pilot Program.

ARC works to share information about and learnings from the Pilot Program with the rare disease drug development community, and RDEA Program team members have presented this Pilot at numerous conferences. 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, and plans are ongoing to conduct a second RDEA workshop.

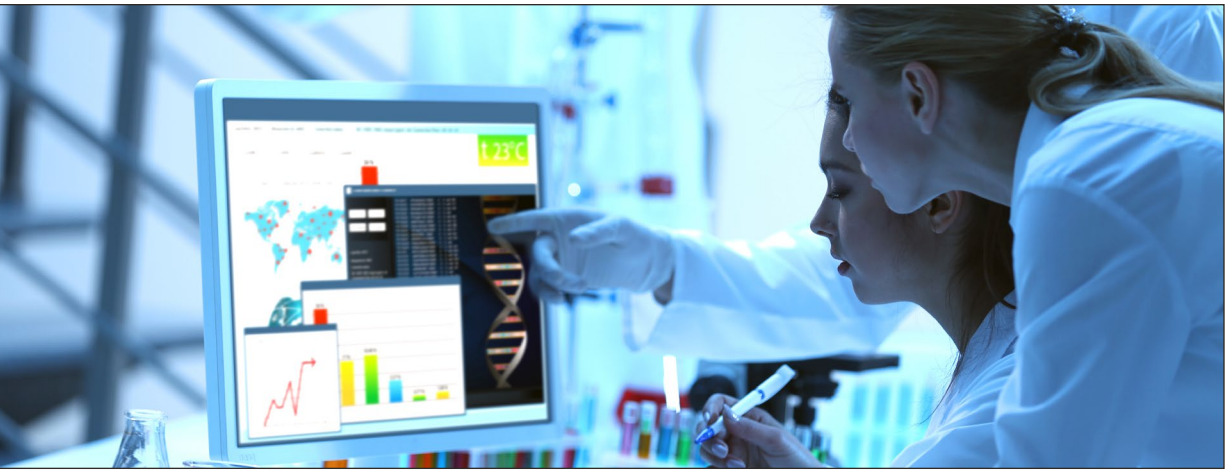
Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis (ALS) (Act for ALS)

During the last year, the Critical Path Institute's Rare Neurodegenerative Disease Program (CP-RND) completed and presented a literature review on clinical outcome assessments used in ALS clinical trials and the utilization of digital health technologies in ALS clinical trials. Findings from these reviews identified areas of unmet need and opportunities to generate needed evidence to support fit-for-purpose clinical outcome assessments and digital health technologies in ALS drug development. In February 2025, FDA funded study entitled "The ALS Functional Rating Scale-Revised (ALSFRS-R) Clinical Outcome Assessment Remote-Use Equivalency Study" was completed. The purpose of this study was to determine

comparability among different modes of administration of the ALSFRS-R and if order of the modes administration impacts the interpretation of the ALSFRS-R total score. The study, which included ALS patient and caregiver advisory committee input and development of standardized training for remote administration of the ALSFR-R, found that the remote modes studied have comparability to the in-person administration of the ALSFRS-R. These findings allow more options for study designs in ALS clinical trials.

The Accelerating Medicines Partnership in Amyotrophic Lateral Sclerosis (AMP ALS), which was launched in May 2024 in collaboration with the Foundation for the NIH, is still active and continuing to 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, identifying and validating biomarkers and therapeutic targets specific to ALS, and advancing clinical outcome assessment options for ALS clinical trials.

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



To accelerate development of novel treatments for unmet medical needs like rare diseases, in 2024 FDA admitted a total of seven development programs into the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program, a joint CDER and CBER pilot.

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 can interact with FDA through enhanced communication mechanisms to address program-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.

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

- Advancing Real-World Evidence Program (RWE),
- CDER's Translational Science Team (TST),
- Complex Innovative trial Design (CID), and
- Rare Disease Endpoint Advancement (RDEA) Pilot Program.

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

In 2024, the following three development programs, intended to treat a neurodegenerative condition (including those of rare genetic metabolic etiology), 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)

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.

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.

Early in development, the TST can provide input to the review 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 review 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 now has completed consults from multiple OND Offices and plans to expand to additional OND offices this year. TST continues to use knowledge management tools to track consults and the implementation of TST recommendations with the goal of continuous improvement.

Message from the Associate Director for Rare Diseases

ARC's Future Look

Dr. Scott Winiecki

Looking ahead, the ARC Program's unwavering dedication to the rare disease community drives our mission to champion safe and effective treatments through strategic partnerships and collaborative innovation. Deliberate efforts and partnerships allow ARC to remain steadfast in its commitment to thoughtfully harmonize the essential work of establishing robust foundations in regulatory science, education, and community engagement while simultaneously pursuing continuous improvement in rare disease therapeutic development.

In its third year, ARC continues to make strides to innovate scientific and regulatory aspects of rare disease drug development. ARC expanded efforts in translational medicine approaches for individual rare diseases through efforts such as the TST and contributed to the clinical and regulatory knowledge that is needed to make informed decisions for rare disease drug development, as evidenced by the multiple publications and research projects from RDT, OCP, and OB. ARC has also strengthened and initiated work that focuses on bolstering the use and development of frameworks to support innovative statistical designs.

Building on our progress throughout 2025, ARC will continue its commitment to engagement and collaboration as we move into 2026, fostering resilience in rare disease drug development through innovation and partnerships. ARC will continue open and ongoing dialogue, engaging the rare disease community through educational materials under the LEADER 3D initiative and workshops such as the "Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub" held on October 16, 2024 in partnership with the Reagan-Udall Foundation (RUF). This foundational workshop helped launch the FDA's new Rare Disease Innovation Hub (RDIH), which serves as a point of collaboration and connectivity between CBER and CDER to improve outcomes for rare disease patients. Since establishment of the RDIH, the ARC Program has collaborated with CBER to engage with the rare disease community through Hub activities.

Information on these and other initiatives, such as the topical organization of guidance documents relevant to rare disease drug development, are accessible through the ARC webpage and represent FDA's direct response to feedback from the rare disease community. The notable utilization and engagement with these resources throughout this past year demonstrates the significant value and accessibility of this centralized approach to serving the rare disease community's informational needs. CDER continues to make considerable progress through PFDD's complimentary program with the National Organization for Rare Disorders (NORD) and its efforts to learn about the rare disease patient experience through PFDD meetings and FDA patient listening sessions. These enduring partnerships exemplify the collaborative approach necessary to address the unique challenges in rare disease therapeutic development.

With a solid foundation in place, CDER's ARC Program is poised to enhance collaboration and drive greater progress in rare disease drug development. ARC will continue empowering innovation to improve rare disease community outcomes. By cultivating resilience through scientific advancement, early planning, and regulatory partnership, we are accelerating the path to safe and effective rare disease therapies.

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
OC	Office of the Commissioner
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
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
RDPPC	Rare Disease Policy and PortfolioCouncil
RDT	Rare Diseases Team
RDIH	Rare Disease Innovation Hub
RISE	Rare disease Innovation, Science, and Exploration
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

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