ALS Guidance on Drug Development
Frequently Asked Questions

What is an FDA Guidance?

Food and Drug Administration (FDA or the Agency) guidance documents explain the Agency’s current views on a regulatory topic and are typically developed within the Agency. They are not binding on the Agency or industry sponsors like law or regulation, but are highly influential in the drug development and approval process. The FDA prepares guidance for industry, its staff and other stakeholders to provide clarity in key areas such as: content and evaluation of applications for products; manufacturing standards; testing of regulated products; and inspection and enforcement. The FDA now accepts and reviews guidances developed outside the Agency, but FDA may or may not adopt any or all parts of such submissions.

Why is it needed?

Currently, there is no FDA guidance for ALS drug development. Without a specific guidance for ALS, there is a lack of clarity and predictability for industry and manufacturers when navigating the drug development and approval process, increasing the amount of time it takes a sponsor to move a potential therapy from initial FDA engagement to approval.

The ALS community’s guidance, which was submitted to the FDA in August 2017, will serve as a roadmap to help industry navigate the development process and provide the Agency with an ALS community-centered view of the disease and how it should approach potential therapies for ALS. The goals of an FDA guidance are to make the drug development process, including clinical trials, more efficient, predictable, faster and effective at assessing drug safety and efficacy. This will accelerate access, reduce costs and help ensure resources are used efficiently. It will also incentivize industry to enter the ALS market and develop new treatments for ALS.

How does it affect ALS drug development?

The ALS guidance will create a roadmap for industry by providing clarification on the Agency’s expectations on key aspects of future submissions and reviews of ALS candidate treatments, ultimately providing greater predictability in that process. The guidance also incorporates critical patient and caregiver insights and data such as benefit-risk preferences and patient reported outcomes in the FDA process. These elements in combination will help attract industry to the field and accelerate regulatory review of potential therapies.

How was the guidance developed?

The guidance project was governed by a steering committee comprised of subject matter experts and representatives of key constituencies within the ALS community such as people with ALS,
Seven working groups (see chart below) were established to oversee and develop specific chapters of the guidance, and were comprised of 7-12 subject matter experts per working group. Each working group had representation from a variety of perspectives (e.g., industry, academia, et.al.) and included at least one person with ALS. Working groups convened approximately every two weeks via conference call and also developed content between conference calls. As content was developed, it was periodically reviewed by both the steering committee and Patient and Caregiver Advisory Committee for revision and further modification. The chapters of the guidance were merged into a cohesive guidance document, which was shared with the greater ALS community in May 2016 for input during a 30-day public comment period. Once final changes were made, the guidance was submitted to the FDA.

Importantly, a Patient and Caregiver Advisory Committee (PCAC) was established to advise the steering committee and working groups. The PCAC provided comments and suggestions on every aspect of the guidance development. Participants on PCAC included nearly 40 people with ALS, caregivers, family members and other ALS organizations.

**FDA Guidance: Project Structure**

![Diagram of FDA Guidance Project Structure]
**Who was involved with the project?**

The guidance development project included representation from throughout the ALS community, including nearly 40 people with ALS and their family members, more than 10 ALS organizations, 45 of the world’s leading ALS researchers and clinicians from 30 different institutions, 15 representatives from 9 biopharmaceutical companies, and 5 government representatives from the three centers at the National Institutes of Health and the Centers for Disease Control and Prevention. This diverse representation helped ensure that the entire ALS community had a voice in the development of the guidance. A full list of participants is available here:

**Did People with ALS and caregivers provide input?**

Yes! The guidance project is a patient-driven initiative, and people with ALS and caregivers played a critical role. The Patient and Caregivers Advisory Committee (PCAC) included nearly 40 people with ALS, caregivers, and ALS patient representatives. The PCAC’s charge was to articulate the needs and perspectives of the patient and caregiver community by reviewing and providing comments on each step of the guidance development process, as well as suggesting content for each section of the guidance itself. There were also patient and caregiver representatives on each of the seven working groups and on the guidance steering committee.

In addition to providing input as members of the PCAC, working groups and steering committee, people with ALS and others from throughout the ALS community had an opportunity to review the guidance and provide additional input during a 30-day public comment period that took place in May 2016 timeframe. That feedback was reviewed and incorporated as appropriate into the final product submitted to the FDA.

The ALS community will also have other opportunities to provide input, including when the FDA docks the ALS community’s guidance on regulations.gov and when the Agency publishes its version of the guidance, during which the FDA will open a public comment period to collect additional feedback from ALS stakeholders. During the latter comment period, The ALS Association expects to host a public workshop in Washington, DC in which FDA leaders would participate to receive in-person feedback from the ALS community.

**Why now?**

At the request of The ALS Association and Muscular Dystrophy Association, the FDA convened the first ever ALS-specific public meeting in February, 2013. During that meeting, the two organizations requested that the Agency develop a guidance document for ALS drug development. Since the FDA does not have the resources to develop guidance for every disease or to bring together an entire disease community to inform the process, The ALS Association
utilized funding made possible by the Ice Bucket Challenge to support this initiative. The effort is particularly timely, as the FDA is increasing its emphasis on patient-focused drug development and allowing guidances to be developed outside of the Agency. With no existing FDA guidance for ALS drug development, The ALS Association recognized that developing such a document, with the patient voice at the center, would be critical to the community.

**Will the FDA make changes to the guidance submitted by the ALS community?**

Yes. We anticipate that the FDA will make changes to the guidance submitted by the ALS community. This is expected because, as encouraged by the FDA, the guidance purposely includes content that would not be appropriate for an FDA-issued guidance and which goes far beyond what typically is found in an FDA guidance, but will serve an educational purpose. We are using the guidance process to provide much broader and in depth input to the FDA on topics that go beyond a guidance document, as most FDA reviewers are not ALS experts. This will help to ensure that we do not simply inform the Agency about the development of a guidance, but also provide the Agency with additional inputs about ALS, the state of the science and the community’s views on key topics. This additional input is critical because it will further inform Agency decision-making and be an extremely valuable resource to the Agency beyond the finalized guidance itself. In fact, the FDA has communicated to the guidance leadership that the broader community-submitted guidance will continue to be a vital resource to the Agency regardless of what ultimately is included in the FDA version of the guidance.

**When will the FDA publish its version of the guidance?**

It’s difficult to say because a number of outside factors could impact timing. The FDA has committed to producing a guidance, made it a priority and has already launched the administrative process to develop the FDA version of the guidance. Therefore, it’s possible that the agency may publish its version in the first half of 2018.

**Will the guidance development process produce additional work products beyond the guidance itself?**

Yes. As the community was developing the guidance, a parallel effort is underway to update the ALS clinical trial guidelines, which originally were published in 1999. The guidance process also may result in additional work products that potentially could include: a formal survey on benefit-risk in ALS and related publications on benefit-risk; enhancements to the National ALS Registry that could include collecting information about benefit-risk, patient reported outcomes, patient preferences and data to support natural history studies; legislative and regulatory initiatives to speed drug development and access to treatments; and publications and/or papers on a variety of other important topics that can further inform ALS research and drug development.
What is the difference between an FDA Guidance and Clinical Trials Guidelines?

FDA guidances are documents that explain the Agency’s interpretation of, or policy on, a regulatory issue, such as evaluating new ALS therapies for approval. Guidances serve as a roadmap to help industry navigate the regulatory process.

Clinical trial guidelines serve as “best practices” for clinical trial design and are used by researchers and industry to provide structure and direction for the design and conduct of clinical trials in ALS. The goal of clinical trial guidelines is to lead to more effective and efficient trials but they do not directly impact the FDA regulatory process.

In light of the fact that both the ALS guidance and updated ALS clinical trials guidelines are being prepared at the same time, the leadership of these two initiatives is shared to ensure consistency and efficiency across both efforts.

The FDA issued a draft Guidance on Drug Development for Rare Diseases. How will that impact this project?

The FDA’s draft guidance for industry around drug development for rare diseases is an important step for providing regulatory clarity and direction to those sponsors, both current and future, that are making investments to address the significant unmet medical need in many rare diseases. The ALS Association and Muscular Dystrophy Association both submitted comments to the FDA about that draft guidance. Links to: Comments from The ALS Association and Comments from the Muscular Dystrophy Association.

It is equally important for the FDA to continue to encourage the rare disease community to engage in a wide array of patient-focused drug development activities including, but not limited to, the preparation and adoption of disease-specific guidance as well. While the overarching draft guidance for rare diseases is an opportunity to address cross-cutting issues in drug development and regulatory interaction, it is a building block for complementary efforts to provide the focus and detail contained in a disease-specific guidance.

The FDA’s guidance on rare diseases informed the ALS project and the FDA has indicated that it is committed to producing a landmark ALS drug development guidance.

Will the Guidance limit industry’s flexibility when submitting a drug for approval?

No. FDA guidances are intended to inform industry of the Agency’s current thinking when evaluating new drugs and therapies and do not serve as requirements or directives that would limit industry’s flexibility when submitting a drug for approval.
Because the science of ALS is evolving rapidly as new discoveries are made, will the guidance be outdated almost as soon as it is published?

No. The guidance submitted to FDA will be a “living document” in that the ALS community can continue to update the FDA guidance to reflect changes, new discoveries and advances in the field.

Were other efforts intended to accelerate ALS drug developments incorporated into this project?

The ALS guidance team committed to engaging with every party it could identify to ensure that a wide array of ideas and recommendations were considered by the guidance development working groups.