ALS Draft Guidance on Drug Development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 draft 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The ALS community’s draft guidance, which will be submitted to the FDA, will serve as a roadmap to help industry navigate the development process and provide the Agency with an ALS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The ALS draft guidance will create a roadmap for industry by providing clarification on the Agency’s expectations on key aspects of future submissions and reviews of ALS candidate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 The draft guidance also will incorporate critical patient and caregiver insights and data such as benefit-risk preferences and patient reported outcomes in the FDA process.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 is the guidance being developed?

The guidance project is governed by a steering committee comprised of subject matter experts and representatives of key constituencies within the ALS community such as people with ALS, caregivers, ALS advocacy organizations, ALS researchers and clinicians, government agencies involved in ALS research and drug development and the biopharmaceutical industry.
Seven working groups (see chart below) have been established to oversee and develop specific chapters of the guidance, which are comprised of 7-12 subject matter experts per working group. Each working group has representation from a variety of perspectives (e.g., industry, academia, et.al.) and includes at least one person with ALS. Working groups convene approximately every two weeks via conference call and also develop content between conference calls. As content is developed, it is periodically reviewed by both the steering committee and Patient and Caregiver Advisory Committee for revision and further modification. Ultimately, the chapters of the guidance will be merged into a cohesive guidance document, which will then be shared with the greater ALS community for input during a 30-day public comment period. Once final changes are made, the draft guidance will be submitted to the FDA.

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

**FDA Guidance: Project Structure**
Who is involved with the project?

The draft guidance development project includes 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 helps to ensure that the entire ALS community has a voice in the development of the draft guidance. A full list of participants is available here: http://www.alsa.org/advocacy/steering-committee-and-working-group-members-full-list.pdf.

Can People with ALS and caregivers provide input?

Yes! The guidance project is a patient-driven initiative, and people with ALS and caregivers play a critical role. The Patient and Caregivers Advisory Committee (PCAC) includes nearly 40 people with ALS, caregivers, and ALS patient representatives. The PCAC’s charge is 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 draft guidance itself. There are 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 will have an opportunity to review the guidance and provide additional input during a 30-day public comment period that is expected to take place in the March-April 2016 timeframe. That feedback will be reviewed and incorporated as appropriate into the final product that will be submitted to the FDA in May of 2016.

The ALS community also will have another opportunity to provide input when the FDA publishes its version of the guidance. At that time, the Agency will open a public comment period to collect additional feedback from the ALS community. During this comment period, The ALS Association expects to host a public forum 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 is utilizing funding made possible by the Ice Bucket Challenge to support this initiative. The effort is particularly timely now as the FDA is increasing its emphasis on patient-focused drug development and allowing draft guidance 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.

**When will the guidance be complete?**

Developing a draft guidance is a labor-intensive effort that requires significant time and effort from academics, clinicians, industry, patients and caregivers to develop content and reach consensus. The project was initiated in February 2015 and will take approximately 15 months to complete, with FDA submission targeted for May of 2016. Once the draft guidance is submitted, the FDA will internally review and revise the draft guidance content to inform and produce an official FDA guidance on ALS Drug Development. The ALS community and FDA leaders have designed a parallel work effort to shorten the time it will take to complete this entire process, potentially shortening the time period by as much as one year.

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

Yes. We anticipate that the FDA will make changes to the draft guidance that is submitted by the ALS community. This is expected because, as encouraged by the FDA, the draft 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 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, including the Congressional budget process. However, the time frame likely will be 6-12 months sooner than originally anticipated. This is because in discussions with the guidance steering committee leadership, 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 during the third or fourth quarter of 2016.
Will the guidance development process produce additional work products beyond the guidance itself?

Yes. As the community is developing the draft 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 draft 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 recently issued a 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 will inform 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 draft guidance be outdated almost as soon as it is published?**

No. The draft 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.

**Will other efforts intended to accelerate ALS drug developments be incorporated into this project?**

The ALS guidance team is engaging with every party it can identify to ensure that a wide array of ideas and recommendations are considered by the guidance development working groups. This outreach and review will continue throughout the drafting process.