Recent FDA Advancements in Rare Diseases – Funding, Partnerships, and Programs

Paucity of therapeutic choices is a reality often acknowledged by the US Food and Drug Administration (FDA) as it reviews applications for new medical products or expansions to approved indications. This is especially true in the case of rare diseases, the majority of which lack any approved treatments. The FDA continues to emphasize the importance of promoting medical product development for rare diseases, including actions taken within the past few months.

"One of the greatest obstacles facing individuals who suffer from rare diseases is the limited treatment options currently available," said FDA Commissioner Robert M. Califf, MD, in a statement issued in October 2022.[1] The agency announced that it had awarded 19 new grants and two new contracts totaling more than $38 million in funding over the next four years to support clinical trials, natural history studies, and regulatory science tools related to rare diseases.

These grants and contracts were funded by the FDA's Orphan Products Grants Program.[2] The agency received 33 clinical trial grant applications, of which 11 were chosen to receive funding (more than $25 million) over the four-year period. Seven of the awards fund studies of rare cancers, largely targeting cancers of the brain and peripheral nerves:[3]

- Phase 2 study of multi-tumor–associated antigen-specific T-cell therapy (MT-401) for the treatment of relapsed/refractory acute myeloid leukemia (AML) patients following allogeneic stem cell transplant.
- Phase 1/2 study of ^{177}Lu-DOTATATE for the treatment of recurrent/progressive high-grade central nervous system (CNS) tumors and meningiomas that express somatostatin type 2A receptors.
- Phase 2 study of ASTX727 (combination of decitabine and cedazuridine) for the treatment of malignant peripheral nerve sheath tumour.
- Phase 2 study of palbociclib (CDK4/6i) plus INCMGA0012 (PD-1 blockade) for the treatment of well-differentiated or dedifferentiated liposarcoma.
- Phase 2 study of SONALA-001 sonodynamic therapy for the treatment of diffuse intrinsic pontine glioma.
- Phase 2 study of neoantigen-specific adoptive T-cell therapy for the treatment of glioblastoma.
- Phase 1 study of RNA-lipid particle vaccines for the treatment of newly diagnosed glioblastoma.

Among the 43 natural history grant applications received by the FDA, eight were chosen to receive more than $11 million over the next four years.[3] Three of the selected natural history studies are related to rare neurodegenerative diseases: 1) a retrospective and prospective study in amyotrophic lateral sclerosis (ALS) of clinic-based multicenter data collection, 2) a prospective study in ataxia-telangiectasia, and 3) a prospective study in myotonic dystrophy type 1 to establish biomarkers and clinical endpoints. These studies serve to meet a requirement under Public Law 117-79, the Accelerating Access to Critical Therapies for ALS Act (ACT for ALS),[4] signed into law in December 2021, for the FDA to award grants or contracts to public and private entities to cover costs of research on and development of interventions intended to prevent, diagnose, mitigate, treat, or cure ALS and other rare neurodegenerative diseases in adults and children.

The two contracts that received funding are also related to rare neurodegenerative diseases. One contract, co-funded by the US National Institutes of Health (NIH) and the FDA, will study whether a physical assessment of ALS patients, usually performed in a healthcare professional's office, can be done remotely at home to minimize patient burden. The second contract is a landscape analysis of patient-preference information studies focused on brain-computer interface (BCI) devices. For this analysis, the FDA is interested in BCI devices that communicate with the brain and provide patients who are no longer able to speak or move with the ability to interact with their families and healthcare professionals.

Research in the area of rare neurodegenerative diseases was bolstered earlier this year when the FDA unveiled its Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis (ALS)[5] in June. Developed in accordance with provisions of the ACT for ALS, the five-year strategy aims to improve and extend the lives of people living with rare neurodegenerative diseases by advancing the development of safe and effective medical products and facilitating patient access to novel treatments. An element of the plan is the ALS Science Strategy, which provides a "forward leaning framework" for FDA activities to evaluate key regulatory science priorities. The focus areas of the ALS Science Strategy relate to characterisation of disease pathogenesis and natural history; patient access to treatments and participation in clinical trials; and clinical trial enhancements (e.g., optimisation of trial design, reduction of development costs).

An additional development relating to rare neurodegenerative diseases occurred in September 2022, when the FDA and the NIH announced the launch of the Critical Path for Rare Neurodegenerative Diseases (CP-RND).[6] A public-private partnership, CP-RND is aimed at advancing the understanding of neurodegenerative diseases and encouraging the development of treatments for ALS and other rare neurodegenerative diseases. Said the FDA's Chief Medical Officer, Hilary Marston, MD, MPH, in the announcement, "There is a crucial need to develop new treatments that can improve and extend the lives of people diagnosed with rare neurodegenerative diseases, including ALS. Collaboration across public and private sectors can accelerate the progress to address this urgent need."

Endpoints for Rare Diseases

In October 2022, a notice published in the *Federal Register* announced that the FDA is establishing a Rare Disease Endpoint Advancement (RDEA) Pilot Program to support novel endpoint efficacy development for drugs that treat rare diseases.[7] The RDEA Pilot Program fulfills a commitment under the seventh iteration of the Prescription Drug User Fee Amendments (PDUFA VII), which required the FDA to establish a pilot program for the development of novel efficacy endpoints in rare disease drug development programs for sponsors with an active investigational new drug application (IND) or pre-IND for the rare disease or sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied.

Via the pilot program, which will run through September 30, 2027, selected sponsors will have the opportunity for increased engagement with FDA experts from the Center for Drug Evaluation and Research (CDER) and/or the Center for Biologics Evaluation and Research (CBER) to discuss novel efficacy endpoints intended to establish substantial evidence of effectiveness for a rare disease treatment. The program includes a series of focused meetings between sponsors and the FDA.

Although the FDA stated that it "welcomes RDEA proposals related to any eligible novel endpoint for a rare disease," it will give preference to proposals that 1) have the potential to impact drug development more broadly (e.g., use a novel approach to develop an efficacy endpoint or an endpoint that could potentially be relevant to other diseases); 2) reflect/impact a range of different types of endpoints; and 3) for surrogate endpoints, those that use novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints. The FDA will begin accepting proposals on a quarterly basis for admission into the RDEA Pilot Program on July 1, 2023.

In his prepared remarks for delivery at the Rare Diseases and Orphan Products Breakthrough Summit, hosted by the National Organization for Rare Disorders (NORD) on October 17–18, 2022, Califf emphasized the importance of engagement and collective work in the field of rare diseases, including collaboration among patients and their advocates, representatives of industry, government, researchers, academia, and many other stakeholders. "Only through these collaborations can we develop efficient and respectful approaches to the necessary clinical trials to sort through treatments and quickly identify those that turn out to be effective while getting rid of ineffective or dangerous treatments,"[8] he stated.

Regarding the rare disease space, Califf noted that the FDA is working "to embrace greater regulatory flexibility to help meet unmet medical needs." Rare diseases require "a unique balance between regulatory flexibility and the scientific evidence necessary to ensure that a product is safe and effective," he said. An example of regulatory flexibility in the context of a rare disease is to accept clinical trials that have lower sample sizes. Califf stressed that any such an approach would not compromise the integrity of the results. Rather, these approaches "are designed and intended to help generate more high quality evidence that could support a drug approval." Any decisions "will be based on the best available science," he said.

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Deborah Komlos

Deborah Komlos, MS, is a Principal Content Editor for the Cortellis suite of life science intelligence solutions at Clarivate. In this role, her coverage centres on FDA advisory committee meetings, workshops, and product approvals. Her previous positions have included writing and editing for magazines, newspapers, online venues, and scientific journals, as well as publication layout and graphic design work.

Email: deborah.komlos@clarivate.com