



U.S. FOOD & DRUG
ADMINISTRATION

Accelerating Rare disease Cures (ARC) Program

YEAR FOUR: Annual Report

*Sustaining Progress, Expanding Possibilities in
Rare Disease Drug Development*

October 2026

Table of Contents

MESSAGE FROM THE DIRECTOR OF THE CENTER FOR DRUG EVALUATION AND RESEARCH.....	3
ABOUT THE ARC PROGRAM	5
ARC STRATEGIC PLAN.....	7
YEAR AT-A-GLANCE	8
ENGAGEMENT AND EDUCATION	9
Commitment to Collaboration and Engagement.....	9
Learning and Education to ADvance and Empower Rare Diseases Drug Developers (LEADER 3D)	11
Patient-Focused Initiatives	12
ARC Online Presence and External Communications	14
SCIENTIFIC AND REGULATORY INNOVATION	16
Regulatory Science Research	17
Innovative Statistical Methodologies.....	19
Rare Disease Drug Development Design (RD4)	21
Clinical Pharmacology and Translational Medicine	22
Rare Disease Endpoint Advancement (RDEA) Pilot Program	23
Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis (ALS) (Act for ALS).....	24
Critical Path Institute (C-Path) Rare Disease Cures Accelerator-Data Analytics Platform (RDCA-DAP).....	25
Support for Clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program.....	26
Translational Science Team (TST).....	27
Rare Disease Cluster	28
MESSAGE FROM THE ACTING ASSOCIATE DIRECTOR FOR RARE DISEASES: ARC'S FUTURE LOOK.....	29
GLOSSARY OF TERMS.....	31

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

As I step into the role of Director of the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), I am honored to carry forward the important work of this Center and to lend my full support to the Accelerating Rare disease Cures (ARC) Program and the broader mission it represents. Now



Michael Davis M.D., Ph.D.

entering its fifth year since launching in May 2022, the ARC Program stands as a powerful testament to what is possible when scientific rigor, regulatory innovation, and deep commitment to patients converge.

My career has been shaped by a profound belief in the power of clinical science to change lives. From my early work in pharmacology and psychiatry, including years as a clinical reviewer and team leader within CDER's own Office of New Drugs, to leading clinical development programs at the bench and bedside, I have seen firsthand how the gap between scientific promise and patient access can be narrowed through thoughtful, rigorous, and collaborative regulatory practice. That experience makes me especially appreciative of what the ARC Program has built and deeply committed to what it can still achieve. As a physician-scientist with extensive experience in clinical trial design, regulatory science, and drug development methodology, I am particularly drawn to ARC's emphasis on rigorous yet innovative approaches to advancing therapies for patients with high unmet medical need. The program's integration of translational science, community engagement, and Agency-wide collaboration reflects the kind of approach that is essential for addressing the complexities of rare disease drug development.

The need has never been more clear. Approximately 25 to 30 million Americans are living with a rare disease, and of the more than 10,000 known rare diseases and conditions, the vast majority still lack FDA-approved treatments. While progress is real and meaningful, with 50% (23 out of 46) of CDER's novel drug approvals in 2025 representing rare disease treatments, the unmet need remains urgent. Small patient populations (often geographically dispersed), limited understanding of disease natural history, and a lack of drug development tools continue to make rare disease drug development among the most challenging work in medicine. The ARC Program exists to meet that challenge for drugs and biologics regulated by CDER.

Now entering its fifth year since launching in May 2022, the ARC Program stands as a powerful testament to what is possible when scientific rigor, regulatory innovation, and deep commitment to patients converge.

This past year has been one of steady growth and impact. ARC's Learning and Education to ADvance and Empower Rare Disease Drug Developers (LEADER 3D) initiative has continued to serve as a critical tool for sponsors navigating complex development challenges. Grounded in insights gathered directly from the rare disease drug development community, LEADER 3D translates real-world needs into practical, high-quality educational resources. This year, the program reached a significant milestone with the publication of six new case studies, bringing the total LEADER 3D case study library to 12 and offering sponsors real-world examples of how to approach some of the most difficult scientific and regulatory challenges in rare disease drug development. These case studies complement the initiative's growing educational video series and collectively reflect the diverse and nuanced landscape of rare disease therapeutics.

Looking ahead, I am energized by the launch of ARC's 2025-2030 Strategic Plan. Organized around three strategic goals, Scientific and Regulatory Innovation, Engagement and Education, and Operations, the Strategic Plan positions ARC to make meaningful and lasting contributions to public health. Through coordinated, cross-cutting collaboration across CDER offices, FDA centers, academic institutions, patient advocacy groups, and international regulatory partners, the 2025-2030 Strategic Plan charts a clear course for accelerating and expanding the development of safe and effective treatments for people living with rare diseases.

The Program's commitment to keeping patient voices at the center of its work is something I hold in the highest regard. ARC Team members are dedicated to ensuring that patients and their advocates who reach out directly receive thoughtful, timely responses to their inquiries. These efforts help ensure that the rare disease patient perspective meaningfully informs the Program's priorities and direction.

My career has been shaped by a profound belief in the power of clinical science to change lives. This experience makes me especially appreciative of what CDER's Rare Diseases Team has built and deeply committed to what the ARC Program and its contributing partners can yet achieve to accelerate the availability of safe and effective treatments for people with rare diseases.

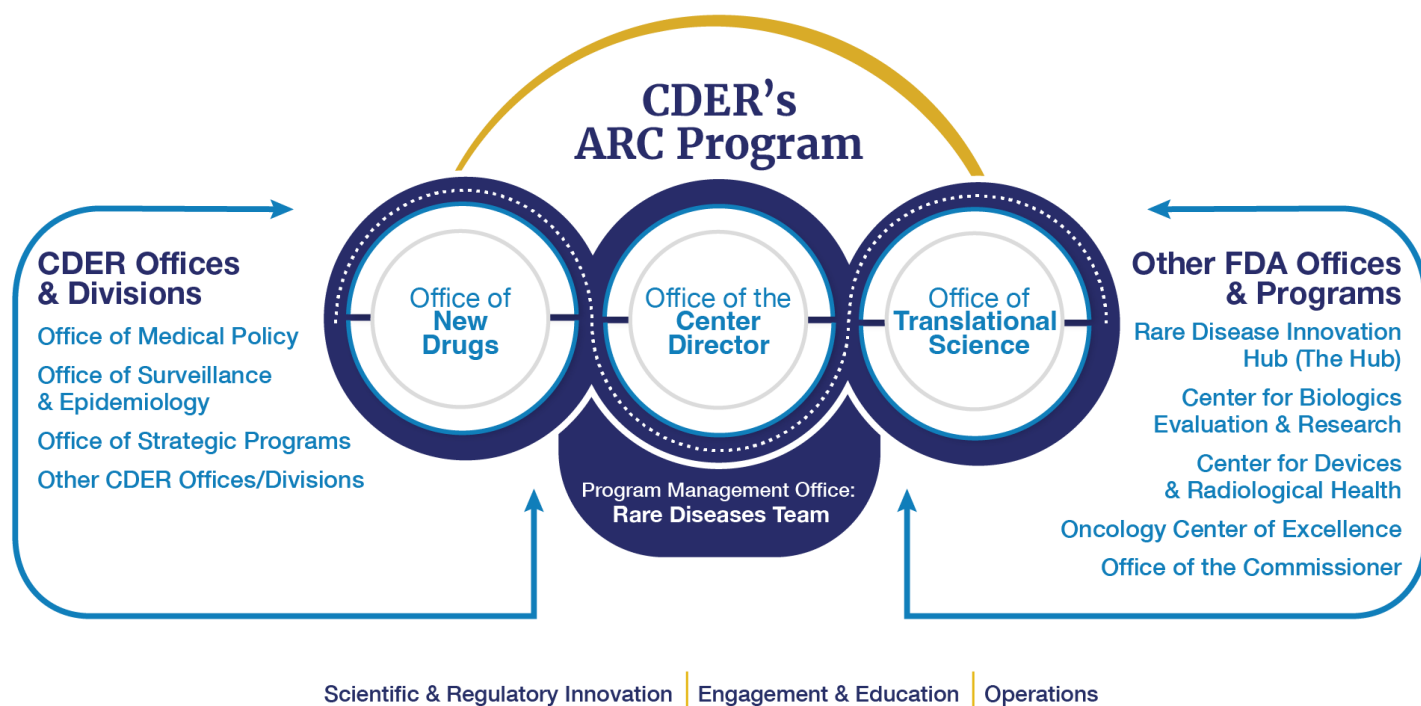
About the ARC Program

A rare disease is any disease that affects fewer than 200,000 people in the U.S. Approximately 25 to 30 million Americans—about 1 in 10—are living with one of the roughly 10,000 known rare diseases. Drug development for 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.
- Limited natural history data make endpoint and biomarker selection more complicated.
- Lack of regulatory precedent for many conditions.

As a result, the vast majority of patients with rare diseases have few or no available treatment options. Launched in 2022, the ARC Program was established to create strategic coordination for CDER rare disease activities and to increase the number of available rare disease treatments by:

- synergizing the efforts and experience of Centers' and Offices' rare disease initiatives,
- promoting and leveraging innovative scientific design,
- developing educational programming,
- providing a deeper understanding of regulatory policies and frameworks, and
- engaging with the rare disease community.



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 unites partners from across the FDA (or the Agency) including the Center for Biologics Evaluation and Research ([CBER](#)), the Center for Devices and Radiological Health ([CDRH](#)), the Oncology Center of Excellence ([OCE](#)), and the Office of the Commissioner ([OC](#)), reflecting the Agency's strong and enduring commitment to advancing treatment options for patients living with rare diseases.

ARC Program day-to-day management and operations are supported by CDER's Rare Disease Team (RDT) within the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM). The RDT leads and facilitates OND's cross-cutting rare disease policy and programming and fulfills Prescription Drug User Fee Act (PDUFA) commitments to advance the development of drugs for rare diseases. By leading the development of cross-cutting rare disease guidance as well as promoting various initiatives and educating staff across the Center, the RDT ensures coordination and consistency across CDER rare disease activities.



ARC Strategic Plan

The ARC Program has released its [2025–2030 Strategic Plan](#), a five-year roadmap that charts the Program’s course to accelerate the development of safe and effective treatments for the millions of Americans living with a rare disease.

The Plan is organized around three strategic goals:

- Scientific and Regulatory Innovation
- Engagement and Education
- Operations

Together, these goals drive the development of regulatory and scientific tools, strengthen dialog with the rare disease community, and build the internal CDER capacity needed to foster innovation in rare disease drug development. ARC’s Strategic Plan reflects its collaborative approach to synergizing the collective expertise of subject matter experts across CDER’s offices and divisions, other Agency partners, and the rare disease drug development community.

The plan is built to grow, adapt, and incorporate advances in rare disease science and the evolving needs of the rare disease community. ARC tracks programmatic growth and ensures its suite of initiatives spanning translational science, novel tools for rare disease clinical trials, regulatory education, and community engagement continues to deliver measurable impact. We invite members of the rare disease community to read the plan and work with us to help speed the availability of treatments that can improve the lives of patients with rare diseases. The Strategic Plan is available [here](#).



Year At-A-Glance

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

Achievements in this annual cycle include:



23

Rare Disease
New Drug Approvals
(in calendar year 2025)



11

Patient Listening Sessions on Rare Diseases
held by the Office of the Commissioner
Public Engagement Staff (OC PES) with
participation from CDER staff



51,000+

CDER Rare Disease News
Subscribers



15+

External engagements, including
public speaking, planning, and hosting of
workshops, and public meetings



12

2 ARC newsletters and 10 ARC
e-mail updates to listserv subscribers



10

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



2025-2030

ARC Program Strategic Plan,
a comprehensive five-year roadmap

Engagement and Education



ARC's engagement and education initiatives focus on internal collaborations and 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 FDA's pathways and processes easier to understand and navigate for the rare disease community. Other initiatives aimed to deliver timely information about CDER rare disease news and activities.

Commitment to Collaboration and Engagement



Ongoing collaborations with other CDER initiatives, activities, and programs allow ARC to synergize CDER's rare disease expertise and share relevant learnings with the rare disease community. Cross Center collaboration is also an integral part of ARC's engagement activities. Through active partnerships with other FDA Offices and programs, ARC helps promote consistency across rare disease medical product review, recognizing Center-specific approaches when appropriate.

For example, ARC supports the Rare Disease Policy and Portfolio Council (RDPPC), a senior-level forum designed to promote dialogue between CDER and CBER on challenging and complex rare disease drug development issues. CDER's RDT co-chairs the RDPPC which includes planning topics and coordinating presenters and discussants to facilitate productive, high-level discussion across Centers. Through its RDPPC role, ARC helps ensure that complex rare disease development questions receive coordinated, consistent consideration across FDA's medical product review Centers.

External Engagement Activities

Acknowledging that external engagement is fundamental to the ARC Program's mission, RDT staff actively participated in **15 public engagements** over the last year as presenters, moderators, panelists, and attendees.

ARC's involvement in rare disease working groups and in the planning of rare disease-related meetings reflects its broader commitment to fostering open, collaborative dialogue that is essential to accelerating progress for patients living with rare diseases.

These meetings, workshops, and conferences provide important forums where diverse stakeholders convene to share experiences, insights, and challenges while exploring future innovations in the field. Through these collaborative dialogues, the ARC Program strengthens its understanding of community needs while sharing regulatory considerations and insights that support ongoing rare disease drug development efforts.

Key activities related to external engagement activities included:

- **Rare Disease Innovation, Science, and Exploration (RISE) Workshops:** ARC/RDT participated in planning and moderating sessions for RISE Workshops, bringing together innovators in drug development, rare disease research, patient advocacy, and regulatory science to tackle challenges that are common across multiple rare diseases or a class of diseases and for which evolving science offers promising solutions.
- **Assessing Novel Efficacy Endpoints in Ophthalmologic Rare Disease Drug and Biologics Development Workshop:** ARC/RDT, in close collaboration with subject matter experts (SMEs) across the Agency, spearheaded the planning of a one-day hybrid public meeting, convened by the Duke-Margolis Institute for Health Policy under a cooperative agreement with FDA, focused on novel efficacy endpoints (or measurements of efficacy in a clinical trial) in rare ophthalmologic drug and biologics development. The meeting brought together researchers, clinicians, and other stakeholders to present and discuss evidence supporting the use of full-field stimulus threshold (FST) testing and ellipsoid zone (EZ) data as tools for regulatory decision-making in clinical trials for patients with severe vision loss. Discussions addressed clinical and statistical considerations for quantifying clinically meaningful change, as well as current limitations and potential strategies to advance the implementation of these tools in the regulatory context. The presentations and discussions generated actionable recommendations that will inform the validation of FST and EZ data as fit-for-purpose efficacy endpoints in regulatory settings, advancing the field's ability to develop and evaluate innovative therapies for patients with severe vision loss.

- **FDA Rare Disease Day:** ARC/RDT plays an integral role in FDA’s Annual Rare Disease Day, serving on the planning committee and contributing as presenters to this high-visibility public event. In 2026, FDA hosted its Rare Disease Day virtual public meeting on February 23rd, in global observance of Rare Disease Week, under the theme “Moving Forward. Looking Ahead. An Event for Patients.” The meeting featured panels on patient-focused FDA initiatives, patient engagement opportunities, the role of AI technology in rare disease development, and the use of real-world data and evidence at FDA, all with the goal of ensuring the patient voice continues to inform medical product development and regulation.
- **Rare Disease Endpoint Advancement (RDEA) Workshops:** As part of FDA’s PDUFA VII commitments and the Food and Drug Omnibus Reform Act of 2022 (FDORA) requirements, the RDT has spearheaded two RDEA workshops. The first RDEA workshop took place in 2023 and discussed the application process and required elements for an RDEA proposal, scientific and technical issues associated with developing study endpoints for rare diseases, and lessons learned from previous PDUFA meeting programs that can be applied to the RDEA Pilot Program. The second workshop, entitled “Rare Disease Endpoint Advancement Pilot Program Workshop: Advancing Novel Surrogate Endpoints for Rare Disease Drug Development,” was held on May 18, 2026. The workshop focused on scientific and regulatory considerations for developing surrogate endpoints for drugs and biological products intended to treat rare diseases, with emphasis on the types of mechanistic, translational, clinical, and methodological evidence that may support their use in regulatory decision-making.

Links to materials from rare disease meetings where ARC played an active role are available on its [News & Events webpage](#), including:

- Assessing Novel Efficacy Endpoints in Ophthalmologic Rare Disease Drug and Biologics Development: September 17, 2025
- Regulatory Submissions with Real-World Evidence: Successes, Challenges, and Lessons Learned: September 23, 2025
- Individualized Therapies on the RISE: November 20, 2025
- Advancing Novel Surrogate Endpoints for Rare Disease Drug Development Workshop: May 18, 2026

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



In July 2026, CDER published new educational materials developed under the [ARC Program’s LEADER 3D initiative](#). These materials are in addition to those published in October 2024 and March/April 2025. CDER’S RDT, in partnership with an independent third-party contractor, continues development of educational materials based on feedback obtained from engagement with members of the rare disease drug development community who design and conduct rare disease clinical trials, to identify regulatory topics that could benefit from new or expanded educational materials. The RDT uses 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 are developed with the assistance of CDER SMEs and reside on a [webpage](#) dedicated to LEADER 3D information and educational materials. The newly published materials include:

- An animated video on Dose-Finding Considerations in Rare Disease Drug Development which covers aspects of planning and conducting dose-finding studies and identifying the most effective treatment dose for rare disease drug programs.
- Six case studies published in July 2026 that include the following topics:
 - o Lumasiran: Leveraging Natural History and Registry Data to Inform Endpoint Selection for a Rare Disease
 - o Mavorixafor: Use of the Win Ratio Method to Demonstrate Clinical Benefit from a Composite Endpoint for a Rare Disease
 - o Belimumab: Bayesian Statistics in Rare Disease Clinical Investigations
 - o Omaveloxolone: A Natural History Study External Control as Confirmatory Evidence for a Rare Disease Drug Approval
 - o Uplizna: A Novel Approach to Identifying a Clinically Meaningful Outcome in a Heterogeneous Population
 - o Chenodiol: Leveraging Existing Biomarker and Natural History Data to Support Drug Repurposing for a Rare Disease

Patient-Focused Initiatives

The perspectives of patients living with rare diseases and their caregivers are essential at every stage of 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 #2 to Discuss Methodologic and Other Challenges Related to Patient Experience Data”](#) held on September 18-19, 2025, and ongoing PFDD meetings. The September 2025 workshop featured presentations and panel discussions with experts on methodological challenges related to patient experience data encountered in the regulatory setting. In addition, this workshop presented a draft version of an updated evidence dossier template to facilitate the submission of evidence to FDA to support a Clinical Outcome Assessment.

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, families, caregivers, and advocates about the signs and symptoms that matter most to them, the impact the disease has on patients' daily lives, and patients' experiences with currently available treatments, if applicable. 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, and design clinical trials. These meetings also provide FDA with important information for sponsor interactions and may offer valuable therapeutic context during the regulatory review process. CDER staff attended and supported the conduct of [ten externally led PFDD meetings](#) focused on rare conditions from July 2025 - July 2026.

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 perspectives and needs related to their condition. From July 2025 to July 2026, Public Engagement Staff from FDA's OC supported 11 [listening sessions](#) for patients with rare diseases.

The Condition-Specific Meeting Reports and Other Information Related to Patients' Experience [web page](#) hosts an alphabetical listing of PFDD meeting reports and PLS Summaries.

CDER recognizes that while patients with rare diseases, 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 and regulations that are involved in developing new drugs, as well as the evidence needed to demonstrate drug safety and effectiveness for regulatory decision-making. Therefore, CDER initiated discussions with the National Organization for Rare Disorders (NORD) and provided advice as needed for the development of [training materials](#) for patients and their families/caregivers to support their ability to play an active role in the drug development process. NORD completed content for a course entitled, "Rare Disease Drug Development: What Patients and Advocates Need to Know." Recently updated, the series includes "Part 1: Foundations and Pre-Clinical Research," "Part 2: Navigating Drug Review and Access," and "Part 3: The Basics of Clinical Trials." Part 1 covers the steps in drug development, the roles of those involved, how to lay a strong foundation during the pre-clinical period, and the transition from pre-clinical to clinical studies. Part 2 covers key topics including the FDA drug review process, expanded access, and drug repurposing, and continues to emphasize the significant role patients and patient advocates can play in advancing rare disease drug development. Part 3 covers clinical trial endpoints and Clinical Outcome Assessments (COAs), designing and conducting clinical trials for small populations, and patient experience data. The entire course is available free of charge in both English and Spanish and can be accessed through NORD's RARE EDU website.



ARC Online Presence and External Communications



The ARC [website](#) remains an essential resource for rare disease patients and drug developers, providing current guidance documents relevant to rare disease drug development organized by topic, information on rare disease events, initiative highlights, funding opportunities, and additional valuable resources. This year, ARC undertook a significant modernization of its external public-facing site on FDA.gov, beginning with a redesign of the highest-visibility pages. [The ARC Program landing page](#) was updated to a visual-first layout with streamlined content, restructured navigation, and updated visuals to communicate key messages more immediately and effectively.

Website Performance Metrics (July 2025 to July 2026):

- The ARC Program website logged **18,869 total views** across 17,708 sessions from 14,608 users, including **2,877 new users**. Notably, the engagement rate climbed to 81.6%, an increase of 8.7 percentage points over the prior year —reflecting a **more engaged and targeted audience** actively seeking out ARC Program resources.
- The Guidance Documents For Rare Diseases Drug Development [webpage](#) captured **12,318 views** across 11,490 sessions, with strong growth in its user base. Total **users increased 20.1%** to 8,226. **New users nearly doubled**, rising 90.5% to 2,660 compared to the prior year period, demonstrating **expanding awareness of and interest in rare disease drug development guidance**.

ARC distributes regular updates on CDER's rare disease related work as part of its ongoing commitment to foster communication among the rare disease community. In keeping with ARC's evolving communications strategy, the Program has transitioned from a quarterly newsletter format to more frequent, thematic ARC Program updates, designed to provide subscribers with timely highlights on Program developments, new drug approvals, conferences, partnerships, and initiatives of interest to the rare disease community. The website redesign aims to more clearly organize and present rare disease news, events, and reports for the public.



The number of readers engaged with ARC communications continues to grow—surpassing **51,000 subscribers**. As part of a broader, integrated strategy to enhance collaboration and foster dialogue among the rare disease community, ARC activities and initiatives will continue to be amplified through social media, e-mail updates, and the [FDA Rare Connections Newsletter](#).

The ARC Program continues to support the Cumulative Approvals Graph which contains original New Drug Applications (NDAs) and non-biosimilar Biologics License Applications (BLAs) 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. The information within FDA-TRACK provides an accessible view to the rare disease community about the development and approval of safe and effective drugs to treat rare diseases.

Fundamental to FDA's mission is engaging the rare disease community to ensure their unique perspectives and experiences remain central as the Agency reviews medical products for rare diseases. To reach a broader audience, ARC maintains a presence on LinkedIn, sharing and amplifying timely news related to rare disease approvals, resources, meetings, guidance documents, and providing the external rare disease community with knowledge about opportunities to engage directly with FDA.

ARC's comprehensive and evolving approach to communications has strengthened the Program's connections with the rare disease community, ensuring that vital information and resources are accessible to the American public through multiple channels.

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 patients living with rare diseases. ARC's activities include:

- Enhancing platforms that facilitate natural history studies.
- Supporting 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 frameworks 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 actively contributed to and led multiple scientific and regulatory initiatives to advance the complex and multidisciplinary considerations involved in rare disease drug development.

Regulatory Science Research



CDER's ARC Program and RDT continue 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 informed regulatory review. The RDT's supported 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:

- **External 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. Recently, this project submitted two manuscripts for publication.
 - **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. Recruitment goals for the Observational Prospective Trial in Modeling UMOD and MUC1 (OPTIMUM) Prospective Study have exceeded expectations, with 209 participants enrolled and strong participant retention demonstrated

through high rates of follow-up visit completion, biomarker collection, and clinical laboratory testing. Significant progress was also made in the OPTIMUM elastography sub study, where kidney ultrasound and shearwave elastography data were analyzed to evaluate kidney size, volume, and elasticity measurements in ADTKD patients and controls.

ARC also funded two internal research projects to advance treatments for rare diseases:

- **Identifying Proteomic Biomarkers of Disease Progression and Severity in Adrenoleukodystrophy**

- o X-linked adrenoleukodystrophy (ALD) is an inherited progressive neurometabolic disease causing heterogeneous clinical manifestations which can include adrenal insufficiency (AI), spinal cord disease, and leukodystrophy (LD) known as cerebral ALD (CALD). Left untreated, CALD can progress rapidly, eventually causing severe disability and death. Predicting the clinical outcome of an individual patient remains impossible due to the lack of genotype-phenotype correlation and informative biomarkers. Therefore, there is an unmet clinical need for sensitive biomarkers to monitor and/or predict disease progression and evaluate therapy efficacy. Plasma proteomics (the systematic study of all proteins circulating in the plasma) has the potential to identify invaluable prognostic and response biomarkers.

- **Sarcomere Cardiomyopathy: Structural and Functional Response to Myosin Modulators**

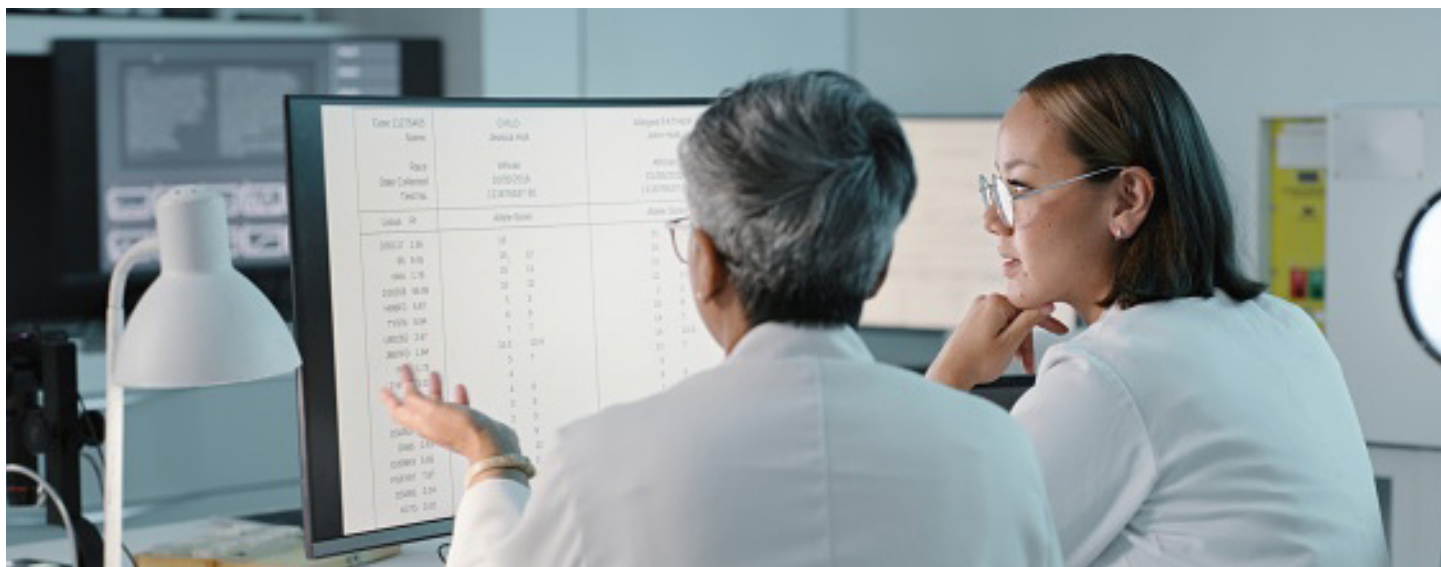
- o This work will include structural and functional evaluation of cardiac stem cell models (complex in vitro models and microphysiological systems) in the context of Dilated Cardiomyopathy (DCM) and Hypertrophic Cardiomyopathy (HCM). Human-based integrated cellular systems will be used to evaluate sarcomere modulators (inhibitors and activators) structural and functional response in the context of DCM and HCM. This project will enable the investigation of four drugs relevant to rare disease patients affected by DCM and HCM, populations that may be difficult to enroll in clinical trials. This work will support regulatory science questions for rare disease therapies, labeling, and patient enrichment.

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 has been developing a new guidance document for industry on statistical considerations for rare diseases. The project aims to develop policy and guidance on statistical considerations in rare disease clinical trials, with a focus on maximizing the chances that such trials can be feasibly conducted and inform reliable conclusions in a timely manner. This guidance will complement the existing published guidance (Rare Diseases: Considerations for the Development of Drugs and Biological Products) on general considerations for rare disease trials.
- **Project 2:** OB produced a document on “Considerations for the Design and Analysis of Clinical Trials in Rare Diseases” to assist statistical reviewers in advising 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. Given the rapid pace of developments in this area, the document will be updated on an ongoing basis to ensure it reflects the most current guidance as the field evolves. Additionally, an OB interest group completed a reviewer’s guide for evaluating surrogate endpoints in rare diseases.
- **Project 3:** OB has been conducting a Rare Disease Scoping Meeting series, providing statistical reviewers an opportunity to seek advice on challenging reviews for rare disease drug development. In the initial implementation stage of 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 4:** As part of the Real-World Evidence (RWE) Scientific Working Group of the American Statistical Association Biopharmaceutical Section, OB staff has 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.
- Project 5:** OB has initiated multiple active research projects addressing critical methodological gaps, including the application of global tests, multicomponent endpoints, Bayesian methods, and surrogate endpoint evaluations. Furthermore, OB presented several innovative methodologies to the Rare Disease Drug Development Design (RD4) workgroup, including Targeted Maximum Likelihood Estimation (TMLE) and rare disease case studies utilizing Bayesian approaches. The RD4 workgroup aims to identify ways to improve rare disease trial design and analysis so that trials are more likely to provide interpretable data that clearly evaluates whether a product is effective. Additionally, OB has collaborated with academia on several BAA projects, such as ‘Modernizing Group Sequential Designs for Rare Diseases’.

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 2023 to address key issues in the design and analysis of trials for rare diseases.

This workgroup, jointly led by CDER [OND](#) and [OB](#), leverages SMEs 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](#)), 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 continues to work 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 trial 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. This year, the RD4 consult team performed consults across four OND divisions, offering advice on topics such as target population, interim analyses, endpoints, and external controls. Consults involved both pre-approval pivotal trials and trials designed to confirm clinical benefit following accelerated approval.

Clinical Pharmacology and Translational Medicine



Understanding how a drug behaves in the body and how the body responds to it is fundamental to developing treatments that are both safe and effective. For patients with rare diseases, this science takes on added urgency: limited clinical data demand that all forms of evidence be integrated in the development of new drugs. FDA's translational science initiatives aim to bridge knowledge from basic science to the clinic. Over the past year, work in this area focused on three interconnected priorities: helping drug developers build stronger development programs, advancing the science that underpins regulatory decision making, and sharing knowledge broadly with the rare disease community.

Drug developers working in the rare disease space – from large pharmaceutical companies to small biotechs and patient foundations – benefit from clear, early guidance on what a complete nonclinical and early-phase clinical pharmacology program should include. Efforts this year focused on providing that clarity, including publication of FDA guidance that helps sponsors understand how to design clinical development programs for highly targeted drugs where the condition may affect only a few patients.^{[1][2]} In addition, the Translational Science Team (TST) played a central role in working on individual drug development programs, providing review teams with specialized expertise to evaluate proposed surrogate endpoints and confirmatory evidence packages, translating complex translational science into clear, actionable guidance for sponsors.

Regulatory science research continued to advance new tools and methods for evaluating rare disease therapies. FDA's collaborative research projects with leading academic institutions explored the use of stem cell-based laboratory models as alternatives to traditional animal testing approaches in rare cardiac diseases. FDA also continued to advance the development and regulatory application of biomarkers to improve rare disease drug development.

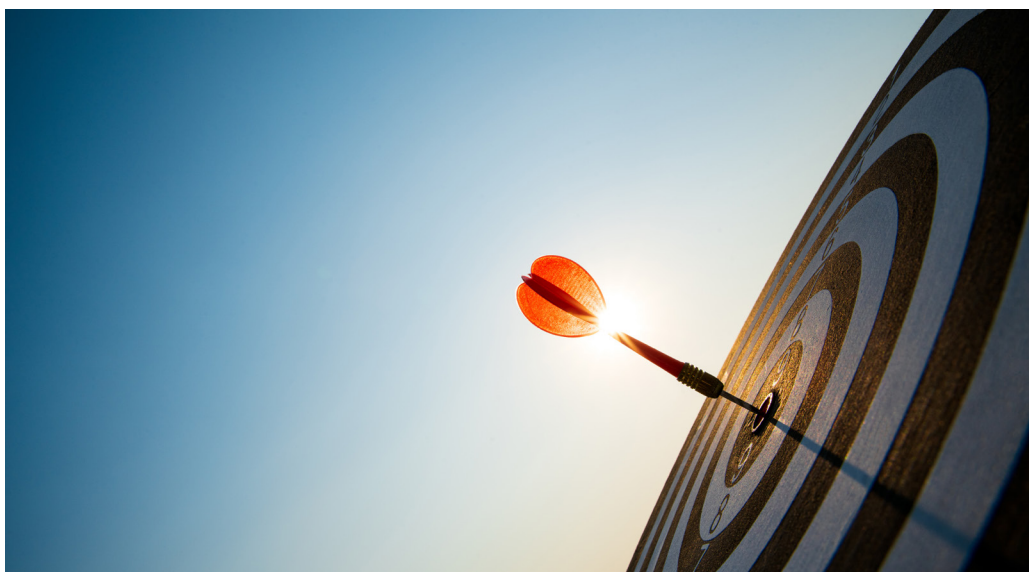
FDA launched the Biomarker Incubator, an initiative designed to foster collaborative development of biomarkers for regulatory use, beginning with a request for information on urinary kidney safety biomarkers.^[3] Looking forward, FDA is currently undertaking research that will help inform the utility of multi-omics approaches in rare disease trials and investing in new approach methodologies.^[4] These projects reflect a broader commitment to developing the scientific infrastructure that rare disease drug development requires, and to doing so in partnership with the external research community.

Communicating with the rare disease community on translational science issues also remained a priority throughout the year. FDA engaged directly with patients, clinicians, and developers through workshops and public forums, contributing to dialogue on how innovative approaches to the development of individualized therapies can be applied in practice^[5] and about use of biomarkers as surrogate endpoints.^[6]

Staff published research and perspectives across a range of topics, from dose optimization in rare diseases^[7] and clinical pharmacology considerations^[8], to pediatric rare disease drug development,^{[9][10]} regulatory approaches for therapies targeting low frequency molecular subsets,^[11] and comprehensive reviews of emerging biomarkers such as neurofilament light chain^[12] and biomarkers for primary mitochondrial diseases.^[13] Presentations at scientific conferences, academic institutions, and rare disease community events extended this reach further.

Together, these efforts demonstrate FDA's commitment to advancing translational science and clinical pharmacology as essential drivers of rare disease drug development. By integrating advances in biology, biomarkers, pharmacology, and regulatory science, FDA is helping to build a more efficient and scientifically robust development ecosystem that supports innovation while maintaining the rigorous standards needed to ensure that patients with rare diseases have access to safe and effective therapies.

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 more opportunities 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.



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. [Thus far, ARC has spearheaded two RDEA public workshops.](#)

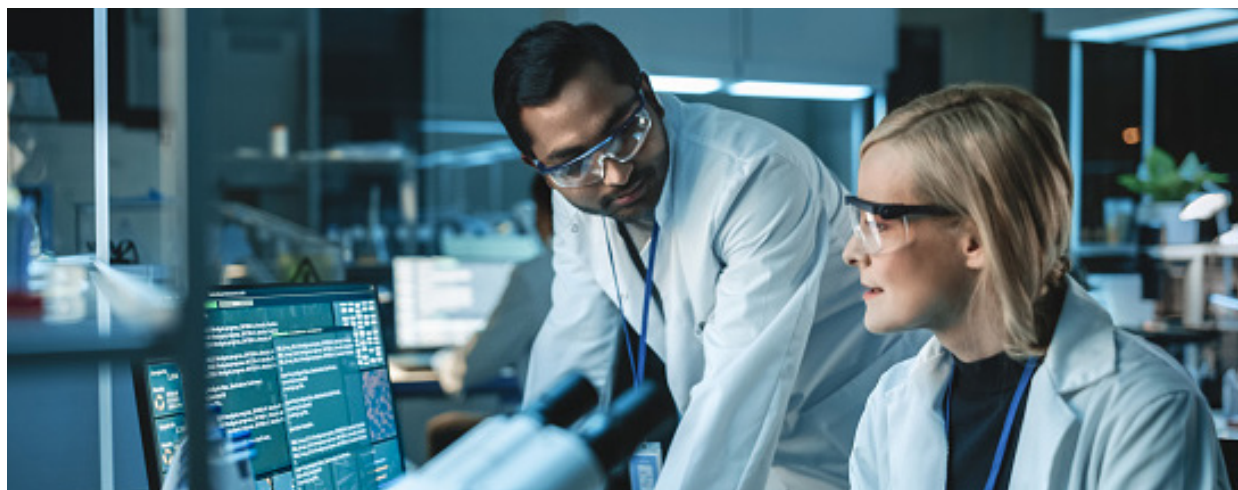
Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis (ALS) (Act for ALS)

During the last year, the Critical Path Institute's Rare Neurodegenerative Disease Program (CP-RND) has continued to develop standard operating procedures for the statistical analyses of the ALSFRS-R, a key outcome assessment used in ALS trials, and 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. Additional work has focused on measuring respiratory function in ALS and developing standard operating procedures for the collection and analyses of Forced Vital Capacity (FVC) and Slow Vital Capacity (SVC). Efforts in examining actigraphy data in ALS and what this data can inform are under curation and data

visualization. FDA funded a qualitative study to collect information from ALS patients and care partners on their lived experience and concepts that could potentially be used to support a clinical trial endpoint. This study is being conducted in conjunction with CP-RND and the Patients with Lived Experience working group under AMP ALS. FDA is also funding efforts to optimize potential endpoints for Huntington's Disease clinical trials. This effort examines existing data from key Huntington's Disease clinical outcome assessments and determines what may be an optimal measurement approach reflecting current Huntington's Disease clinical trials.

The Accelerating Medicines Partnership in Amyotrophic Lateral Sclerosis ([AMPALS](#)), 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.

Critical Path Institute (C-Path) Rare Disease Cures Accelerator–Data Analytics Platform (RDCA–DAP)



CDER has a cooperative agreement grant with the Critical Path Institute (C-Path) to advance regulatory science, improve drug development, and enrich patient experience during clinical trials. As part of this grant, the ARC Program supports the RDCA-DAP.

The RDCA-DAP provides a centralized and standardized data infrastructure to support characterization of rare diseases with the goal of accelerating development of treatments for these diseases. Specifically, RDCA DAP makes widely available a collaborative, non-competitive space to share rare disease patient-level data from diverse sources, including clinical trials, longitudinal observational studies, patient registries and real world data (e.g., electronic health data). The data in RDCA-DAP can be accessed by external users to inform clinical trial design based on the scientific merit of their research project, educational reasons or a public interest rationale.

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



To accelerate development of novel treatments for unmet medical needs like rare diseases, 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-BLA or pre-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.

ARC is excited to continue to engage the rare disease community to advance the development of the selected START Pilot participating projects and will work to synthesize learnings from this Pilot 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 novel surrogate biomarkers and confirmatory evidence
- Support regulatory evaluation of novel surrogate biomarkers and confirmatory evidence
- Where appropriate, support 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 SMEs 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, the CDER OB, the CDER Quantitative Medicine Center of Excellence, 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 shared with 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.

To date, the TST has completed over 20 consults for multiple OND review divisions. The impact of this work is reflected by the approval of three drugs which benefitted from a TST consult, two of which received accelerated approval based on biomarker-based endpoints.

Rare Disease Cluster



Rare diseases affect patients around the world, and developing treatments for these conditions benefits from a coordinated international response. The International Rare Diseases Cluster brings together FDA, the European Medicines Agency (EMA), and Health Canada to identify and address regulatory science and policy barriers to rare disease drug development. Through regularly scheduled teleconferences and targeted ad hoc discussions, Cluster participants exchange information and experiences on critical topics such as trial endpoint selection, innovative trial designs for small populations, regulatory flexibility, safety determinations, and post-marketing study design. The Cluster also serves as a confidential channel for sharing draft documents and safety reports, helping to establish a global safety net for rare disease therapies.

Since its inception in 2016, the Rare Disease Cluster has held 83 meetings and discussed a cumulative total of 203 topics, with 12 topics discussed between July 2025 and July 2026.

Message from the Acting Associate Director for Rare Diseases: ARC's Future Look

I am honored to serve as the Acting Associate Director of Rare Diseases. Having spent my FDA career promoting innovation in drug development, advancing regulatory science and policy, and overseeing regulatory review of rare disease applications, I bring a deep commitment to facilitate and expedite the development of safe and effective treatments for the millions of Americans living with rare diseases. With a background rooted in scientific leadership, stakeholder engagement, and cross-center collaboration, I look forward to channeling that experience into ARC's continued growth.



Elizabeth Hart, M.D.

This past year marked a significant milestone for the ARC Program with the release of our 2025–2030 Strategic Plan, a five-year roadmap that charts the Program's course to accelerate the development of safe and effective treatment options for the millions of individuals with a rare disease. Developed with input from experts across CDER, FDA, and the rare disease drug development community, the Plan is built

to grow and adapt alongside advances in rare disease science and the evolving needs of this community.

Entering its fifth year, the ARC Program continues to advance scientific methodologies to meet regulatory requirements and increase educational resources for stakeholders. ARC expanded its translational medicine efforts through the Translational Science Team (TST), a multi-disciplinary unit that supports rare disease drug application review teams across CDER by providing focused expertise in the evaluation of novel surrogate biomarkers and confirmatory evidence. The TST has expanded its reach across OND review divisions supporting more rare diseases, demonstrating the increasing demand for and value of this collaborative, science-driven approach to rare disease drug development.

The Rare Disease Drug Development and Design (RD4) has advanced the field by addressing critical challenges in rare disease trial design and analysis. This past year, RD4 launched a pilot consult service delivering targeted expert advice to OND review teams on key study design and statistical considerations. RD4 has also continued to develop tools to facilitate assessment and application of innovative methodologies for small populations. This year, LEADER 3D substantially expanded its educational portfolio with the publication of six new case studies and a new video, directly responding to the needs of the rare disease

drug development community. The ongoing integration and utilization of LEADER 3D as a resource built for external stakeholders reflects the program's real and demonstrable value as a driver of more informed, more efficient drug development for patients with rare diseases.

The ARC Program unwavering dedication to the rare disease community drives our mission to accelerate the availability of safe and effective treatments through strategic coordination and collaborative innovation. Deliberate partnerships and community engagement allow ARC to remain steadfast in its commitment to innovate regulatory science and enhance educational resources to help facilitate rare disease drug development.

As ARC moves into its next chapter, our resolve to serve the rare disease community remains strong, and we are eager to meet the challenges and opportunities ahead. The strides we have made reflect the dedication of our Rare Diseases Team, the strength of our partnerships, and the critical nature of our mission. Through scientific and regulatory innovation, engagement, and education, ARC will continue to facilitate, support, and accelerate the development of CDER-regulated drug and biologic products for the benefit of patients with rare diseases.

The ARC Program's unwavering dedication to the rare disease community drives our mission to accelerate the availability of safe and effective treatments through strategic coordination and collaborative innovation.

Glossary of Terms

Act for ALS	Accelerating Access to Critical Therapies for Amyotrophic Lateral Sclerosis	FVC	Forced Vital Capacity
ADTKD	Autosomal Dominant Tubulointerstitial Kidney Disease	HCM	Hypertrophic Cardiomyopathy
AI	Adrenal Insufficiency	IND	Investigational New Drug
ALD	X-linked Adrenoleukodystrophy	LD	Leukodystrophy
ALS	Amyotrophic Lateral Sclerosis	LEADER 3D	Learning and Education to ADvance and Empower Rare Disease Drug Developers
AMP ALS	Accelerating Medicines Partnership in Amyotrophic Lateral Sclerosis	NDA	New Drug Application
ARC	Accelerating Rare disease Cures Program	NIH	National Institutes of Health
BAA	Broad Agency Announcement	NORD	National Organization for Rare Disorders
BLA	Biologics License Application	OB	Office of Biostatistics
CALD	Cerebral Adrenoleukodystrophy	OBPV	Office of Biostatistics and Pharmacovigilance
CBER	Center for Biologics Evaluation and Research	OC	Office of the Commissioner
CDER	Center for Drug Evaluation and Research	OCD	Office of the Center Director
CDRH	Center for Devices and Radiological Health	OCE	Oncology Center of Excellence
CP-RND	Critical Path Institute's Rare and Orphan Disease Program	OCP	Office of Clinical Pharmacology
DARS	Division of Applied Regulatory Science	OCPES	Office of the Commissioner Patient Engagement Staff
DCM	Dilated Cardiomyopathy	ON	Office of Neuroscience
DRDMG	Division of Rare Diseases, Pediatrics, Urologic and Medical Genetics	OND	Office of New Drugs
DTPM	Division of Translational and Precision Medicine	OPTIMUM	Observational Prospective Trial in Modeling UMOD and MUC1
EMA	European Medicines Agency	ORPURM	Office of Rare Diseases, Pediatrics, Urologic and Medical Genetics
EZ	Ellipsoid Zone	OTP	CBER Office of Therapeutic Products
FDA	Food and Drug Administration	OTS	Office of Translational Science
FDORA	Food and Drug Omnibus Reform Act of 2022	PDUFA	Prescription Drug User Fee Act
FST	Full-Field Stimulus Threshold	PDUFA VII letter	Reauthorization Performance Goals and Procedures Prescription Drug User Fee Act
PFDD	Patient-Focused Drug Development Program	RDT	Rare Diseases Team
PLS	Patient Listening Sessions	RISE	Rare disease Innovation, Science, and Exploration

Glossary of Terms

RD4	Rare Disease Drug Development Design	RWE	Real-World Evidence Program
RDCA-DAP	Rare Disease Cures Accelerator–Data Analytics Platform	START	Support for clinical Trials Advancing Rare disease Therapeutics Pilot Program
RDEA	Rare Disease Endpoint Advancement	SVC	Slow Vital Capacity
RDPPC	Rare Disease Policy and Portfolio Council	TMLE	Targeted Maximum Likelihood Estimation



U.S. FOOD & DRUG
ADMINISTRATION

U.S. Food and Drug Administration
www.fda.gov

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