Congress of the United States

Washington, DC 20515

July 15, 2022

The Honorable Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

Dear Commissioner Califf:

People living with aggressive, fatal neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) need access to safe therapies. With several novel therapies currently being studied or under review, we are hopefully on the cusp of medical breakthroughs to treat this debilitating disease. To this end, on July 29, 2021, the House Energy and Commerce Health Subcommittee held a hearing entitled *The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases.* Further, on December 23, 2021, the bipartisan *Accelerating Access to Critical Therapies for ALS Act (P.L. 117-179)* was signed into law. We are writing to better understand how the U.S. Food and Drug Administration (FDA) is using its September 2019 industry guidance, the drug development approval pathways authorized by Congress, and the *Accelerating Access to Critical Therapies for ALS Act*, to ensure ALS patients with unmet need have access to therapies.

We strongly support the ALS Guidance published by the FDA in 2019, *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment*, and strongly urge the FDA to reaffirm and act upon its stated goals. In particular, we support the use of appropriate regulatory flexibility in the approval of ALS treatments. FDA seems to apply requirements inconsistently, which creates uncertainty amongst drug developers that may delay or hinder potentially effective drugs from coming to market. In addition, we applaud the recent publication of the FDA's *Action Plan for Rare Neurodegenerative Diseases including ALS* and look forward to continuing to work with Agency to create a modern, advanced clinical trial infrastructure for rare neurodegenerative diseases.

The FDA has employed a rapid regulatory approach to approve drugs in areas like oncology. We believe the Agency should look to its approach in oncology and apply any best practices that could be used for ALS drug development given the unmet need and the seriousness of ALS. All divisions at the FDA, including the Office of Neuroscience, must act urgently on behalf of people living with fatal diseases. In that spirit, we request you provide answers to the following questions by July 29, 2022:

1. Leading ALS physicians and researchers who testified at the hearing agree that ALS is a heterogeneous disease that impacts each patient differently. They stated that there will be therapies which work for some patients (but not all) and that there may never be a single treatment for ALS because it likely will require a combination of therapies to change the trajectory of this disease from 100% fatal to treatable.

   How does the FDA identify clinical benefit among a subset in a trial and take that benefit into account for drug approval for serious diseases with unmet need? How does FDA use post-hoc analyses to demonstrate effectiveness?

2. In response to the Questions for the Record from the July 2021 hearing, the FDA stated that it has "approved drugs where the overall average effect in the trial was statistically significant yet quite small, but where there was a subset of patients on whom the drug had a large and clearly meaningful effect."

The Agency went on to state that the effect of the drug is also viewed in the context of the seriousness of the disease and the unmet need. For patients facing a fast-moving, terminal disease "a large and clearly meaningful effect" may be a simple improvement in function for day-to-day living rather than a clear improvement for survival.

How does the FDA balance patient and provider input when defining "meaningful effect" for the efficacy and approval of a drug?

3. Witnesses at the hearing also stated that unlike cancer, there are no validated clinical biomarkers for ALS and other neurodegenerative diseases. However, many ALS clinical trials include biomarker evaluation across multiple disease pathways thought important in ALS which researchers could use as reasonably likely surrogate endpoints.

   Is FDA considering the use of reasonably likely surrogate endpoints from other disease pathways in clinical trials until ALS biomarkers are validated? If not, why?

4. At the July 2021 hearing, Center for Drug Evaluation and Research (CDER) Director Patrizia Cavazzoni, M.D., stated that the FDA has the flexibility it needs to approve therapies for diseases like ALS.

   Please provide specific examples of regulatory flexibilities, including the flexibilities described in the 2019 industry guidance for ALS clinical trials, that have been used to facilitate and accelerate the development of therapies to treat ALS and other neurodegenerative diseases.

5. The FDA's 2019 industry guidance for ALS clinical trials states "[w]hen making regulatory decisions about drugs to treat ALS, the FDA will consider patient tolerance for risk and the serious and life-threatening nature of the condition in the context of statutory requirements for safety and efficacy."

   How does the FDA define regulatory flexibility for ALS treatments? Please provide specific examples of how this flexibility has been used to benefit patients living with ALS.

6. The FDA's 2019 industry guidance for ALS clinical trials states "Various strategies can be applied to expedite ALS trials and minimize unnecessary exposure to placebo. For example, master protocols (which use a single infrastructure, trial design, and protocol) allow for the simultaneous evaluation of multiple drugs, with a common or shared placebo group, and have the potential to greatly expedite the development of new drugs. Sponsors should also consider adaptive designs (including the use of Bayesian features) and enrichment strategies." FDA's recently-published *Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis* lists "Explore Innovative Trial Designs" and "Enhancing Clinical Trial Infrastructure and Agility" as two longer-term (FY 2025 – FY 2026) FDA activities to tackle neurodegenerative diseases.

   Please describe any activities that the FDA has undertaken to promote or advance the use of master protocols and/or adaptive designs for trials in neurodegenerative disease in the period following the 2019 guidance.

   Please describe any barriers that may prevent the FDA from exploring innovative trial designs and enhancing clinical trial infrastructure and agility in the near term.

7. In the *Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis*, FDA states that it will "continue to communicate with the ALS community to engage their support and expertise and partner with them on our efforts as possible."

   Please describe the efforts that FDA has undertaken in the past three years to communicate with the ALS community, including a description of whom FDA has worked with and how the information gathered has been used in FDA work.

We thank you in advance for your cooperation and should you have any questions, you can contact Aisling.McDonough@mail.house.gov. We look forward to your prompt response and remain committed to being partners with the FDA as we work together to ensure that patients have access to promising new treatments for ALS and other neurodegenerative diseases.

Sincerely,

Anna G. Eshoo
Member of Congress

Brett Guthrie
Member of Congress

Jan Schakowsky
Member of Congress

Gus M. Bilirakis
Member of Congress

Mike Quigley
Member of Congress

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