

August 4, 2022

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
5630 Fishers Lane
Rockville, Maryland 20852

Dear Commissioner Califf:

On behalf of The ALS Association and the people we serve, I am writing to provide feedback on the Food and Drug Administration's (FDA) recently announced Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis (Plan). We appreciate the timely attention to this element of the Accelerating Access to Critical Therapies for ALS Act (P.L. 117-79) and believe coordinated efforts at the FDA and across the public and private sectors can accelerate the development of new treatments for people living with ALS. We are committed to being an active participant in this critical work.

Overall, the Plan is an important engagement with several key issues to be addressed in facilitating therapies and cures for rare neurodegenerative diseases, with ALS as "the tip of the spear". The statute refers to this activity as the "ALS and Other Rare Neurodegenerative Disease Action Plan." We certainly hope that progress in confronting ALS across various research domains can benefit other conditions, while being mindful of the need for focused effort on the inherent complexities of ALS.

In terms of feedback on the Plan, we offer the following overarching points for the FDA's consideration.

1. Speed is essential. ALS is a rapidly progressing, fatal disease that demands a similarly urgent approach to research, development, and access to treatments. In its current form, the Plan has limited details on how to prioritize the various proposed activities and on implementation pathways and milestones. Both prioritization and milestones are necessary for the rapid improvements the ALS community needs. We recommend this detail be developed in the next several months to guide both FDA and any aligned external efforts.
2. Accountability drives results. It is unclear from the document who within the agency is responsible for both the overall management of the Plan, as well as where the individual elements are situated. It will be useful to identify these leaders to help ensure efforts remain active and focused across the timeframe.
3. Inclusivity builds momentum. We believe proactive engagement of stakeholders and regular reporting to the public will build momentum across the ALS therapy development community. To that end, it is important for the Plan to have a clear mechanism for providing updates on implementation progress and accomplishments.



OUR VISION: Create a world without ALS.

OUR MISSION: To discover treatments and a cure for ALS, and to serve, advocate for, and empower people affected by ALS to live their lives to the fullest.

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The attachment to this letter offers additional comments at the Plan activity level which flow from the recommendations above. Thank you for considering these views as the FDA undertakes important new work under the Plan to accelerate ALS therapies. We would welcome the opportunity to discuss these comments in greater detail and, as always, to collaborate with the FDA and other stakeholders in this initiative.

Sincerely,

A handwritten signature in blue ink, appearing to read "Neil Thakur".

Neil Thakur
Chief Mission Officer

cc: Patrizia Cavazzoni, M.D.
Billy Dunn, M.D.

ATTACHMENT

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FDA Rare Neurodegenerative Diseases Task Force

In their overview of rare neurodegenerative diseases (RND), the FDA noted unknown disease mechanisms and related pathogenesis hamper advances in ALS treatment. The establishment of the FDA RND Task Force and the related Accelerating Rare disease Cures (ARC) program are laudable; however, as currently constituted, they appear to be an FDA-only pursuit. An agency specific approach risks wasteful redundancy and misses the potential for more focused and larger scale collaborative approaches that can generate results faster.

The FDA has the opportunity to engage entities which can address the known barriers of unsolved molecular mechanisms through a coordinated effort with various NIH components (*e.g.*, NCATS), industry, and academia to promote more cohesive, collaborative efforts in respective RNDs. This will help avoid undue duplication of efforts across those investigating mechanisms and, conversely, address gaps in mechanistic approaches. The FDA should take an assertive role in coordinating (or at least advising on) an inventory of current programs across all stakeholders and an assessment of where programs overlap or leave chasms in the development of interventions.

Most importantly, we want the FDA and the whole enterprise focused on advancing the health of people with ALS and other rare neurodegenerative diseases as quickly as possible. A taskforce like this can either focus on scientific and regulatory bottlenecks that are slowing the development of cures, or they can reinforce those bottlenecks by shifting resources away from efforts that prioritize speed to clinic and towards research in fundamental discoveries that could benefit treatment development in decades ahead. People living with ALS now will not live to benefit from that work. Speed must be a priority.

Public-Private Partnership for Rare Neurodegenerative Diseases

At this point, the detail in this section is sparse. It is conceivable the coordination needs identified in the RND Task Force section above could be addressed, at least in part, through this platform. More detail on how specific public-private partnerships will be pursued and selected would be helpful.

Leverage Ongoing FDA Regulatory Science Efforts

The outline of this section is conceptually encouraging and would benefit again from a more extensive articulation of the who, when, and how elements planned for each program such as the accountability and timelines/deliverables anticipated for each of the ARC, CPIM, and other listed programs. We also believe a compilation of foundational work already accomplished by various stakeholders would be instructive (*e.g.*, NORD/C-Path/FDA work in the RDCA-DAP project).

Science Strategy for Amyotrophic Lateral Sclerosis

Overall, this strategy does not convey a clear sense of focus and urgency. Again, the most important element of any strategy to improve the health of people with ALS needs to be speed. More specifically, the specific citations in the "Overview of the ALS Science Strategy," introduction mentions "four focus areas" but goes on to describe three focus areas that we address below.

[1] Improve characterization of disease pathogenesis and natural history: An assessment focused on where FDA perceives gaps in natural history and a plan to address them could be helpful. However, the scientific community could easily spend decades on improving the characterization of disease pathogenesis and studying natural history. It already has invested a great deal, and the NIH and others

continue to fund this work. Further efforts in these areas by the FDA need to include an expectation of when they may lead to improvements in ALS treatment. The more time it will take this work to result in human benefit, the lower priority it should have.

[2] Facilitate access to investigational new drugs: This area focuses on participation in clinical trials and could benefit from cross-learning and information-sharing with other non-communicable chronic disease communities for seeking best practices.

[3] Enhance clinical trial infrastructure and agility: Here again, we believe this work could springboard via benchmarking with other investigative communities.

Near-term Activities (FY 22)

Establish FDA Rare Neurodegenerative Diseases Task Force's ALS Working Group

As noted earlier, the establishment of the FDA RND ALS working group is to be applauded, with the hope that stakeholder liaison and involvement will be maximized by FDA leadership and focused on advancing the health of people with ALS as quickly as possible.

Support Translational Science Research

While the offer for FDA to share their expertise is welcome, it would be more helpful if the plan also offered objectives or milestones in addition to a process of sharing. Can FDA set an intention to use their expertise to make ALS trial reviews faster, for example?

Medium-term Activities (FY 23 to FY 24)

The timelines and deliverables for elements here will be impacted by the success of the preceding near-term activity plans. We believe it would be reasonable to consider accelerating some of the medium-term targets into the FY 22 plan. Comments on specific medium-term activities follow.

Explore Gaps in Understanding of ALS Natural History

As noted above, we believe the gap analysis and targeted natural history studies to address needs for the FDA could be valuable, particularly when done with the intention to achieve benefits for people living with ALS as quickly as possible.

Collect Patient Perspectives on Clinical Trial Participation

This is an important priority for the Association and the community. The ALS Focus platform (<https://www.als.org/research/als-focus>) could be used to help generate this patient and caregiver perspective data. While the emphasis on decentralized trials is logical, the Agency is encouraged to take an unbiased approach to this issue and remain open to the possibility that this research will identify other types of barriers that could limit trial participation. The Agency is also encouraged to develop a plan for sharing data and conclusions from this type of research project.

Facilitate and Encourage Data Sharing

Data by itself have limited utility, and are much more useful if they are linked to specimens. There are already considerable shared resources (data, specimens, animal models, etc.) in the ALS space supported by the NIH, The National ALS Registry, The Association and other groups. In a rare disease space with a limited workforce and research funding, the limiting factor to full utilization of shared

resources could be research support to take full advantage of the resources available, not the availability of resources themselves.

Support the Development of Study Data Standards for ALS

The ALS Association has a strong record of supporting the development of various tools to advance clinical studies, including the ALS clinical trial guidelines. We are prepared to discuss how this element can be addressed in a collaborative manner with FDA and other partners, particularly industry sponsors of clinical trials.

Longer-term Activities (FY 25 to FY 26)

Explore Innovative Trial Designs

There may be an opportunity to accelerate this activity into an early stage of the Plan. As new ALS treatments are approved the complexity of running standard of care control arms, and the potential for combination therapies to rapidly improve the patient experience, will both increase. The FDA should anticipate and guide the ALS community in adapting to these changes.

Enhancing Clinical Trial Infrastructure and Agility

As changes to infrastructure can take significant time to implement, the Agency is encouraged to begin this process as soon as possible, perhaps by moving now to establish the partnerships with existing clinical trial networks that are mentioned in the Plan.

Implementation of the ALS Science Strategy

The timely and accountable implementation of the Plan and its ALS Science Strategy is paramount. We would encourage the FDA to have a mechanism for engagement of external stakeholders and regular reporting on both progress and challenges. This work will not be done in a silo, so it is essential that the FDA staff who are leading the initiative be identified and a structured approach used to advance this complex set of goals and associated activities.

Leveraging Scientific Advancements Across Rare Neurodegenerative Diseases

As we have observed, the Association sees considerable advantage in advancing the plan as a highly collaborative effort both across federal partners and with the surrounding research and development ecosystem. The creation and operation of the CBER NEURO Team is a particularly important concept in this section given the shared challenges across cell and gene therapy development.

FDA Office of Orphan Products Development's Grant Program

The underlying statutory basis for the Plan, the ACT for ALS, also authorizes a Rare Neurodegenerative Disease Grant Program. The FDA should align the awards made from this program, as well as those from the Orphan Products Grants Program, with the Plan implementation.