U.S. FOOD & DRUG ADMINISTRATION

Accelerating Rare disease Cures (ARC) Program

YEAR ONE: Anniversary Update

Driving Innovation through Collaboration and Engagement with Rare Disease Stakeholders

June 2023

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Anniversary Message

From the ARC Program Chair: The Director of the Center for Drug Evaluation and Research

Dr. Patrizia Cavazzoni

Accelerating the development of safe and effective drugs is the core mission of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA), and our rigorous evaluation standards ensure that American consumers have access to safe and advanced pharmaceuticals. At the same time, we at CDER also recognize the unique challenges which drug developers face in demonstrating the safety and effectiveness of drugs that treat rare diseases. In May 2022, CDER was proud to launch the Accelerating Rare disease Cures (ARC) Program to bridge the gap between the complexities of rare disease drug development and the pressing needs of patients with rare diseases to have treatment options.

Since launching one year ago, the ARC Program has emerged as a conduit for empowering rare disease stakeholders (including patients, patient advocates, drug developers, researchers, and federal partners) to harness their collective experiences and expertise to drive progress. One notable initiative launched is the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) project by CDER's Rare Diseases Team (RDT). The project aims to better understand the unique challenges in bringing rare disease products to market and produce educational materials on fundamental topics. The program also launched the ARC Quarterly Newsletter, which will act as a source for CDER rare disease news and updates regarding new and existing initiatives, like LEADER 3D, and announce conferences and partnerships that accelerate rare disease drug development.

ARC was also excited to see the launch of programs like the Rare Disease Endpoint Advancement (RDEA) Pilot Program, which CDER launched in partnership with the Center for Biologics Evaluation and Research (CBER), and activities related to the cross-agency Accelerating Access to Critical Therapies for ALS Act (ACT for ALS). These initiatives, while not directly led out of the ARC Program, are notable as they have the potential to drive new scientific innovations in the rare disease space. As an umbrella program for CDER's rare disease collaborations, ARC will work to share information and learnings from these programs more broadly across rare disease stakeholders.

Patient engagement is integral to ARC's mission, as patients with rare diseases inform and enhance innovative approaches to drug development. ARC's emphasis on engagement and collaboration in its first year is affirmation of this essential role that patients and their advocates play. Similarly, engagement with academics and drug developers is also crucial to the innovation and development of rare disease therapies. In the pages of this Program Anniversary Update, you will learn more about how CDER has innovated in various aspects of our work to propel the development of safe and effective rare disease treatments.

My admiration for our passionate and dedicated staff cannot be overstated, and I am in awe of the many important initiatives they have undertaken in just one year. I am proud of the important work that ARC has accomplished already in its first year, and I am excited for the future of rare disease drug advancements and the benefits they may bring to patients and their families.

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 one in ten people). Drug development for the approximately 7,000-10,000 rare diseases and conditions can be complex for many reasons, such as:

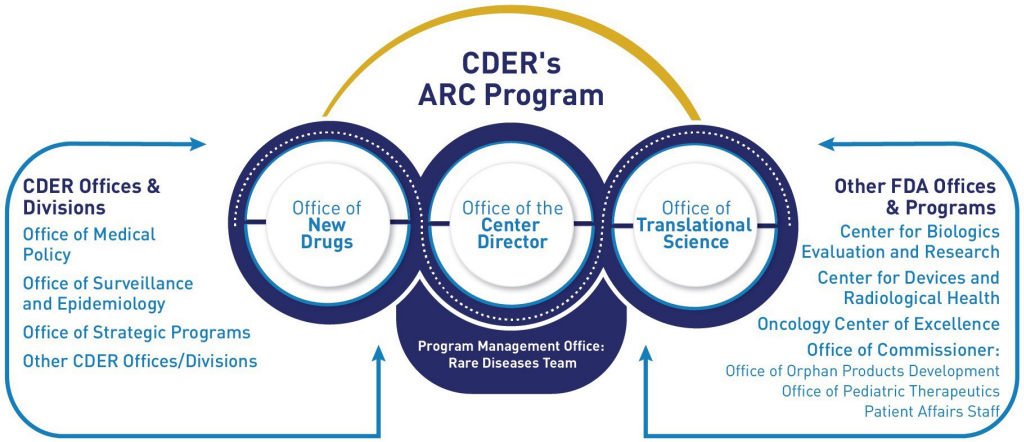
- There can be challenges with using well-established trial designs.
- Endpoint selection can be complicated if there is a limited understanding of the natural history of the disease.
- Small patient populations can make it difficult to perform and interpret rare disease clinical trials.

For these and other reasons, many rare diseases have few or no available treatments for patients who suffer from them. The ARC Program 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 their advocates.

OUR VISION
Speeding and increasing the development of effective and safe treatment options to address the unmet needs of patients with rare diseases.

OUR MISSION
Drive scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

CDER's Accelerating Rare disease Cures Program



ARC is a CDER-wide collaborative effort between the Office of New Drugs (OND), the Office of the Center Director (OCD), the Office of Translational Sciences (OTS) and other CDER offices. For cross-cutting rare disease considerations, ARC also brings together other FDA Offices and Programs, such as 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, underscoring the FDA's strong collaborations that advance treatment options for rare diseases and conditions. The program's management and operations are supported by CDER's Rare Diseases Team (RDT). Coordination and

consistency for rare disease treatments is critical to ARC's endeavors. The RDT works closely across FDA's rare disease stakeholders to fulfill its Prescription Drug User Fee Act VII commitments to facilitate, support, and accelerate the development of drug and biologic products by supporting the agency's activities dedicated to the development and review of treatments for the benefit of patients with rare disorders, in addition to leading cross-cutting rare disease guidances and ensuring that policies and practices are shared across the Center.

In its first year, the ARC Program has focused on strengthening internal and external partnerships with stakeholders and engaging with external experts to help identify solutions for the challenges in rare disease drug development. The following sections take a more comprehensive look into some of these activities and the significant milestones that have already been reached in Year One.

One Year At-A-Glance

Since the launch of the ARC Program in May 2022, CDER had a successful year establishing and supporting various activities to drive rare disease drug development, working hand-in-hand with other offices across the FDA.

Between May 2022 through May 2023, there were:

22

Rare Disease
New Drug Approvals

23

Patient Listening Sessions on Rare Diseases:

16 held by the Office of the Commissioner Patient Affairs Staff (PAS) with participation from CDER staff, and
7 organized by CDER's Professional Affairs and Stakeholder Engagement (PASE)

OVER

25

public speaking engagements featuring the ARC Program

MORE THAN

10,000

CDER Rare Disease News Subscribers

19

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

4

ARC Quarterly Newsletters

Outreach and Education

ARC's outreach and education initiatives focus on engaging with stakeholders to leverage expertise and innovation in the rare diseases space. This collaboration was a top priority in the program's first year. Input from patients living with rare diseases is crucial throughout the drug development process, and FDA staff undertook several initiatives to deepen the understanding of the regulatory framework. Other initiatives were aimed at providing more accessible information about CDER rare disease news and initiatives to the rare disease community.

Patient-Focused Initiatives

Patients' perspectives on rare diseases provide important insight to our work at FDA. Patient Listening Sessions are one of many ways the patient and advocacy community can share their experiences and perspectives by talking directly with FDA staff. Sessions are small, informal, non-regulatory, non-public teleconference meetings that allow participants to connect with FDA staff firsthand to share their experiences, perspectives, and needs related to their health or a disease. Between May 2022 and May 2023, Patient Affairs Staff (PAS) from the FDA's Office of the Commissioner **supported 16 listening sessions for patients with rare diseases**,

with participation from CDER staff. Additionally, CDER's Professional Affairs and Stakeholder Engagement (PASE) Staff supported seven listening sessions, covering rare diseases such as Prader Willi syndrome, atypical hemolytic uremic syndrome, and epidermolysis bullosa.

[It's important] 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.

Relatedly, FDA's Patient-Focused Drug Development (PFDD) program aims to more systematically obtain the patient perspective on specific diseases and their treatments in order to understand the context in which regulatory decisions are made for new drugs. PFDD meetings give FDA and other key stakeholders (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 inform FDA's decisions and oversight both during drug development and during our review of a marketing application. CDER staff supported the conduct of **19 externally-led PFDD meetings** between May 2022 and May 2023.

While patients with rare diseases and their families have extensive direct experience living with their disease and available drug treatments, CDER recognizes that they often have more limited information on the research processes that are involved in developing new drugs, as well as the evidence needed to demonstrate their effectiveness. In late summer 2022, PFDD initiated discussions with the National Organization for Rare Disorders (NORD) to develop some advanced tools and related training for rare disease patients and their families. Some goals of this initiative include **providing patients and families with a deeper knowledge of the drug development and regulatory process**, and providing tools to help patients and families secure maximum effective use of their own contributions of time and data. The tools will support their ability to play a more active role in the drug development and regulatory process as well as to promote the most effective drug development programs for their disease areas.

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

In September 2022, CDER's Rare Diseases Team (RDT) inaugurated the Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) initiative to **better understand the unique challenges in bringing rare disease products to the market**. As part of this initiative, the RDT engaged with stakeholders who design and conduct rare disease drug development programs. The goal was to identify regulatory topics that could benefit from the development or expansion of educational materials. RDT is working to develop educational resources that will provide deeper understanding about the regulatory fitness and advancement of drugs and biologics for rare diseases. A docket for public comments was also opened in December 2022 to gather additional stakeholder input. Some emerging themes from our outreach efforts to-date include the potential need for additional clarity on the importance and use of natural history studies, establishing novel endpoints for rare disease regulatory submissions, leveraging real-world evidence for regulatory submissions, and much more.

We appreciate the ongoing support and engagement of our rare disease drug development stakeholders as we continue the LEADER 3D initiative and work towards accelerating the development of treatments for patients with rare diseases.

ARC Quarterly Newsletter

As part of our efforts to foster communication among rare disease stakeholders, ARC created a new FDA GovDelivery email list, "CDER Rare Disease News." ARC distributes a quarterly newsletter to its subscribers, providing them with program updates, information on new drug approvals, as well as highlighting any relevant conferences, partnerships, or initiatives of interest to the rare disease community. Our mailing list has grown significantly since its launch – as of May 2023, there are **over 10,000 subscribers**. As the number continues to increase in coming years,

we hope that the mailing list will act as a powerful virtual tool to enhance collaboration among the rare disease community.

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

FDA-TRACK

In February 2023, the ARC Program announced the addition of "Original Rare Disease Application Approval" and "Novel Rare Disease Drugs Approval" filters to 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.

With this new filter, 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 currently displayed data from the February launch only includes approvals from the last quarter (October-December) of 2022. Additional data will be updated quarterly in the future, with the next update to be posted early this summer. This information within FDA-TRACK will provide a more accessible view to the rare disease community about the development and approval of safe and effective drugs to treat rare diseases.

Conferences, Workshops, and External Speaking Engagements

During the past year there have been numerous conferences and workshops centered on rare disease drug development. These meetings are an important nexus of exchange where various stakeholders in the rare disease community come together to share their experiences, insights, challenges, and innovations for the future. As external outreach lies at the core of the ARC Program, FDA staff have participated in **over 25 public speaking engagements** over the last year as speakers, panelists, and audience members to amplify CDER rare disease initiatives, in addition to listening to the efforts and experiences of other rare disease stakeholders, including patients and drug developers.

These meetings are an important nexus of exchange where various stakeholders in the rare disease community come together to share their experiences, insights, challenges, and innovations for the future.

ARC was featured at FDA's Rare Disease Day 2023, a virtual public meeting whose theme this year was "Intersections with Rare Diseases – A patient focused event." Kerry Jo Lee, MD, Associate Director for Rare Diseases, spoke in a cross-center session which highlighted the ARC Program. The session, entitled "FDA initiatives to advance medical product development for rare diseases," underscored the strength of FDA's cross-center collaboration in evaluating policies and practices related to the review of drugs and biologics intended to treat rare diseases. Ongoing teamwork between CDER's RDT and CBER provides that policies and practices are applied consistently across review divisions, ensuring the availability of safe and effective treatments for patients living with rare diseases.

Information, recordings, and meeting materials for the following events conducted as part of engagement and education initiatives are accessible for rare disease stakeholders on the ARC Program's webpage:

- FDA CDER and National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) Regulatory Fitness in Rare Disease Clinical Trials Workshop: May 16-17, 2022
- FDA and Duke-Margolis Public Workshop: Translational Science in Drug Development: Surrogate Endpoints, Biomarkers and More: May 24-25, 2022
- FDA CDER and Johns Hopkins University Centers of Excellence in Regulatory Science and Innovation (CERSI) Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools Workshop: May 2-3, 2023
- FDA CDER and University of Maryland CERSI Creating a Roadmap to Quantitative Systems Pharmacology-informed Rare Disease Drug Development: May 11, 2023

Scientific and Regulatory Initiatives

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

Following a productive year of approvals for rare disease therapies, offices and divisions in the Office of New Drugs (OND) have contributed to and led many of the scientific and regulatory initiatives to advance the complex and multi-disciplinary considerations of rare disease drug development.

By promoting innovative scientific design, providing a deeper understanding of regulatory policies, and sharing learnings from all rare disease programs across CDER, ARC strives to accelerate the availability of treatments for patients with rare diseases.

Complex and Innovative Methodologies

FDA has taken steps to advance the use of complex and innovative methodologies in our work. One area of development has been Bayesian statistical methods, which have the **potential to increase trial efficiencies with particular benefit to rare diseases**.

FDA collaborated with Medidata on a project that focused on Bayesian methods in Acute Lymphoblastic Leukemia (ALL). On January 4, 2023, the project findings were published in the Journal of Biopharmaceutical Statistics in a paper entitled, "Utility of Propensity Score-based Bayesian Borrowing of External Adult Data in Pediatric Trials: A Pragmatic Evaluation Through a Vase Study in Acute Lymphoblastic Leukemia (ALL)." A fully powered randomized controlled cancer trial can be challenging to conduct in children because of difficulties in enrollment of pediatric patients due to low disease incidence. According to their research, one mechanism to improve the feasibility of trials in pediatric patients, when clinically appropriate, is through borrowing information from comparable external adult trials in the same disease. Bayesian statistical analysis of a pediatric trial provides a way of seamlessly augmenting pediatric trial efficacy data with data from external adult trials.

Additionally, CDER's Office of Biostatistics (OB) has been participating in the Biostatistics Limited-Duration Integration Innovation Team (LIIT). The Biostatistics LIIT is part of the Medicines Development Modernization Initiative (MDMI) and is a short-term tactical initiative intended to test and understand methodologies and strategies for overcoming barriers to the integration of medicines development tools, stakeholders, and information. The goal of the Biostatistics LIIT is to develop training on Bayesian methods for non-statisticians, which may aid in rare disease drug development.

FDA staff have also presented their research on innovative designs at several conferences and workshops this year. For example, Dionne Price, Ph.D., Director, Division of Biometrics IV, Office of Biostatistics, gave a presentation entitled, "The FDA Rare Disease Cures (ARC) Program: Opportunity for Innovation" at the March 2023 Spring Meeting of the Eastern North American Region of

the International Biometrics Society. Similarly, the FDA CDER and Johns Hopkins University (JHU) Center of Excellence in Regulatory Science and Innovation (CERSI) Workshop, "Addressing Challenges in the Design and Analysis of Rare Disease Clinical Trials: Considerations and Tools," occurred on May 2-3, 2023. OB was actively involved in the workshop planning, and Day 2 was dedicated specifically to clinical trial design and analysis methods.

Clinical Pharmacology and Translational Medicine

The Office of Clinical Pharmacology (OCP) is a dynamic, purpose-driven organization dedicated to promoting and protecting global public health through the application of clinical pharmacology and translational medicine principles.

Characterizing the clinical pharmacology of medical products is an essential part of drug development to find the right dosage, select the right patients, and tailor drug use based on various factors like drug interactions. A variety of approaches, ranging from in vitro trials to modeling and simulation, hold great potential to facilitate the transition of new treatments from bench to bedside, particularly when it comes to getting the dose right and establishing evidence of effectiveness, which is critically important for rare diseases where so few patients may be studied in clinical trials.

During the first year of ARC, OCP had several activities that aimed to advance science for the benefit of patients with rare diseases and bolster patient-centered engagement. Beyond working with companies on specific drug development programs, some selected accomplishments include the following:

- **Publishing in the peer-reviewed scientific literature on major clinical pharmacology considerations for rare disease drug development**, including dose-finding practices, conduct of traditional clinical pharmacokinetic and pharmacodynamic investigations, use of model-informed drug development approaches, and expansion of indications using in vitro data. These papers provide a foundational landscape from which future progress in rare disease drug development can be measured.

- **Participating in multiple workshops and professional conferences**. OCP collaborated with the University of Maryland (under the CERSI program) to hold two workshops to discuss emerging scientific issues like quantitative systems pharmacology approaches in rare disease drug development, and the use of artificial intelligence and machine learning. Interacting with diverse stakeholder communities in different forums enables FDA's clinical pharmacologists to hear from experts about new science and share perspectives on best practices for rare disease drug development.
- **Conducting research to evaluate innovative approaches for rare disease drug development**. Representative research projects aim to develop laboratory models that could complement human trials and streamline clinical development, describe translational science approaches that inform patient selection for clinical trials, define approaches to validate biomarkers for use as surrogate endpoints or confirmatory evidence, and develop models of disease progression to guide patient selection or endpoint development. These regulatory science initiatives help FDA create novel tools or approaches that can facilitate rare disease drug development and identify opportunities for innovate approaches.
- **Developing partnerships across therapeutic areas and disciplines**. OCP established a Rare Disease Scientific Interest Group (RaD-SIG) to facilitate communication among clinical pharmacologists working on different rare diseases, as well as create a venue for external experts to educate OCP's staff. In addition, OCP contributes to many CDER-wide and FDA-wide working groups, like the Individualized Therapies Task Force (for new drug designed for a single patient), Biomarkers Working Group, and others. These efforts ensure communication across various parts of FDA, and that FDA's clinical pharmacologists stay abreast of emerging science.
- **Promoting consistency in regulatory review through guidance and policy**. Among the many guidances that OCP has published for drug development in general, OCP published draft guidance on clinical pharmacology considerations for oligonucleotide therapeutics, which are often developed for rare diseases. These efforts support the quality and consistency of FDA's regulatory evaluations.

The benefits of the initiatives such as those described above have been realized in the review of marketing applications. For example, modeling work aided in the development of endpoints to support approval of a novel drug for amyotrophic lateral sclerosis (ALS). In the coming year, OCP will continue to focus its efforts on working with stakeholders to develop and implement innovations that improve drug development for rare diseases.

RDEA (Rare Disease Endpoint Advancement) Pilot Program

Announced in a Federal Register notice on October 27, 2022, 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 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 (endpoints are measurements of what happens to people in a clinical trial). Sponsors whose RDEA proposals are admitted into the RDEA Pilot Program will have increased opportunity to interact with interdisciplinary FDA experts in endpoint development, as well as the associated clinical review division, in a series of up to four focused meetings to discuss their proposed novel endpoint.

Sponsors whose RDEA proposals are admitted into the RDEA Pilot Program will have increased opportunity to interact with interdisciplinary FDA experts in endpoint development

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.

FDA will begin accepting proposals on a quarterly basis for admission into the RDEA Pilot Program on July 1, 2023, and FDA will accept a maximum of one RDEA proposal for the quarter ending September 30, 2023. For fiscal years 2024

through 2027, FDA will accept up to one RDEA proposal per quarter with a maximum of three RDEA proposals per year. 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 is June 30, 2027

FDA will give preference to proposals that have the potential to impact drug development in rare disease more broadly, such as one that uses a novel approach to develop an efficacy endpoint or an endpoint that could potentially be relevant to other rare diseases. FDA will also give preference to proposals that reflect a range of different types of endpoints. For surrogate endpoint proposals, FDA will give preference to those with novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints.

All program updates, including required elements of the RDEA proposal, meeting package, and disclosure as well as RDEA proposal submission instructions, will be posted on the RDEA Pilot Program webpage prior to the program opening for proposal submissions on July 1, 2023. A list of RDEA Pilot Program frequently asked questions with responses is also available.

PDUFA VII and FDORA also include a performance goal and requirement, respectively, for the conduct of 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. The Federal Register notice announcing this public workshop also opened a docket for public comment, which closes on July 23, 2023. While the RDEA Pilot Program is not directly led out of the ARC Program, **ARC will work to disseminate learnings** from this pilot across internal and external stakeholders in rare disease drug development.

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Accelerating Access to Critical Therapies for ALS Act (ACT for ALS)

On December 23, 2021, President Biden signed the Accelerating Access to Critical Therapies for ALS Act (ACT for ALS) into law. As stipulated in the law, in June 2022 CDER's Office of New Drugs (OND), in cooperation with CDER's Office of Translational Sciences and CBER, published a five-year action plan (and opened a docket for public comment) that outlines the program enhancements, policy development, regulatory science initiatives, and other relevant initiatives to foster drug development to treat amyotrophic lateral sclerosis (ALS), commonly referred to as Lou Gehrig's disease, and other rare neurodegenerative diseases, and to facilitate access to investigational drugs. The action plan also identifies representatives within the FDA responsible for external collaborations and in considering cross-cutting clinical and regulatory policy issues (such as consistency of regulatory advice and decisions).

In September 2022, FDA and the National Institutes of Health (NIH) announced the launch of the Critical Path for Rare Neurodegenerative Diseases (CP-RND)—a

public-private partnership with the Critical Path Institute (C-Path) aimed at **advancing the understanding of neurodegenerative diseases and fostering the development of treatments for ALS and other rare neurodegenerative diseases**. On March 15, 2023, C-Path held a webinar to share an overview of CP-RND to the patient stakeholder group and provide the opportunity for feedback and questions from participants. A recording of this webinar can be accessed here: CP-RND: An Introduction to the Patient Community.

FDA also initiated the FDA Rare Neurodegenerative Disease Grant Program, through which grants and contracts will be awarded to public and private entities to cover costs of research and development of interventions intended to prevent, diagnose, mitigate, treat or cure ALS and other rare neurodegenerative diseases in adults and children. These awards will be administered by the Office of Orphan Products Development, which administers programs that provide incentives for sponsors to develop products for rare diseases. Grants and contracts will be used for the development of tools, methods, and processes to characterize the natural history of the neurodegenerative diseases, to identify molecular targets for these diseases, and to increase efficiency and productivity of clinical development of therapies.

Additionally, in November 2022, FDA launched its internal ACT for ALS Taskforce with the goal of facilitating the development of products to address rare neurodegenerative diseases. The Taskforce will achieve this goal by providing strategic direction for initiatives that are focused on the development of regulatory and scientific tools to support rare neurodegenerative disease drug development, leverage internal expertise and innovation, strengthen dialogue, and promote effective collaboration.

Lastly, two new drugs to treat ALS were approved since May 2022:

- Radicava ORS (edaravone): an orally administered version of Radicava, which was originally approved in 2017 as an intravenous (IV) infusion to treat ALS. Radicava is approved to treat adults with ALS.
- Qalsody (tofersen): an intrathecally administered drug (through spinal injection) for patients with ALS with a mutation in the superoxide dismutase 1 (SOD1) gene (SOD1-ALS).

Two new drugs to treat ALS were approved since May 2022

Like the RDEA Pilot Program, FDA efforts under ACT for ALS are not directly led out of the ARC Program. However, as the umbrella program for CDER's rare disease collaborations, ARC will work to share learnings more broadly across rare disease stakeholders from these efforts for regulatory science and innovation for ALS and other neurodegenerative diseases.

From the Associate Director for Rare Diseases and ARC Program Manager:

ARC's Future Outlook

Dr. Kerry Jo Lee

As demonstrated by the various efforts outlined in this Anniversary Update, ARC is committed to accelerating safe and effective treatments for rare diseases. Through deliberate engagement and outreach, we have cultivated a robust network with patients, patient advocates, drug developers, and researchers, which we will continue to nurture and grow in years to come.

In Year One, our focus has been on engagement in order to inform the program's strategic direction and consider how ARC's growth trajectory aligns with current and future initiatives. Through introspection and dialogue with rare disease stakeholders, we will continue to reevaluate how ARC can develop to achieve its mission of accelerating treatments for rare diseases. In 2023, we will continue our outreach efforts to empower the rare disease community. Specific areas of focus for this work will include creating and disseminating educational materials produced through initiatives like LEADER 3D and PFDD's complimentary program with NORD, as well as sharing learnings more broadly from the use of novel endpoints for rare disease therapies from the RDEA Pilot Program. We will also diligently continue our efforts to learn about the rare disease patient perspective.

ARC also aims to make strides in the scientific and regulatory aspects of rare disease drug development in its second year. This includes expanding efforts in translational medicine approaches for individual rare diseases. Through ongoing regulatory research in confirmatory evidence and surrogate biomarkers, as well as developing initiatives to enhance translational science considerations in rare disease application review, ARC hopes to contribute to the clinical and regulatory knowledge available that is needed to make informed decisions for rare disease drug development. Additional work is continuing to bolster the use and development of frameworks such as complex innovative designs, including Bayesian statistical approaches, and supporting platforms which facilitate natural history studies. Such innovative scientific approaches to rare disease research have the potential to increase the number of safe and effective drugs available to treat rare diseases, and we are excited to provide the mechanisms to support them.

The strides which ARC has already made in its first year have laid the groundwork for future outreach and scientific innovation across FDA in 2023. We look forward to the development of engagements, programs, and educational tools that will help spur advancements in making new, safe, and effective rare disease treatments available to the public.

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Accelerating Rare disease Cures Program

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