



**FDA U.S. FOOD & DRUG  
ADMINISTRATION**

**TESTIMONY OF**

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**BEFORE THE**

**SUBCOMMITTEE ON HEALTH**

**COMMITTEE ON ENERGY AND COMMERCE**

**U.S. HOUSE OF REPRESENTATIVES**

**“THE PATH FORWARD: ADVANCING TREATMENTS AND CURES FOR  
NEURODEGENERATIVE DISEASES”**

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**RELEASE ONLY UPON DELIVERY**

## INTRODUCTION

Chair Eshoo and Ranking Member Guthrie, thank you for the opportunity to testify before you today on neurodegenerative disease drug development and approval. I have spent a substantial portion of my medical career researching and treating disorders and diseases of the brain, and I am particularly gratified to come before this Committee for the first time in my capacity as Director of the Food and Drug Administration's (FDA or the Agency) Center for Drug Evaluation and Research (CDER) to testify on the topic of neuroscience. Neuroscience is an area of medicine where there is tremendous unmet need for safe and effective treatments and for research that can guide the development of new therapies.

## CURRENT DRUG DEVELOPMENT CLIMATE

The pace of drug development in the United States has advanced to a point where FDA is steadily approving new therapies that make major improvements in the lives of patients with a wide range of diseases. In the last several years, FDA has increased the number of drugs approved that improve and prolong the lives of, or even cure, patients who suffer from devastating, and in some cases, previously fatal diseases.

In 2020, CDER approved 53 novel drugs, either as new molecular entities (NMEs) under New Drug Applications (NDAs), or as new biological products under Biologics License Applications (BLAs), forty percent of which were first-in-class approvals. Also in 2020, the Center for Biologics Evaluation and Research (CBER) approved eight new BLAs. In neurology specifically, in 2020, FDA approved novel therapies for patients with Parkinson's disease, multiple sclerosis, spinal muscular atrophy, Duchenne muscular dystrophy, tuberous sclerosis complex, Dravet syndrome, migraine headaches, and neuromyelitis optica spectrum disorder. So far in 2021, the Agency has approved 31 novel drugs, including the approval of Aduhelm (aducanumab), a treatment for Alzheimer's disease.<sup>1</sup>

Although great strides have been made in drug development across many therapeutic areas, progress has not been even. At FDA, we put patients at the forefront of everything that we do, so we remain committed to working with sponsors, patients, and other stakeholders to advance safe and effective treatments for patients when new therapies are submitted to us for evaluation, particularly when an unmet medical need remains. Our focus is heightened when that unmet medical need involves a progressive and fatal disease.

## NEURODEGENERATIVE DISEASES

Neurodegenerative disease is an overarching term for a variety of progressive conditions that affect the neurons of the nervous system, resulting in the damage and death of those cells. These diseases are relentless, often fatal, and affect fundamental functions – things like moving, breathing, speaking, and thinking. Neurodegenerative diseases are particularly challenging from both a research and a drug development perspective. Though advances in this field have been more limited compared to other therapeutic areas, drug development is nonetheless encouraging for some diseases. For example, patients suffering from neuromyelitis optica spectrum disorder (NMOSD), a rare autoimmune disease affecting the brain and optic nerve, had no FDA-approved treatments available to them until 2019, when

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<sup>1</sup> <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021>

we approved Soliris (eculizumab). Subsequent approvals for Uplinza (inebilizumab-cdon) and Enspryng (satralizumab-mwge) in 2020 brought the total number of FDA-approved therapies for this disorder to three. In a just a few years, patients with this condition saw tremendous advances in available—and quite effective—therapies. Unfortunately, most neurodegenerative diseases do not have this scope of treatment options.

Although there has been great progress in basic and preclinical research for neurodegenerative disease, we have yet to identify the key underlying molecular defects or pathways that give rise to many of these conditions, like Amyotrophic Lateral Sclerosis (ALS) — observations which would yield precise targets for novel drugs. To expand on this point, it is important to note that there are numerous challenges impeding drug development for neurodegenerative disease. For example, disease pathophysiology—the basic mechanisms of disease at the molecular level—remains incompletely characterized. Although some diseases are linked to genetic mutations—that is, known, specific gene variations that can induce molecular defects precipitating the illness—in many cases there is no identified defect. Further, for many diseases, animal models are “translational”—that is, they help predict the likelihood of response to a novel drug in humans with the disease. Unfortunately, translational animal models for neurodegenerative diseases that could help prioritize which drugs to bring forward for clinical testing most rapidly are not as advanced, or predictive of benefit in patients with the disease, as in other areas.

In addition to the lack of both molecular defects that can be targeted by drugs and “translational” animal models, clinical studies of new drugs for neurodegenerative diseases also present major challenges. While we have seen advances in some neurodegenerative diseases, in many other instances, such as with ALS, there are no easily measured biomarkers that are reliable predictors (or surrogates) for the rate of progression in individual patients. Such tools could improve the precision with which drug response could be evaluated, providing researchers with much more robust, and earlier, insights to distinguish the more promising drugs from those that are less likely to succeed. Unfortunately, clinical trial experience for these diseases has been challenging with many failed studies, reflecting the difficulty in drug development when the disease is not well understood. Researchers are continuing their work to understand the pathogenesis of neurodegenerative diseases, which could lead to better prognostic and diagnostic biomarkers.

The current limitations present significant challenges in the development of treatments for neurodegenerative diseases. I have no doubt that many of the unsuccessful drug development efforts are in large part due to inadequate disease characterization. We – the scientific and medical community broadly – simply do not have a sufficient understanding of the pathophysiology of many of these diseases, their direct causes, and why or how these diseases can present differently in different patients, among other factors. We simply do not know enough about the basic underlying causes of these terrible diseases or how to predict and monitor their progression, to have all of the tools we need to develop treatments to fight, or better yet, cure them.

While these challenges are significant and cannot be ignored, they have not stopped FDA, and they do not mean progress is impossible. I would like to emphasize two points. First, making progress on expanding our basic, scientific understanding of neurodegenerative diseases is absolutely critical to making progress on developing treatments. Comparisons are often made to the amazing advancements that we have made in treatments for cancer and HIV. While these advancements are stunning, these were made possible by a deep understanding of the underlying disease processes. For example, the discovery of specific molecular defects in different types of cancer has led to drugs specifically targeting these defects — and has resulted in numerous, targeted novel drugs approved — drugs which have

prolonged the lives of patients and even offered cures to many. Without that, I have no doubt that we would not be where we are today in the treatment of cancer. Second, I can assure you that FDA is not simply standing by while waiting for science to advance. We are using every tool at our disposal to help facilitate the development of treatments for neurodegenerative diseases, as I will lay out for you. For example, in 2019 FDA issued a final guidance, *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment*, to provide industry with FDA's current scientific thinking so that effective treatments with a favorable benefit to risk profile can be most efficiently developed, studied, and ultimately made available to patients.

## **Regulatory Framework for Neurodegenerative Diseases**

I can tell you from experience that drug development is not linear, and instead consists of many stops and starts along the way. In many cases, what may have been thought of as a promising compound on the lab bench does not bear out in early trials. Sometimes, these disappointments happen later, during late-stage clinical trials.<sup>2</sup>

I believe the challenges to developing meaningful therapies to target neurodegenerative diseases are serious but not insurmountable. In oncology, we can objectively measure whether a tumor shrinks or its growth is arrested. We do not have those same parameters for many neurodegenerative diseases because the origin and disease course of many of these conditions are not known, and we have not yet identified sensitive biological markers to monitor the progression of these diseases.

However, I remain optimistic about our prospects for future breakthroughs for neurodegenerative conditions. For example, the National Institutes of Health's (NIH) recent funding initiative to spur exceptionally creative, high-risk, high-reward ALS research (\$25 million over the next five years) has the potential to advance our understanding of ALS, and I commend those efforts. We are committed to doing all we can to ensure the development of treatments, and go beyond the drugs currently approved for neurodegenerative diseases. I am eager to discuss ways in which FDA can further our efforts in this area.

Each disease or condition comes with its own unique presentation and diagnosis. FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to medical products for serious diseases with unmet medical needs, while preserving appropriate assurance that they are effective and have a favorable benefit to risk profile. We stand ready to thoroughly evaluate and act on applications for products that treat serious and life-threatening diseases.

An example of the Agency working proactively to advance the development of new therapies is the approval of Radicava (edaravone). In 2017, FDA approved Radicava to treat ALS. This drug came to the attention of FDA staff after the drug was approved in Japan, and they worked with the company as it submitted an application to FDA, ultimately resulting in the drug's approval. It represented the first new treatment for ALS in the United States in years. We stand ready to thoroughly evaluate and act on applications for products that treat serious and life-threatening diseases.

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<sup>2</sup> See *22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results*, January 2017, <https://www.fda.gov/media/102332/download> page 17, which explains that while Phase 2 trial results looked promising for lithium as a treatment for ALS, a Phase 3 trial showed no benefit.

## **Patient Perspectives**

The incorporation of patients' experiences, perspectives, and priorities in drug development and evaluation is a critical aspect of drug development. Among other things, it supports the development of therapeutics with a meaningful impact on patients' quality of life, focused on what they consider the most important aspects of their disease. This emphasis on patients' experiences is exemplified through CDER's Patient-Focused Drug Development Program, which also includes CBER. FDA participates in multiple patient engagement opportunities to learn from patients through listening sessions, external engagement, patient-focused drug development meetings and collaboration in the pre-competitive space.

For example, this past January 2021, we convened a meeting with the Duke-Robert J. Margolis, MD, Center for Health Policy to discuss the unmet need for effective therapies for ALS. This meeting discussed topics on basic research, clinical trial infrastructure, and community engagement needed to advance and support drug development for treatment of ALS. As an outcome of this meeting, a framework on how to approach these needs is under development.

## **Clinical Trial Design**

Although our prior experiences in trials for some neurodegenerative diseases have led to useful, standard trial endpoints and study designs, we are open to and supportive of efforts to further improve the approaches to study drugs to treat other neurodegenerative diseases. Innovative clinical trial designs may be helpful in accelerating therapeutic development for neurodegenerative diseases. Drug developers— in many instances aided by FDA guidance—are exploring and implementing innovative approaches to clinical trial design, including platform and adaptive designs to maximize the statistical power of trials and to minimize study duration, risk to participants, and the overall number of participants required for trial conduct. They also continue to seek out more innovative approaches to capture and incorporate patient-reported outcomes in trials and to maintain and utilize shared data.

Drug developers are also undertaking approaches to improve access to clinical trials across the spectrum of the patient and volunteer community, including ethnic and racial minorities and patients living in rural areas. These approaches include: decentralized trials, which are designs that essentially bring the trial to the participant, to increase access and enrollment for individuals who are not located near a research center, or for whom travel to an investigational site can be very burdensome; remote monitoring used alongside digital tools to reduce the need for travel for those with limited mobility; the design of trial randomization schemes to increase the number of participants able to access an investigational treatment during the trial; and open-label extension studies to provide expedited access to the trial drug for those randomized to a placebo comparator in the placebo-controlled phase of a clinical trial.

We fully recognize the concerns that clinical trial participants share with us about the use of placebo-controlled studies, and understand their frustration with such designs. However, the track record for new drugs shows us that for every successful treatment, about 40 drugs failed — many of which were touted as highly promising. While we strongly desire a curative therapy, a treatment that provides a meaningful incremental benefit would still be desirable. A drug with a dramatic effect size might be adequately evaluated without a comparator, but to detect a more modest, yet very relevant benefit, only a controlled trial — comparing the candidate to placebo — can serve. It is also important to note

that in these trials, patients receive standard of care treatment (when it is available) in addition to the experimental drug or placebo. Even though we recognize the need for such trial designs, we work with sponsors to minimize the use of placebo — by employing unequal randomization (more participants getting the study drug) and by keeping the placebo-controlled period as limited in duration as needed to assess the response to the drug. Moreover, participants completing the placebo-controlled period are then offered entry into open-label treatment periods with the study drug.

FDA is working hand-in-hand with researchers to support and encourage these innovations.

## **Expanded Access**

Because of the continuing unmet medical need for approved treatments, we also know that many patients with neurodegenerative diseases are seeking access to investigational products for these devastating diseases. FDA remains committed to helping patients and health care professionals evaluate options for accessing investigational products, such as participating in a clinical trial or obtaining access to an unapproved, investigational product outside of a clinical trial through expanded access (commonly referred to as compassionate use). Although FDA has no involvement in the manufacturers' or sponsors' decisions to provide such access to eligible investigational drug products under expanded access, we do play a role in approving the requests. However, under the "Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017," also known as the Right to Try Act, we generally do not have a role in access to investigational products, or approval of such requests, although we provide information for patients on our website.

In some cases, like with ALS and certain other diseases, we have also encouraged sponsors to offer access to investigational products after clinical trials are completed when continued access to a promising medicine would be appropriate under the expanded access program. However, it is important to note, as stated before, that FDA cannot require a company to provide a product under expanded access, so in order for a patient to receive a treatment under this mechanism, the manufacturer or sponsor must be willing to provide it. In addition, while FDA reviews clinical trials and authorizes expanded access, the Agency does not authorize requests for use of eligible investigational drugs under the Right to Try Act.

As important as individualized access is to patients, through expanded access to investigational products or otherwise, there are tradeoffs. Patients administered an experimental therapy in the context of FDA's expanded access program may not be eligible to participate in clinical trials of potential new therapies. We are particularly cognizant of this impact on drug development for rare diseases. In May 2020, we requested public comment on establishing Rare Disease Clinical Trial Networks, an important step in development of a Rare Disease Cures Accelerator. We envision this Accelerator would be a cooperative scientific initiative for the development of common, standardized platforms that can improve the characterization of rare diseases, incorporate the patient's perspective in clinical outcome assessment measures, and build clinical trial readiness in the pre-market space.

## **FDA ACTIONS ON NEURODEGENERATIVE DISEASES**

A little over a year ago, CDER reorganized its Office of New Drugs (OND), and among other changes, we stood up an Office of Neuroscience. The reorganization of OND was the culmination of three years of effort. We undertook this reorganization to modernize OND in part to align interrelated disease areas

and divisions with clearer and more focused areas of expertise. The Office of Neuroscience's new structure allows the office to provide a more holistic approach to the regulation and review of neuroscience drugs, and to leverage expertise across the office so that all divisions within the office benefit from shared knowledge and ensure greater consistency in regulatory approaches.

In addition to this internal realignment, we also have focused on providing scientific guidance and leadership outside the Agency, including to individual drug sponsors as well as industry more broadly. I would also like to acknowledge CBER's efforts in this area. Both CDER and CBER work closely together on cross-cutting issues, including guidance documents and both centers work closely with sponsors to facilitate the development of medical products to treat neurodegenerative diseases.

In 2021, FDA issued two guidances for developers of antisense oligonucleotide (ASO) drug products for severely debilitating or life-threatening diseases. The first covers administrative and procedural aspects of interacting with FDA for sponsors seeking to develop individualized investigational ASO drug products.<sup>3</sup> The second guidance (released in April) explains the Agency's recommendations for the non-clinical testing that should support first-in-human use for these investigational drug products.<sup>4</sup> ASO drugs, including those that are designed for single or a small number of individuals, show promise in treating genetically-targeted diseases, including neurodegenerative disease. We intend to issue an additional guidance on ASO manufacturing by the end of 2021.

## **The Status of Science of ALS**

I'll now focus on ALS as an illustrative example of some of the difficulties we encounter. ALS is a neurodegenerative disease affecting motor neurons. Approximately 5,000 people each year in the United States are diagnosed with ALS. Disease progression is often characterized by progressive muscle weakness with death occurring, only three to five years (on average) after disease onset. Thus, ALS is relentlessly progressive, with no cure. In addition, most cases of ALS have, as of yet, no known cause. Further complicating matters, ALS is a disease with varied presentations, including weakness, spasticity, cramps, and fasciculations (muscle twitches) in different parts of the body, along with varying rates of progression.

Over the course of the last four decades, over 80 randomized controlled clinical trials have been conducted for ALS. However, to date, the drug products approved to treat ALS in the United States all contain one of only two active ingredients, edaravone and riluzole. This unfortunate track record of repeated failures—despite promising early data—illustrates that despite repeated efforts to find treatments for ALS, many potential treatments have failed to show benefit when carefully evaluated in clinical trials. Despite years of research and the availability of some approved therapies, we know the lack of new treatments for ALS is deeply frustrating for patients and caregivers, and for us at FDA as well.

Many of the challenges involved with the development of drugs for neurodegenerative disease that I described earlier present obstacles to the development of new treatments for ALS. A lack of understanding of the fundamental cause of ALS, the need for improved translational models, and the absence of biomarkers to assist in drug development all present critical challenges. The science needs to press forward to address these needs.

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<sup>3</sup> See <https://www.fda.gov/media/144872/download>

<sup>4</sup> See <https://www.fda.gov/media/147876/download>

## Conclusion

While I used ALS as an illustrative example, I recognize that there are other neurodegenerative diseases including Friedreich's ataxia, Huntington's disease, Lewy body dementia, Parkinson's disease, Alzheimer's disease, and many more diseases for which there are no or limited therapies. It is imperative that FDA, researchers and drug developers work together to find solutions that bring therapeutics forward for all of these disease states.

We appreciate Congress' attention to these devastating conditions, and we stand ready to assist. Many of us have been personally impacted by neurodegenerative diseases, whether it be through personal experience with a diagnosis of a friend or relative, or by hearing tragic stories in the many listening sessions that we have held with patients and caregivers. At FDA, patients are at the forefront of everything that we do. We remain steadfast in our deep commitment to support the patient advocacy community in its efforts to fight the terrible toll that these diseases take on all those affected.

We stand ready to use the expedited development and approval programs that are available to FDA in order to help bring new treatments to patients as quickly as possible. We recognize the impact these diseases have on patients and their loved ones, and share in the common goal of wanting to advance the development of treatments with a positive benefit-risk profile that can help patients. I look forward to continuing the discussion with you about ways we can work together to advance the science and provide much-needed answers for patients.