Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases"
July 29, 2021

Patrizia Cavazzoni, M.D., Director, Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

The Honorable Frank Pallone, Jr. (D-NJ)

1. *How does FDA decide which clinical endpoints show evidence of clinical benefit? What are the challenges FDA faces in identifying these clinical benefits*?

The selection of clinical endpoints is a critical aspect of trial design, and FDA's acceptance that an endpoint can support an important regulatory decision such as a new drug approval, approval of a new indication for an already-approved drug, or other claims in labeling, is based upon an extensive evaluation of the proposed endpoint. FDA works with drug developers to identify endpoints that can best demonstrate that a candidate drug improves how a patient suffering from a particular disease feels, functions, or survives. Endpoints showing that a drug improves survival are, of course, most straightforward; a drug which offers a survival advantage or reduces the occurrence of outcomes that would lead to reduced survival is generally considered acceptable. So, for example, a reduction in the occurrence of acute, severe events such as hospitalizations for serious disease-related complications, or events of organ failure, or, of course, improved survival, are usually accepted as evidence of clinical benefit (assuming such endpoints accurately capture such events).

Clinical endpoints that are intended to reflect how patients feel or function are more challenging. Such endpoints typically are developed using a detailed, stepwise process that can ensure that the endpoint actually measures an effect on a disease or condition that is meaningful to patients. This generally starts with obtaining perspectives from a wide range of patients with a disease to understand how the disease affects their lives and functioning and determining what most troubles them—what most limits their full participation in important aspects of their lives. Subsequent steps in the development process for a new clinical endpoint must show that the endpoint measures what is important to patients, is sufficiently sensitive to change, and is accurate and reliable across populations of patients with the disease, among other important characteristics.

`

FDA is currently working on a series of four guidances[1] that provide a detailed, thorough, step-by-step process for developing new endpoints or modifying existing endpoints.

Clinical endpoints that FDA recommends for use in clinical investigations of a new drug are a point of focus in many of the Agency's disease-specific guidances so that sponsors can understand our expectations. These guidances typically note that sponsors interested in developing new or modified endpoints should contact the clinical division and set up meetings to discuss the proposed new or modified endpoints.

It is worth noting that FDA has several pathways by which new clinical endpoints can be developed and accepted to support regulatory decisions. First, a sponsor can discuss a new endpoint in the context of an investigational new drug (IND) development program. Such discussions are often a focus of a "Type C" meeting, a Type B / End-of-Phase 2 meeting, or a meeting specifically focused on a new proposed surrogate endpoint. Second, FDA has an active biomarker qualification program that can lead to "qualification" of a new biomarker or clinical endpoint. Through this program, sponsors can gain broad acceptance ("qualification") of a particular biomarker or clinical endpoint when used in a specific disease setting for a specific purpose in a clinical trial. This pathway has a series of steps leading to the development of data that supports the role of the biomarker in predicting disease outcomes or the relevance of the clinical endpoint, and, if sufficiently clear and supportive, leads to qualification of the endpoint, such that any drug sponsor can use this endpoint in the specific disease and for the specific purpose for which the endpoint has been qualified.

With regard to challenges, FDA considers it essential that a proposed clinical endpoint accurately measure aspects of a disease that are important to patients. We find that many proposed endpoints are unable to reliably measure changes in how a patient feels or functions (e.g., the proposed endpoints are insensitive to change) or do not accurately reflect aspects of the disease important to patients, so FDA must work with the sponsor to further develop the proposed endpoint or recommend use of an endpoint that has been established to measure changes in how a patient feels or functions in a clinically meaningful way. Properly developing a clinical endpoint often requires the stepwise approach and data generation discussed above. A major challenge FDA faces is when a sponsor has already incorporated into their trials an endpoint that has not been properly developed and may not reflect what is important to patients FDA encourages sponsors to discuss endpoint development as early as possible in a clinical development program to mitigate this challenge.

FDA realizes that in rare diseases, endpoint development can be particularly challenging, given the limited number of patients with the disease. In this situation, FDA encourages consortia that may include patient and family groups, academics with a focus on the particular disease, and clinicians caring for these patients, to work together towards endpoint development. In addition, FDA recognizes the challenges of developing new endpoints, and attempts to use greater flexibility in applying requirements for, endpoint acceptance for rare diseases. Moreover, one of the programs industry and FDA have proposed to be included in the upcoming Prescription Drug

[1] https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

`

User Fee Act reauthorization (PDUFA VII) is an effort to enhance development of endpoints for rare diseases in which FDA will offer increased interactions with a sponsor focused on developing such an endpoint.

2. *FDA guidance for accelerated approvals allows for the review of surrogate endpoints if the endpoint is reasonably likely to predict a clinical benefit. Can you describe the progress being made to identify surrogate endpoints for diseases like ALS, which currently have no identifiable surrogate endpoints?*

Use of accelerated approval requires a showing of a drug's effect on either a surrogate endpoint that FDA has concluded is reasonably likely to predict clinical benefit, or an intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit that is sustained. FDA uses two "types" of surrogate endpoints: "reasonably likely" surrogates, which can support accelerated approval, and "validated" surrogate endpoints, which can support traditional approval.[2]

The identification of surrogate endpoints is particularly important for serious diseases that may be slowly progressive and may have a variable course across affected patients. In such settings, clinical trials may require a very large patient sample (often in the many thousands) and be very long in duration (often many years). The challenge is that a surrogate must be identified such that the change induced in that surrogate by the drug is reasonably likely to predict eventual clinical benefit. Finding such a surrogate is often possible in a disease where the pathogenesis of the disease is well described. A good example of such a surrogate (one that is considered "validated") is low density lipoprotein cholesterol (LDL-C). Based upon extensive epidemiological data showing the relationship of higher LDL-C and vascular events, and clinical trial data that showed that reduction in LDL-C, through different drug mechanisms, lowers the occurrence of vascular events, this has been accepted as a validated surrogate endpoint for vascular events. LDL-C has been shown to be a key mediator of vascular damage that leads to disease manifestations. There are numerous diseases where the "pathogenesis" (the sequence of events from inciting cause to disease outcome) allows the identification of a "biomarker" in the pathway of disease-induced injury, that can be shown to predict outcome, and the drug-induced modification of which can be shown to reduce the risk of disease outcomes.

For validated surrogates, extensive data is required (for example, extensive epidemiology data, animal model data, and interventional trial data, among other sources) that has established the surrogate as predictive of outcome. In the case of "reasonably likely" surrogates, the data set still must be robust, but typically includes "mechanistic" information showing the role of the endpoint in the pathogenesis of disease and epidemiological data showing the relationship of the level of the endpoint and disease outcome; data showing a correspondence between reduction in the surrogate with treatment(s) and clinical benefit endpoints, if such data is available, would

[2] A list of surrogate endpoints that have been used to support either accelerated or traditional approval can be found at the following URL: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

`

also be very useful and supportive. FDA accepts some uncertainty in accepting the endpoint as "reasonably likely" to predict benefit.

The challenge in many diseases, including many neurological diseases, is that there is very limited understanding of the pathogenesis that leads to disease complications and progression. Even though there may be many different biomarkers that are altered in the disease (such as imaging findings, or abnormalities of particular proteins in the cerebrospinal fluid, or altered circulating proteins), whether these measures actually are in the direct sequence of pathogenesis is often unknown. A drug, with a range of effects, may alter a particular biomarker, but whether that change actually means that the drug will improve the clinical course of the disease, and therefore lead to a positive change in the way a patient feels or functions, may be unclear. In such cases, where the understanding of the relationship between the biomarker and the progression of the disease is limited, or that the improvement in the biomarker corresponds to improvement in the disease, the conclusion that a change in the biomarker is "reasonably likely" to predict clinical benefit may not be supportable.

One important source of information used to identify surrogate endpoints for other diseases are animal models of disease. If the animal recapitulates the human disease, and the biomarker is measurable in that model, and the modulation of the biomarker predicts improvement in outcome in the model, this can provide useful support. A major limitation in many neurodegenerative diseases is that robust, translational, animal models are lacking. Many animal models of diseases do not fully recapitulate key aspects of the human disease and are not "translational"—meaning that apparent drug "benefit" observed in such models fails to predict drug benefit in clinical studies. Therefore, an important approach is to collect a range of biomarkers in clinical trials in the disease for which a surrogate endpoint is sought and try to relate the changes in these biomarkers to clinical outcomes. Unfortunately, this process takes time as evidence emerges that leads to an understanding of the role of a particular biomarker as a predictor of clinical outcomes so that it can serve as a "reasonably likely"—and eventually even a validated—surrogate endpoint.

FDA continually reviews emerging animal model, epidemiological, and clinical data to determine if there is a biomarker that appears to be sufficiently reliable to be considered "reasonably likely" to predict benefit. However, the main effort in finding such biomarkers is research that can enhance our understanding of the pathogenetic sequence, thereby identifying possible biomarkers which can be clinically studied. For diseases like ALS, the basic challenge is the lack of an understanding of the pathogenesis of the disease, from a primary event that precipitates the disease, to the sequence of "downstream" alterations that lead to neurological damage. Research in this disease may ultimately address this challenge. While at this point there are no known surrogates that are reasonably likely to predict clinical benefit for ALS, it is worth noting that there has been extensive experience with clinical endpoints in ALS. The ALS functional rating scale-revised (ALS-FRS) can detect change and therefore is a useful endpoint in trials of drugs for ALS, allowing the identification of drugs with even modest benefits with trials of 6-12 months in duration and with trial sizes of 100-200 patients. Because ALS is rapidly progressive, clinical deterioration or any drug effects in slowing such deterioration can be detected over a relatively short period of time in relatively small trials, making the use of biomarkers (even if those were identified) potentially less useful in shortening the duration of

`

clinical trials compared to a more slowly progressive condition such as Alzheimer's disease, for instance. Of course, a biomarker that could predict benefit could be hugely valuable in early development of drugs for ALS (for example, in helping to provide early "proof of concept" and in dose selection).

3. *How does FDA evaluate the patient tolerance for risk when making decisions about drug approvals for a debilitating and terminal condition like ALS? How can patients inform FDA on their tolerance for risk?*

The decision to approve a drug includes a demonstration that there is substantial evidence of effectiveness—as described in the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 505(d) and a demonstration that the benefit of the drug outweighs the risk. Both of these steps are informed by our understanding of what matters to patients, including their tolerance for risk. Although every drug approved must have substantial evidence of effectiveness, FDA understands that for a rare, serious disease, there is often greater flexibility in how this is assessed. This is discussed in the recent draft guidance FDA issued on meeting substantial evidence[3]. Weighing benefit relative to risk is critically informed by our understanding of the seriousness of the disease, the unmet medical need the drug may address, and, particularly, by the patient tolerance for risk, and how they value the potential benefit the drug offers. FDA meets with patient and other stakeholder groups regularly, for example in Patient-Focused Drug Development sessions (PFDD) and informal meetings requested by patient groups or by FDA, and very carefully listens to patients' experience of their disease and their willingness to accept risk.

In our discussions of whether to approve a drug, we focus on our benefit-risk framework that includes, among other components, the consideration of unmet needs, informed by what we have heard from patients. We recognize that often patients are willing to accept relatively more risks, or more uncertainty about benefit and risk, where the disease is serious, progressive, and fatal, to obtain the opportunity to experience benefit. FDA still must determine that the substantial evidence standard has been met, even with flexibility in how this determination is made, and would only approve a drug if the overall benefit-risk determination was positive. For example, if there is evidence that a drug may provide a relatively small benefit, but also carries substantial risks of harm that cannot be mitigated by labeling or a Risk Evaluation and Mitigation Strategy (REMS), we may conclude that the drug does not have a favorable benefit risk balance even in the treatment of a life-threatening disease. In contrast, if there is evidence that a drug provides a more substantial benefit relative to available therapy, it may still have a positive benefit-risk balance, and be approvable, even if it carries important risks that cannot be mitigated or prevented.

---

[3] See draft Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products. When final, this guidance will represent the Agency's current thinking on this topic.

`

FDA has issued a draft guidance titled "Benefit-Risk assessment for New Drug and Biological Products Guidance for Industry"[4] for public comment on our approach to assessment of benefit-risk calculations including: the therapeutic context, the evidence, the uncertainties, and FDA's regulatory options. Among other things, this document states that therapeutic context plays an important role in FDA's assessment of the acceptability of uncertainty:

> *"A higher degree of uncertainty is common in drug development programs for rare diseases, where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations. FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met. FDA therefore often exercises greater regulatory flexibility in these cases, in particular by accepting clinical trials that have lower sample sizes. This flexibility means that to be respectful of patients' willingness to participate in studies, it is important to maximize the potential for such clinical trials to provide interpretable scientific evidence about the drug's benefits and risks beginning from the earliest stages of drug development. Patient contribution is optimized in small sample size studies by minimizing bias and maximizing precision with trial design features such as randomization, blinding, enrichment procedures, and adequate trial duration.*

4. *We have heard concerns from some in the ALS patient community that regulators do not give due consideration to the heterogeneity of the disease, and they suggest that clinical trials on ALS treatments often show a clinical benefit to a for [sic] some ALS patients in the trial, but not others, which might cloud a clear clinical benefit from being shown for the population as a whole. How does FDA consider these results, and what do we need to better understand different types of ALS, and what challenges does the agency have in identifying clinical benefit among a subset in a trial and separating that from statistical noise?*

FDA recognizes that many serious diseases are heterogeneous in their clinical expression and course. The reasons for this heterogeneity are diverse and often not fully understood or predictable. Even for many diseases that are progressive, some patients may have a rapid course of functional loss, and others may progress slowly, or even may have "downturns" and periods of improvement or stability. This variability in the course of the disease may reflect differences in the underlying disease mechanisms (e.g., different genetic causes), differences among racial and ethnic subgroups due to genetic variability, different environmental factors, differences in support the patient receives, or other intercurrent factors that may not be readily recognized. This variability makes the use of randomized clinical trials particularly critical. In a disease with

[4] See draft Guidance for Industry, *Benefit-Risk Assessment for New Drug and Biological Products for Industry*, available at https://www.fda.gov/media/130964/download. When final, this guidance will represent the Agency's current thinking on this topic.

`

heterogeneity of clinical expression, interpreting uncontrolled trials that purport to show benefit is highly challenging and fraught with limitations.

There are numerous examples of drugs that seemed to show benefit in an open-label clinical trial, and then show no benefit in a randomized, double-blinded trial. This is particularly a concern when the drug effect size is modest. A drug that dramatically alters the course of a disease, for example, preventing any deterioration in a high proportion of patients over a period where deterioration would certainly have occurred, may be interpretable. Unfortunately, many useful drugs for neurodegenerative diseases do not have such dramatic effects and therefore require trial designs that are able to sort out variable natural history from a true drug response.
This disease variability must be considered when randomized clinical trials are designed, in particular in the endpoint used, and in the size of the study population, so that the study can detect improvement despite the variable disease natural history. FDA recognizes that there may only be a subset of patients that have a clinically meaningful response to the drug. One important step is to start with a population who are expected to be most likely to respond to a particular drug. For example, if a drug is designed to treat a particular genetic cause of a neurodegenerative disease, identifying patients with this genetic defect, and enrolling them in the trial may be critical to a proper evaluation of the drug. On the other hand, such predictors of response are often unknown when the trial is being designed. In this case, ensuring that the trial population is sufficiently large to detect a smaller but meaningful overall drug response is essential.

For a trial that shows overall benefit of a drug on the clinical endpoint assessed, examining the responses across the trial population may allow detection of subgroups who are particularly responsive to the drug. However, when a trial fails to show any overall benefit for the drug, the situation can be very challenging. Your question raises an important issue of how such situations are considered. It is important to note that in failed trials, when a range of subgroup analyses are conducted, it is not unusual to observe that, due to chance alone, some subgroups appear to have a response to the drug above the average response and others appear to have a response below the average response. FDA's experience is that subsequent trials to assess apparently favorable subgroup effects usually fail to demonstrate any benefit—this is the risk of placing substantial weight on subgroup analyses in failed trials. However, sometimes a subgroup response, even in a failed trial, may be relevant—perhaps identifying a subgroup particularly responsive to the drug. Sorting out the more common situation where apparently favorable subgroup responses are actually due to chance, from the situation where the subgroup response is meaningful, is a challenge. In general, we consider a favorable subgroup effect to be "hypothesis-generating," meaning that further study may be warranted, but the results are usually insufficiently reliable to support an approval.

Nonetheless, FDA reviews information from all trial analyses thoroughly and in detail, especially for serious diseases with unmet need. FDA recognizes the challenge of trials in many serious diseases and is open to a full evaluation of the trial responses. If there are subgroups that show a response that is consistent with the understanding of disease pathogenesis and drug mechanism, and the analysis in the subgroup was prespecified (i.e., part of the original planned analysis, rather than a post-hoc analysis that may be conducted to mine the data outside the prespecified plan), and there is other animal model and clinical data supporting the effect, then FDA may

`

consider this information as relevant to the regulatory decision. FDA is generally cautious in considering efficacy in specific patient subgroups where the overall trial has failed, but there are infrequent instances when FDA has performed extensive post-hoc analyses that have persuasively demonstrated effectiveness. However, it is important to again emphasize that post-hoc identification of non-prespecified subgroups with apparent benefit, with no scientific basis to suggest this subgroup would benefit, are likely not to reflect a real benefit, but, unfortunately, more likely to reflect a chance effect.

5. *Can you explain what an open-label extension study is, and when FDA allows it? What safety considerations does FDA make when considering whether to allow an open-label safety study? How does this differ from expanded access to treatments?*

Open label extensions are commonly used for patients completing the randomized double-blind period of a trial. Monitoring the safety of the investigational agent is critical throughout the development, starting from the conduct of preclinical studies and including careful monitoring for safety by the investigator who enrolled the patient, by the sponsor performing overall study medical monitoring, and, often, by an independent data monitoring committee, with appropriate reporting to FDA. Once sufficient data on effectiveness is obtained there is no reason to continue blinding and placebo arms but there is value in continuing to collect safety data. The intent of the open-label extension is generally to develop longer-term safety information as part of a clinical trial, to see if there are safety events that occur that may only be seen over longer exposures to the drug. Since these trial extensions are uncontrolled, their potential for the evaluation of effectiveness is more limited. Nonetheless, for diseases with well-established natural histories, the course of patient disease during treatment in an open-label extension may, in some instances, provide relevant information to evaluate drug effectiveness.

Expanded access is specifically intended to allow access to an investigational drug to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. The availability of expanded access may provide a pathway for patients unable to participate in a clinical trial (e.g., at a different disease stage, or geographically not near an investigational site) to access an investigational drug. In contrast to the primary purpose of an open-label extension, which is to further research on the investigational drug's safety within the context of a clinical trial (with standardized procedures to assess safety and efficacy, and a specific study visit schedule), the primary purpose of expanded access is to treat a patient's disease or condition. Notably, in expanded access, the evaluation of safety and of efficacy are not based upon standard procedures for monitoring patients at protocol-specified timepoints, as occurs in a clinical study. As a result, we would not expect safety and efficacy information from expanded access to be as comprehensive or robust as from a clinical trial. Despite the difference in the purpose of an open-label extension and expanded access, it can be noted that in certain cases, where the clinical course of the disease is predictable and well understood and a therapy leads to significant clinical improvement that would be highly unlikely to occur in the absence of an intervention, relevant

`

information on both safety and effectiveness has emerged from expanded access treatment.[5] For rare diseases with such characteristics, expanded access treatment results may add to the information filed in a new drug application or a biological license application.

The Honorable Anna G. Eshoo (D-CA)

1. *In your written statement, you say that "a treatment that provides meaningful incremental benefit would still be desirable" when speaking about the regulatory flexibility needed for ALS treatments. Many ALS advocates think that the statistically significant outcome in the Amylyx trial that showed a near 3-point improvement was incremental, but meaningful. In your best professional judgment, how would you define a desirable "meaningful incremental benefit" in an ALS trial? What incremental steps can FDA take?*

Without commenting on specific applications that may have been submitted to FDA, consistent with federal statutes and FDA's implementing regulations concerning the confidentiality of commercial information and to protect the integrity of the review process, FDA generally cannot disclose information about pending applications and the status of the Agency's review of a particular drug product.[6] Therefore, the Agency is unable to provide you with updates about specific pending applications, including clinical trial information.

Generally speaking, our approval of drugs is based upon endpoints that show that the drug provides meaningful improvements in how patients feel, function, or survive. Where a drug provides a statistically significant improvement in survival (or on the occurrence of serious outcome events of the disease), FDA generally considers those endpoints sufficient to support a finding of effectiveness if the trial results are robust and persuasive. FDA's determination that the results are robust and persuasive is based upon our detailed evaluation of the submitted data, and our assessment of trial conduct and data quality. Even trials that may seem to show an outcome benefit on survival or on apparent improvements in serious disease outcomes may have limitations based upon how measures were collected, trial quality issues, or issues in how the analyses of trial data was performed that may lead to the results not being considered as persuasive.

With respect to endpoints that reflect how patients feel and function, we have commented on the importance of well-designed endpoints to accurately measure aspects of disease that are meaningful to patients. However, another important consideration is the size of the effect observed. In general, we want to see an effect that is both statistically significant (so we can

[5] See for example the Report from the Reagan Udall Foundation for FDA on Leveraging Real-World Treatment Experience from Expanded Access Protocols https://navigator.reaganudall.org/resources/report-leveraging-real-world-treatment-experience-expanded-access-protocols

[6] Relevant law includes the Trade Secrets Act (18 U.S.C. 1905), the Federal Food, Drug, and Cosmetic Act (2 1 U.S.C. 33l(j)), and FDA regulations (21 CFR 20.6 1(c); 21 CFR 312.130(b); 21 CFR 314.430(c) and (d)(l)).

`

consider the results reliable and reproducible) and of an extent that is clinically meaningful to patients. Determining whether the extent of improvement is clinically meaningful to patients is based upon information from both within the trial and from discussions with patients about the aspect[s] of the disease that appears to be improved with use of the drug. We examine these issues very carefully, using well-established approaches that have been developed by academic and industry experts on endpoint design working closely with FDA and other health agencies. To approve a drug that has risks (as all drugs do) that provides only a minimal improvement in an aspect of a disease, that patients do not even perceive, would not be appropriate. Thus, incorporating information from patients is essential to ensure that the observed drug response actually provides them a meaningful improvement in their experience of the disease.

It is worth also noting that we assess not just the overall drug effect across all patients who received the investigational drug, but also evaluate whether there is a subset of patients who are particularly benefitted. For example, we have 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. So, FDA considers not just the overall effect that patients in the trial experienced, but whether there are patients who experienced a larger effect.

With respect to an ALS trial, the approach would be similar, as noted above. Indeed, in the first drug that was approved for ALS, riluzole, two clinical trials were submitted in support of establishing substantial evidence of effectiveness. As noted in the review, in one study, the overall favorable treatment effect was largely seen in the patients who had bulbar onset of their disease, but the drug was indicated broadly for ALS.

However, it is important to note that the extent of the effect of the drug is viewed in the context of the seriousness of the disease, the nature of the benefit observed, and the unmet need. For example, an average minimal effect, not even discernible by patients—or without any subset seeing a larger important effect—may not support approval even for a drug to treat a serious disease. Yet, in this setting, even a modest effect or a smaller average effect with a larger effect size in a subset of patients may support approval. As emphasized previously, input from patients from within the trial (for example, asking their assessment of their overall symptom improvements during the treatment period), and hearing from patients about the importance of the aspect of the disease being treated, and how much improvement would be meaningful to them, weighs heavily in our approval decisions.

2. *As an example, advocates think that the Amylyx drug, which is a combination of drugs that are already on the market with a high safety profile, has an acceptable risk for its marginal benefit. In your best professional judgement, how do you define the acceptable risk of a drug that is being taken by people who are usually told they only have 2 to 5 years to live?*

Without commenting on specific applications that may have been submitted to FDA, consistent with federal statutes and FDA's implementing regulations concerning the confidentiality of commercial information, and to protect the integrity of the review process, FDA generally cannot disclose information about pending applications and the status of the Agency's review of a

`

particular drug product.[7] Therefore, the Agency is unable to provide you with updates about specific pending applications, including clinical trial information.

In general, the decision to approve a drug includes, first, the demonstration that there is substantial evidence of effectiveness, as described in the FD&C Act, section 505(d), and, second that the benefit of the drug outweighs the risk. Both of these steps are informed by input from patients. Weighing benefit and risk is critically informed by our understanding of the seriousness of the disease, the unmet medical need the drug may address, and, particularly, by the patients' tolerance for risk. FDA meets with patient and other stakeholder groups regularly, for example in Patient-Focused Drug Development sessions (PFDD) and in other settings such as informal listening sessions requested by patient groups or by FDA, and very carefully considers the patient's experience of their disease and their willingness to accept risk, as well as how they value the benefit that the drug may offer.

In our discussions of whether to approve a drug, we focus on our benefit-risk framework that includes, among other components, the consideration of unmet needs, informed by what we have heard from patients. As our recently published draft guidance on benefit risk assessment in regulatory decision-making states:

> *"Patients are experts in the experience of their disease or condition, and they are the ultimate stakeholders in the outcomes of medical treatment. Patient experience data can inform nearly every aspect of FDA's benefit-risk assessment throughout the drug lifecycle..."*
>
> and:
>
> *"FDA must balance the perspectives of patients with the judgments it must make regarding overall benefit-risk of a drug to the patient population. For example, even if some patients may derive benefit from a drug and express the desire for access to a drug, FDA would not approve the drug if it FDA concludes that the drug would lead to more harm in the indicated population overall–for example, if the drug is associated with significant risk, benefit is likely to be limited, and there is no way to identify those individuals who might benefit through the use of predictive biomarkers or other means. Nonetheless, FDA carefully weighs and considers the patient perspective. When patients indicate that a benefit is important to them in the treatment of their condition, this informs FDA's assessment of the extent of benefit."*

We recognize that often patients are willing to accept substantial risks where the disease is serious, progressive, and fatal, to obtain the opportunity to experience benefit. However, FDA still must determine that the substantial evidence standard has been met—even with flexibility in how this determination is made—and would only approve a drug if the overall benefit-risk

[7] Relevant law includes the Trade Secrets Act (18 U.S.C. 1905), the Federal Food, Drug, and Cosmetic Act (2 1 U.S.C. 33l(j)), and FDA regulations (21 CFR 20.6 1(c); 21 CFR 312.130(b); 21 CFR 314.430(c) and (d)(l)).

`

determination was positive. However, as noted above, the first threshold for approval, before we consider the risks and benefits, is whether there is demonstration of effectiveness on a meaningful clinical outcome. Approval of a non-effective drug, even if has minimal safety risks, does not serve patients. Your question raises the issue of whether an effective drug with a more modest benefit would be approvable for a serious, progressively fatal disease with unmet needs. If a drug provides a small but clinically meaningful benefit on how a patient feels, functions, or survives, then such a drug may have a favorable benefit-risk balance and be approvable, even if the drug has important risks; the benefit risk balance may be considered favorable if other therapy is not available and risks are clearly outlined in labeling so that patients, their families, and their health care providers could make individual decisions about using the drug.

In addition, while this does not factor into our approval decision, if drugs are approved which provide no meaningful clinical benefit, even if the safety profile is favorable, this can slow development of more effective alternatives because patients who go on a new drug may not be willing to enter research or there may be interactions with a new investigational agent that prevents their enrollment. When there is marginal impact on disease course, patients may not be able to perceive whether they are failing a therapy and not take advantage of clinical trials where far more effective medications may be developed.

3. *Because of the "critical unmet need" the 2019 FDA Guidance Document indicates the FDA will utilize a different "risk-benefit" test for ALS therapies. Can you please identify examples in the last two years where the FDA has modified its risk-benefit assessment in an ALS therapy?*

As noted in response to Question 2, FDA does consider benefit risk decisions in the context of the seriousness of the disease, unmet need, and patient acceptance of risk and how they value the potential benefits. This is not a "different" risk-benefit assessment than we would apply to other serious diseases with unmet needs, however, and for all approved drugs, the same statutory requirements for demonstrating safety and effectiveness apply. As the recent (2019) FDA ALS guidance states:

> *"When making regulatory decisions about drugs to treat ALS, 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."*

These considerations are similarly discussed in our recently released guidance on benefit risk where we state

> *"For a drug intended to treat a serious disease with unmet needs, FDA may accept greater uncertainties about benefit or risk at the time of approval…. FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met. FDA therefore often exercises greater regulatory flexibility in these cases…"*

`

FDA does not "modify" its benefit risk assessment specifically for ALS, but, as for serious diseases like ALS that have substantial unmet needs, the patient perspectives and needs, and the seriousness of the disease are very much considered in our regulatory actions.

4. *Knowing the FDA Guidance is used by drug sponsors to inform clinical trial design, please give specific instances since the 2019 issuance in which the FDA has worked alone or with sponsors to expedite clinical trial duration or review timelines for ALS therapies. Please explain how the FDA has changed its processes for evaluating clinical trials pre- and post-2019 Guidance issuance, noting specific process changes and when they were instituted.*

Without commenting on specific applications that may have been submitted to FDA, consistent with federal statutes and FDA's implementing regulations concerning the confidentiality of commercial information, and to protect the integrity of the review process, FDA generally cannot disclose information about pending applications and the status of the Agency's review of a particular drug product.[8] Therefore, the Agency is unable to provide you with updates about specific pending applications, including clinical trial information. However, we note that for serious diseases with unmet needs, including ALS, we are open to meeting with sponsors whenever they need our input and guidance on trial design elements. Our Office of Neuroscience has made clear to sponsors of drugs for serious diseases with unmet needs that we will seek to meet with them to discuss endpoints and other trial design elements as and when needed. We recognize that there may be sponsors working in the area of neurodegenerative diseases who are not very experienced in drug development, and therefore may need more interactions with the Agency to make progress on their programs. In such instances, we are particularly sensitive to the need for more meetings with the Agency to encourage and foster their development efforts.

5. *Europe has a conditional approval pathway for drugs that address life-threatening diseases and have promising but incomplete efficacy data. In these cases, the drug is approved on the condition that they will be evaluated further while on the market. A similar pathway is not currently available for ALS drugs in the U.S. This means the Amylyx drug may be available to European patients 2 to 3 years before American patients. If FDA had a similar authority for a conditional approval pathway, would that give FDA more flexibility in getting potentially promising therapies to dying patients sooner? Do you have concerns with how the conditional approval pathway has been used in Europe that the Committee should be aware of?*

Both the conditional approval pathway in the EU and the accelerated approval pathway in the US share common elements: both allow approval of a drug when there remains uncertainty about clinical benefit, with additional data being accrued while the drug is on the market. For accelerated approval, the substantial evidence of effectiveness standard, which is required for

[8] Relevant law includes the Trade Secrets Act (18 U.S.C. 1905), the Federal Food, Drug, and Cosmetic Act (2 1 U.S.C. 33l(j)), and FDA regulations (21 CFR 20.6 1(c); 21 CFR 312.130(b); 21 CFR 314.430(c) and (d)(l)).

`

drug approval, is still applied. In this context, it requires either evidence of a drug's effect on an intermediate clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit. This allows us to be confident that the drug is effective on modifying these surrogate endpoints while the Agency awaits confirmation that the drug has the expected effect on the ultimate clinical endpoints of interest. For this pathway, the uncertainty relates to whether the surrogate endpoint, or intermediate clinical endpoint, predicts clinical benefit of the drug. In contrast, conditional marketing, as described by the EMA, is when a medication is made available on less comprehensive and less robust clinical data than normally required for traditional approval. Here the uncertainty is whether the preliminary clinical data will be confirmed by subsequent larger clinical study results. It is important to note that in our approval decisions, FDA does not apply a "one size fits all" approach to meeting substantial evidence. In our recently released draft guidance on drug effectiveness[9], focused on what can constitute substantial evidence, we discuss in detail the flexibility the agency has shown regarding the design of studies, analytic approaches, and in the level of uncertainty we may accept to support a conclusion of substantial evidence when considering the approval of drugs for rare serious diseases with unmet needs. Although accelerated approval is an important tool that can be deployed for many programs—specifically where a reasonably likely surrogate or an intermediate clinical endpoint is available—this is not the only tool that FDA applies in an effort to bring effective new drugs to patients with rare, serious diseases. Our assessment is that the range of tools and approaches FDA has at its disposal provides the needed flexibility to bring drugs to patients expeditiously—when there is sufficient evidence to support the safety and effectiveness of the drug.

The Honorable Nanette Diaz Barragán (D-CA)

1. *As Congress authorizes new additional research funding into neurodegenerative diseases, it's critical that the FDA have the staff capacity and capability to move promising treatments through the approval process.*

   What investments should Congress be making to modernize FDA so that you're able to do the work we're asking you to?

We greatly appreciate the support that Congress has provided over the years that enables FDA staff to spend more time advising sponsors on drug development. This facilitates new approvals and in 2020, we approved new drugs for spinal muscular atrophy, multiple sclerosis and Parkinson's disease. We do note that for rare and neurodegenerative diseases, and in particular rare neurodegenerative diseases, there are still scientific challenges in developing reliable endpoints, identifying biomarkers that could speed drug development and designing clinical trials that meet both patients' and FDA's needs. As a result, there is greater demand for FDA staff advice than can be met. We will continue to focus resources on meeting the needs of patients and will continue to work with our leadership at HHS to identify areas where targeted

9 See Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products)

`

investment may accelerate our work on bringing promising treatments through the approval process.

2. *My mother is one of millions of Americans suffering from Alzheimer's disease, so this is not theoretical for me, it's very real, day to day living. On behalf of those patients, and the families that are supporting them, I'm wondering what we in the federal government can do to help find a cure.*

    a. *Do you think that if the federal government treated these neurological diseases as public health crises, and gave them a name like Operation Stop Alzheimer's, and attached a timeline and funding goal to them like we did with Covid, that that would help yield concrete results?*

For Alzheimer's disease, we hope that the recent progress in identifying reduction in amyloid levels as a surrogate marker that is reasonably likely to predict clinical benefit and our understanding of the reasons for failures in previous drug development programs may signal an inflection point in drug development for Alzheimer's. We are encouraged by the number of late-stage trials for Alzheimer's disease. Certainly, this development does not mean that there is still not further need to understand the mechanisms of the disease—what precipitates the disease, and what subsequent sequence of pathological alterations (the "pathogenesis") leads to neuronal loss resulting in functional deficits and may ultimately lead to the patient's death. Such understanding is likely to lead to the identification of additional molecular targets that may alter the disease course and lead to the development of effective therapeutics.

The recent history of cancer therapies provides a relevant example. Advances in cancer treatment were painfully slow until the 1990s when the genetic basis of cancer was increasingly understood. Molecular "drivers" of cancer began to be identified, and there was an increasing understanding—and ability to modulate—cancer immunobiology. These advances led to the identification of numerous important molecular targets, which, in turn, has led to an explosion in the number of therapies for cancer, many first approved under accelerated approval. Many of these new specifically targeted therapies are providing dramatic improvements in cancer outcomes and even cures of previously incurable tumors. Identification of such molecular targets is a necessary first critical step in making meaningful progress in the treatment for any disease.

As recently occurred with Aduhelm in Alzheimer's disease, when we identify a biomarker, establish that the biomarker is a surrogate that is reasonably likely to lead to clinical benefit and identify a drug that has a significant and consistent effect on that surrogate, accelerated approval becomes a viable option that FDA could use to bring therapies for neurological diseases to patients sooner.

    b. *What else can we do to increase the urgency needed to find a cure?*

See answer to c.

`

c. *Do we need to focus on building our understanding of underlying disease biology, or do we need to strengthen the regulatory and reimbursement systems to incentivize investment, including ensuring appropriate reimbursement for innovative diagnostics that are critical to identify the right patients for clinical studies, or is it some combination of all these things?*

As mentioned in the previous question, understanding the underlying disease biology to identify druggable targets and potential surrogate endpoints are the key to accelerating drug discovery. In addition, the approval of the first drug for Alzheimer's disease in decades may be stimulating investment.[10]

Reimbursement policy is not germane to FDA's authorities, so we are not able to comment on reimbursement policies.

3. *We know that there are equity issues and health disparities that must be addressed when it comes to neurodegenerative diseases. For example, Black and Latinx individuals are disproportionately affected by Alzheimer's Disease and other dementias and are also more likely to face obstacles to timely diagnosis, enrollment in clinical trials, and access to adequate care following a diagnosis.*

    a. *What steps can be taken to ensure diverse populations have broader access to, and better representation in, clinical trials?*

Clinical trials provide a crucial base of evidence for evaluating whether a medical product is safe and effective, thus enrollment in clinical trials should reflect the diversity of the population that will ultimately use the medical product. FDA has continued its ongoing efforts to help increase the participation of racial and ethnic minorities and other underrepresented populations in FDA-regulated clinical trials through hosting public meetings, issuing guidance documents, developing tools; and encouraging the use of innovative trial designs.

In November 2020, FDA issued a final guidance for industry titled, *Enhancing the Diversity of Clinical Trial Populations; Eligibility Criteria, Enrollment Practices, and Trial Designs*. This guidance recommends approaches that sponsors of clinical trials to support a new drug application or a biologics license application can take to broaden eligibility criteria, when scientifically and clinically appropriate, and to increase enrollment of underrepresented populations in their clinical trials. Specifically, the guidance recommends using inclusive trial practices and considering trial design approaches that make trial participation less burdensome and to address barriers, such as the location of clinical research facilities, travel, work, and family care responsibilities. The guidance recommends the use of decentralized clinical trials – a trial design that brings the trial to the patient – with the potential to increase diversity in clinical research by utilizing telemedicine and mobile/digital technologies to increase access to

[10] Biogen's Aduhelm Win has Potential to Reinvigorate Alzheimer's Investment https://www.biospace.com/article/biogen-s-anuhelm-win-has-potential-to-reinvigorate-alzheimer-s-investment/

`

populations or communities—rural or remote—that may not have access to major medical and research centers.

FDA has also published other guidances supporting clinical trial diversity, including, *Collection of Race and Ethnicities in Clinical Trials* (2016), *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (2018), *ICH E7 Studies in Support of Special Populations; Geriatrics (1994): Inclusion of Older Adults in Cancer Clinical Trials (Draft 2020).*

Additionally, in support of these efforts, the FDA Office of Minority Health and Health Equity (OMHHE) developed the Diversity in Clinical Trials Initiative, which includes an ongoing multi-media, public education and outreach campaign to help address some of the barriers preventing diverse groups from participating in clinical trials through a variety of culturally and linguistically tailored strategies, tools, and resources (https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity). The campaign aims to combat myths, educate consumers about key issues, provide positive messaging reflecting diverse spokespersons who are representative of diverse communities, stimulate dialogue among peers and peer-to-provider groups, and tailor resources to be culturally and linguistically appropriate and translated into multiple languages.

FDA's Center for Drug Evaluation and Research has also developed Drug Trials Snapshots (DTS) as part of an overall FDA effort to make certain demographic data more available and transparent, available at: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots. The information provided highlights whether there were any differences in the clinical benefits and side effects among sex, race, and age groups. DTS published a 5-year summary report of demographic data from pivotal trials for 231 novel drugs approved between 2015 and 2019 representing 292,766 clinical trial participants. While the majority of the clinical trial participants were from outside the United States, the United States represented the highest proportion of participants from a single country. Additionally, for U.S. Data: 78% of participants were White, 16% of participants were Black or African American, 2% Asian, 1% American Indian or Alaska Native, and 15% Hispanic or Latino; among DTS Global Data (i.e., including international participants): 76% of participants were White, 11% Asian, 7% Black or African American, 1% were American Indian or Alaska Native, and 13% Hispanic/Latino.

FDA is committed to ongoing and future efforts to advance diverse participation and enrollment in clinical trials.

b. When it comes to coverage and payment policies for existing diagnostics, how can those be improved to ensure broader access to care?

FDA does not have jurisdiction or expertise in coverage and payment policies so cannot comment on how they can be improved.

c. Is the recently introduced FIND Act a step in the right direction?

As stated above, payment is not under our jurisdiction.

`

4. *Do you believe the ALSFRS-R tool is statistically valid and reliable?*

As we have outlined in detail in our ALS guidance (2019), ALSFRS-R has proven to be a valuable endpoint, reflecting important clinical aspects of how the disease affects patients. Its characteristics allow detection of potentially meaningful clinical benefits in 6-12 months and with trial sizes that are practical and feasible to enroll.

5. *Can you describe what the ceiling effect and floor effect are in the ALSFRS-R scores?*

Ceiling and floor effects reflect the range response options of an instrument, specifically the item responses at upper and lower range of the response options of an instrument. A ceiling effect is observed when a large concentration of participants' scores is at or near the upper limit of the scale score of the instrument. Conversely, a floor effect is observed when a large concentration of participants' scores is at or near the lower limit of the scale score of the instrument. Either situation may occur when an instrument does not contain items capable of sensitively detecting changes at the extremes of what is being measured in a population. With the ALSFRS-R, ceiling and floor effects may be observed in very early-stage patients who have not yet developed substantial functional impairment or in late-stage patients who have lost ambulation or require ventilatory support. Ceiling and floor effects are common in all instruments/clinical outcome assessments. If floor or ceiling changes in a proposed instrument limit the ability to detect changes in a proposed ALS study population, sponsors may request a meeting with FDA to discuss alternative approaches to assessing clinically meaningful change in that population.

6. *For each domain, can you identify all flaws in the ALSFRS-R scale?*

FDA acknowledges that there are limitations to the use of the ALSFRS-R, as there are with all instruments used to measure clinical outcomes in trials. As previously discussed, ceiling and floor effects may be observed with the ALSFRS-R in very early-stage patients who have not yet developed substantial functional impairment or in late-stage patients who have lost ambulation or require ventilatory support. Nonetheless, the ALSFRS-R is an endpoint that has demonstrated the ability to capture clinically meaningful changes in function in ALS patients. If sponsors believe their drug may provide clinically relevant benefits that are not adequately reflected in the ALSFRS-R, sponsors may request a meeting with FDA to discuss alternative approaches to assessing clinically meaningful benefits.

7. *Can you identify any drugs that would have met the FDA's "substantial evidence" test for drug approval if they had only been tested against a trial endpoint of one domain on the ALSFRS-R scale instead of against all four domains?*

FDA cannot comment on unapproved applications; however, the Agency is open to considering treatment effects on an individual domain of the ALSFRS-R to support a marketing application if those effects represent a clinically meaningful benefit for ALS patients.

`

The value of using the ALSFRS-R is that it measures changes across the domains of function that are most commonly affected in patients with ALS. Drugs that target, and attenuate, the basic pathology of ALS would likely provide improvements in all functional domains. On the other hand, a drug that provided clinically meaningful benefit in only one domain could still be approvable. One issue, which is discussed in the response to Question 13from Hon. Nanette Diaz Barragán, is what we refer to as "post-hoc" data dredging. In a trial that shows no benefit (the primary endpoint is not "positive"), it is not uncommon to see "subsets" of the endpoint that appear to show an effect. This poses the challenge of "multiple testing"—where the risk of a false finding of benefit increases. However, if a drug is expected to particularly benefit one domain, and the study is designed so that the primary study endpoint is focused on that domain, then a clinically meaningful benefit in that domain could support an approval decision.

8. *Can you explain how the ROADS test developed at Emory University differs from the ALSFRS-R tool? How long will it take before that tool could be validated and implemented as a measure for the primary endpoint in ALS trials?*

The ROADS test and ALFRS-R are both instruments that assess changes in function that may occur in patients with ALS. Although the Office of Neuroscience does not have experience with the use of the ROADS test in clinical trials with ALS, it is open to the inclusion of novel clinical outcome assessments in clinical trials, including ALS clinical trials. Sponsors who wish to include novel clinical outcome assessments in their trials should come to the Agency early to discuss inclusion of these assessments, and how to optimize these assessments to inform clinical trial endpoints.

9. *What do you believe the top five most promising biomarkers are for ALS?*

There are many biomarkers under investigation for ALS and the utility of a given biomarker will depend on the patient population being studied (e.g., sporadic ALS or ALS associated with a specific genetic mutation) and the mechanism of action of the therapy being studied. As discussed in the 2019 ALS Guidance, FDA encourages sponsors to incorporate exploratory biomarkers, including fluid biomarkers and digital biomarkers, in all phases of development of ALS drugs. Biomarkers are frequently used in clinical trials for ALS for selection criteria, to assess target engagement, and to assess for proof-of-concept. In the future, greater scientific understanding of ALS may provide opportunities for discussion of surrogate endpoints that are reasonably likely to predict clinical benefit and that might serve as a basis for accelerated approval.

10. *ALS Centers of Excellence such as MGH, UMass, Columbia, MAYO, likely have a much higher percentage of their patient population enrolled in clinical trials than smaller clinics in less populated states. Do Mass General or Columbia collect data on what the distribution of patients is across the states, and can the FDA provide that data so that we may assess the availability of access to clinical trials to people in underserved communities?*

`

We cannot speak to the data collected by Mass General or Columbia. We would note that on www.Clinicaltrials.gov, one can search pharmaceutical interventional clinical trials for ALS and find the clinical trial sites for those trials.

11. *The CDC Registry for ALS is predominantly white males in major metropolitan areas. Would making ALS a mandatorily reported disease help to more accurately reflect the diversity of this disease and help us identify personalized medicine options for people of different ethnicities?*

Registries can be very useful for providing information on the natural history of a disease that can inform clinical development and facilitate recruitment into clinical trials. The key to a successful registry is patient engagement over time and a willingness to share data. Making ALS a reportable disease would provide timely incidence data but would not necessarily add to the important information that comes from patients volunteering to join a registry and share their data over time.

As for diversity, we certainly support enrollment of a racially and ethnically diverse population. We would also note that a 2015 study[11] looked at racial and ethnic differences among US ALS patients from three states and 8 metropolitan areas. The project areas were selected to over-represent minority populations compared with the racial and ethnic distribution of the US population. Of the 5,883 patients, 74.8% were identified as white, 9.3% as African American/Black, 3.6% Asian and 12% unknown race. With respect to ethnicity, 77.5% were identified as non-Hispanic, 10.8% Hispanic and 11.7% were unknown ethnicity.

12. *Can you opine if there are features of another country's regulatory structures that would help expedite drug approval for ALS without jeopardizing safety?*

We do not know of any regulatory frameworks that provides clear advantages over existing FDA regulatory tools. FDA has a suite of regulatory tools (e.g., expedited development programs and accelerated approval) that help speed promising drugs through to approval and has additional flexibility in determining the type of evidence needed to establish effectiveness when considering drugs for rare and life-threatening diseases. The limiting factor is often the scientific knowledge regarding molecular targets that alter the course of the disease.

13. *Can you explain what "data dredging" is?*

Data dredging generally refers to the practice of analyzing data many times to find a favorable result without proper statistical controls. The FD&C Act's requirement that a drug demonstrate substantial evidence of effectiveness prior to approval acts to avoid circumstances where inadequate or flawed, uncontrolled data could be used to support regulatory decisions. There are numerous examples of uncontrolled studies, studies without pre-specification of the primary endpoint, or studies that have undergone extensive "post-hoc" analyses, that purport to show that a drug provides benefit. Such results typically are not reproducible when the drug is subjected to

[11]Lindsay Rechtman, Heather Jordan, Laurie Wagner, et. al., , Racial and ethnic differences among amyotrophic lateral sclerosis cases in the United States, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2015; 16: 65–71

`

properly conducted randomized, double-blinded trials. FDA is acutely aware of the need to find useful, beneficial therapies for patients with serious diseases with unmet needs, but the Agency is also aware of the danger of approving ineffective drugs that give patients false hope and may mislead them into using the ineffective drug or foregoing the opportunity to use an effective drug. FDA's regulations describe the key features of studies that can be considered "adequate and well-controlled" – features that help distinguish studies that support robust, reliable conclusions from trials that do not.

The example in this article on a subgroup analysis may be informative
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068511/

14. *In your statement and in an article in STATNews, you opined that the "science isn't there yet" with regard to ALS therapies. Is that an opinion based on your own personal experiences & investigations or is that the agency's position with regard to ALS?*

    If it's not your own personal opinion formed based upon your own experiences and investigations, can you please identify all people within the agency with whom you discussed this opinion.

This is the viewpoint of neuroscience experts at FDA and at NIH who have detailed and extensive expertise in ALS and other neurodegenerative diseases. Rapid progress in development of effective drugs must start with molecular targets that are established to drive the pathogenesis of the disease. In addition, a more complete understanding of the pathogenetic changes that lead to functional decline could lead to identification of surrogate endpoints that could be used to provide earlier readouts of effectiveness. This understanding underlies the remarkable advances in cancer therapeutics, and also in our ability to find therapies for COVID-19 in record time. Unfortunately, for many neurodegenerative diseases, expert opinion has concluded that we do not yet have any detailed understanding of either disease-precipitating factors or the sequence of pathological alterations that leads to neurological damage and functional loss, and ultimately to patient demise. Although there have been advances, especially in recognizing precipitating factors, such as genetic disease-causing mutations in small subsets of patients with ALS, for the vast majority of ALS patients, no such disease understanding yet exists.

15. *Since 2000, please identify the number of drugs, by disease category, that have been approved for Phase 4 post-marketing studies in neurodegenerative diseases versus oncology.*

We are assuming that for this question when you say approved for Phase 4 post-marketing studies you are referring to drugs approved under the accelerated approval pathway. From 2000 until December 31, 2020, there were 147 accelerated approvals (AA) for oncology products. From January 2000 until the approval of aducanumab for Alzheimer's disease, there was one other accelerated approval for a neurodegenerative disease.

    a. *How often have those drugs been removed from the market?*

`

A recent analysis of oncology AAs, which constitute the overwhelming majority of AAs in the last decade, found that of 166 AAs granted from 1992 to 2021, only 13 (8%) had been withdrawn. FDA considers that the "reasonably likely" standard should mean that in a high proportion of instances, but not in all, the drug approved through accelerated approval will subsequently be verified to offer clinical benefit. The experience to date is consistent with FDA's approach and risk tolerance for uncertainty.

b. How often is the label changed as a result of information discovered during Phase 4 studies?

FDA does require post-marketing studies for drugs approved under accelerated approval as well as for drugs approved under traditional approval if there is a particular safety issue that needs to be further explored. Labeling is updated as appropriate based on those studies. However, we do not have the specific number of label changes made in response to these studies and it would take considerable staff time to try to quantify this with precision. FDA did publish a study looking at the relationship between the size of the pre-market safety database and post marketing safety labeling changes[12]. The study looked at 278 small molecule new molecular entities and 61 new therapeutic biologics. Ten percent of the sample was approved under AA. Products approved under AA using a surrogate endpoint had a higher median number of safety labeling updates compared to drugs approved under traditional approval, i.e., a clinical endpoint, and that this did not seem to vary with the size of the safety population pre-approval. However, the significance of this finding must be taken in the context that drugs for AA are for serious or life-threatening diseases where there may be more tolerance for a drug that may have more potential safety issues. In addition, the analysis did not look at whether these safety updates were a result of more structured collection of safety information during the post-marketing studies where adverse events are actively solicited as opposed to being reported spontaneously reported after the drug is marketed, which is not likely to be as complete.

We would also note that the degree of safety data available at the time of accelerated approval is variable because not all drugs that received indications under the AA pathway are new molecular or biologic entities. In a review of AAs for oncology, the FDA noted that many of the AA indications are efficacy supplements of already-approved drugs with large safety information and postmarketing safety data.[13]

c. What is the average time that passes for those Phase 4 studies?

As mentioned in several previous responses, the advancements in understanding of the genetic and immunomodulatory drivers in cancer has led to significant advances in therapeutics and identification of surrogate endpoints. As a result, in the past 10 years about 85% of accelerated approvals (AA) have been granted in oncology. Out of 166 AAs from 1992 through August

[12] Cherkaoui, S., et al The Impact of Variability in Patient Exposure During Premarket Clinical Development on Postmarket Safety Outcomes, Received April 5, 2021; accepted May 14, 2021. doi:10.1002/cpt.2320

[13] Beaver, J, et al A 25 Year Experience of the US Food and Drug Administration Accelerated Approval of Malignancy Hematology and Oncology Drugs and Biologics, JAMA Oncol. 2018;4(6):849-856. doi:10.1001/jamaoncol.2017.5618

`

2021, 48% have converted to traditional approval for the accelerated approval indication in a median of 3 years. Of note, between January 2018 and December 2020, there were 51 AAs approved for oncology.

16. *Recognizing that Phase 1 studies are not "powered for efficacy," how does the FDA consider evidence of efficacy demonstrated in a Phase 1 study*?

Phase 1 studies are typically intended to assess a drug's safety and tolerability, as well as its pharmacokinetics—how much drug exposure occurs with rising doses of the drug, and how the drug is excreted from the body. Often such Phase 1 trials are in healthy volunteers, providing no opportunity to develop meaningful efficacy data. However, Phase 1 trials can also be conducted in patients with the disease and when conducted in patients, may provide early signals of efficacy (based on clinical endpoints or biomarkers, when available). However, these trials are typically very short in duration (typically 2 weeks or less), and small in size (typically 10-30 patients). Such a short duration and small trial size can only provide limited useful efficacy data for neurodegenerative diseases, which progress over months to years.

17. *Before this Committee's hearing in 2015, former Commissioner Gottlieb testified that "adverse events" in EAPs had never impacted drug approval. FDA officials authored 2 studies validating his statement and then FDA training called that a "myth" perpetuated by drug sponsors. Are you aware of any updates to that research in the last five years?*

No, we have not updated that research, but based on our extensive experience with the use of EA we are not aware of anything that would change our conclusion. To further communicate this to sponsors, in 2016 we updated our Guidance for Sponsors Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers[14] by adding the following Q&A:

Q. Why does FDA review adverse event data for expanded access INDs?

A. From a public health perspective, early identification of important adverse events is beneficial. For example, a relatively rare adverse event might be detected during expanded access use, or such use might contribute safety information for a population not exposed to the drug in clinical trials. FDA is aware of a small number of cases in which clinical safety data from expanded access treatment was used to help assess the risks and benefits of the drug. In a very small number of cases, adverse event information from expanded access has contributed to safety information reflected in the FDA-approved labeling for a drug product. FDA is not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug. FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted and will evaluate any adverse event data obtained from an expanded access submission within that context. For example, FDA reviewers recognize that: 1) expanded access treatment generally occurs outside a controlled clinical trial setting; 2) patients who receive a drug through expanded access may suffer from

[14] https://www.fda.gov/media/85675/download

`

a more advanced stage of the disease or condition than patients participating in a clinical trial; 3) patients who receive a drug through expanded access may be receiving other therapies for their disease or condition at the same time as the drug they are receiving through expanded access; and 4) patients who receive a drug through expanded access may suffer from one or more comorbidities. All of these factors make it difficult to link an expanded access treatment to a particular adverse event. Moreover, it is very rare for FDA to place an IND on clinical hold due to adverse events observed in expanded access treatment. For all of these reasons, it is highly unusual for safety information from expanded access treatment to lead to an adverse regulatory decision for the drug.

18. *We know the FDA approves over 99 percent of EAP applications. With the exception of the Healey Platform trial at MGH with Dr. Cudkowicz, please identify how many single person, intermediate & widespread treatment EAPs have been approved in the last decade for:*

    a. *ALS;*

In the last decade, CDER has authorized approximately 50 expanded access INDs or protocols for ALS.

    b. *neurodegenerative diseases;*

In the same period, CDER has authorized approximately 90 expanded access INDs or protocols for neurodegenerative diseases, which includes the 50 for ALS.

    c. *Small Pharma without existing drug revenue versus big pharma?*

We currently do not collect data on the number of small pharmaceutical companies without existing drug revenue versus larger companies. We are aware that for smaller companies it may be more difficult to provide drugs under expanded access. FDA's regulations do allow companies to capture the cost of manufacturing and other costs when providing a drug under expanded access. However, we are also aware that when there are competing resources—expanded access versus clinical trials in support of approval—the more rapidly a drug can be approved, the broader the access.

19. *In your career*:

I note that as the Director of CDER it is my responsibility to understand drug development and our regulatory framework, and to bring executive leadership to our decisions. CDER approves drugs across many diseases, some quite rare and others quite common. For this reason, we hire clinical experts across many different areas to bring their disease specific expertise to the review of a new drugs.

    a. *In how many ALS trials have you been a principal investigator?*

`

I am a psychiatrist by training and my research experience is in that field. I have not been a principal investigator on an ALS trial.

b. How many peer-reviewed studies have you authored for ALS?

I have not authored a peer-reviewed study on ALS.

c. How many ALS patients do you estimate you have seen?

Patients with ALS should be treated by physicians with specialty training in neurology and other than the psychiatric symptoms of ALS it would be unusual for a psychiatrist to see ALS patients.

20. Can you estimate how many times in your career have you had to deliver the bad news to a patient that they have ALS?

A diagnosis of ALS should be made and communicated by a neurologist.

21. *For the neurologists on the ALS review teams at the FDA's CDER & CBER, please provide the following:*

a. How many ALS trials on which have they been a principal investigator?

b. How many peer-reviewed studies have each authored for ALS?

c. How many ALS patients do you estimate you have seen in clinic?

d. When was the last time they treated an ALS patient?

We acknowledge that clinical and clinical trial experience are important experiences for our FDA review staff. Within the Division of Neurology 1, which reviews applications for ALS drug products in the Office of Neuroscience, many review staff have prior experience as investigators in clinical research and clinical trials for neurodegenerative diseases and have authored peer-reviewed studies. Several staff members have trained or worked at NIH prior to joining the Office of Neuroscience. Most review staff are board-certified neurologists with prior clinical experience caring for patients with neurodegenerative diseases, including ALS. Notably, the ALS clinical review staff includes a neurologist who worked as the medical director at an ALS Association-certified ALS Center of Excellence clinic for several years and has been involved in clinical studies in ALS patients as recently 2021. We also note that many of our review staff have had personal experience with family or loved ones with neurodegenerative diseases, including ALS.

22. The FDA implemented the ALS Guidance Document in September of 2019. Can you explain how the agency has implemented the 2019 Guidance Document and what specific actions the agency has taken?

`

The 2019 guidance reflects our current thinking with respect to the design of development programs and trial designs for drugs for ALS. We continue to apply the concepts outlined in this guidance, tailored appropriately to different development programs for candidate drugs for ALS.

23. In June of 2019, then CDER Director said to the ALS community:

> *"If it improves your function and you can prove it, we'll approve it." What specific language in the 2019 Guidance Document for trial design would support this proof of efficacy?*

The ALS guidance points to the usefulness of the ALSFRS-R since it measures a range of important aspects of the clinical features of ALS. The guidance, however, also provides sponsors the flexibility to identify and propose other meaningful endpoints that reflect potential benefits to patients with this disease, including, for example, improvements in muscle strength or in respiratory function (given how important loss of such function is in the progression and mortality with this disease). Since the ALSFRS-R does measure important functional losses in patients with ALS, the Office of Neuroscience considers that this measure can robustly and sensitively detect the clinical benefits of effective drugs for ALS. Nonetheless, if sponsors believe their drug may provide other clinically relevant benefits, not properly "captured" by ALSFRS-R, then sponsors are welcome to request meetings to discuss alternative approaches, as long as clinically meaningful benefits are measured.

24. Please describe the pathophysiology and phenotypical heterogeneity in ALS that could impact a drug achieving its desired p-value.

ALS is a disease which has heterogeneity in its clinical presentation and its natural history, although the main manifestations of the disease with progressive neuronal loss, tragically, eventually compromises muscle strength and leads to respiratory dysfunction in all patients with this disease. Heterogeneity in presentation and natural history is a feature of many diseases; in the design of all clinical trials, it is important to develop well-functioning endpoints that measure important aspects of the disease, and to ensure that the study population size is sufficiently large to detect clinically meaningful benefits. The determination of study size is typically done by considering prior trial experiences—based upon an understanding of the variability of the endpoint used (here typically ALSFRS-R)—so as to include sufficient patients to detect benefit. This is the process of "powering" of a clinical trial. Fortunately, with many prior trials using ALSFRS-R, the variability of this endpoint is well understood, allowing trials to be designed that can robustly evaluate drug response in trials of 6-12 months in duration and with samples that are feasible to recruit.

25. What percentage of ALS cases have limb onset?

Approximately 70-75% of patients have limb onset ALS.

a. What percentage are upper limb versus lower limb onset?

`

Approximately 30-40% of patients have either upper or lower limb onset. The percentage of upper limb versus lower limb onset are roughly the same.

b. What is the percentage that have asymmetric onset?

The most common presentation of ALS is asymmetric limb weakness, occurring in 70-75% of the cases.[15] [16]

26. In the 21st Century Cures Act, Congress encouraged the use of "Real World" evidence to avoid the need for placebos in trials. It is my understanding that there is a database called PRO-ACT that contains data from 10,000s patients in placebo-controlled ALS trials. Can you help us understand why that database is not sufficient to eliminate placebo-controlled trials in ALS?

Historical controls (a type of external control) are one of the types of control groups recognized in FDA regulations outlining the characteristics of adequate and well-controlled studies (21 CFR 314.126). Use of external controls in clinical investigations has important limitations requiring that such use be limited to appropriate settings. One approach for externally controlled studies, illustrated by the cited example, is to pool large numbers of placebo groups from prior trials, and attempt to "match" patients from these pooled groups with patients entering a single arm open-label trial. This "matching" set of patients serves as the "control" group for comparison to patients in the single-arm trial. The limitations of this approach are that the pooled group comes from trials with a range of patients who are at differing stages of disease, from trials with a range of different enrollment criteria, enrolled over time periods that may go back many years when concomitant treatments differed from current treatments and, to the extent survival was not the primary endpoint in the trial, the timing and nature of clinical assessments may evolve. Moreover, patients may vary in ways that cannot always be well characterized, as all of the factors (what are referred to as "covariates") that predict a patient's course of disease are not fully understood.

These limitations are not seen in randomized clinical trials since randomization creates balanced treatment groups—that is, groups where the above listed patient characteristics are balanced. Nonetheless, external control groups, such as the use of pooled placebo patients from prior trials, can still be a useful approach, especially when the natural history of the disease is generally predictable, and when the drug being studied has a large treatment effect. These two characteristics, however, are not the case in many neurodegenerative diseases, including ALS. In these settings, the disease is heterogeneous, with variable presentation and variable natural history, and the drugs often currently being studied are expected to provide only a modest extent of benefit—still important for a disease with limited treatment options, but not detectable unless the trial is robust in design. There are many settings in which FDA is open to consideration of externally controlled trials—including the use of pooled placebo groups from prior trials of the

[15] Raymond et al. Clinical characteristics of a large cohort of US participants enrolled in the National Amyotrophic Lateral Sclerosis (ALS) Registry, 2010–2015. Amyotroph Lateral Scler Frontotemporal Degener. 2019 August ; 20(5-6): 413–420

[16] Gromicho et al. Spreading in ALS: The relative impact of upper and lower motor neuron involvement. Annals of Clinical and Translational Neurology 2020; 7(7): 1181–1192.

`

same disease—and has worked with sponsors to develop trial designs utilizing this approach. However, this approach is not "fit-for-purpose" in the ALS setting and would risk failing to find an effect where there is a treatment benefit with a drug or finding an apparent benefit that does not actually reflect a true effect of the drug, but rather is due to inadequate matching of the single arm trial patients with those patients from the pooled placebo group.

27. *Because of the "critical unmet need," the 2019 FDA Guidance Document indicates the FDA will utilize a different "risk-benefit" test for ALS therapies. Can you please identify examples in the last two years wherein the FDA has modified its risk-benefit assessment in an ALS therapy?*

FDA does consider benefit risk decisions in the context of the seriousness of the disease, unmet need, and patient acceptance of risk and how they value the potential benefits. There is not, however, a modified risk-benefit assessment for ALS therapies or for other serious diseases with unmet needs. As for all approved drugs, the same statutory requirements for demonstrating safety and effectiveness apply to drugs for ALS. As the recent (2019) FDA ALS guidance states:

> *"When making regulatory decisions about drugs to treat ALS, 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."*

These considerations are similarly discussed in our recently released guidance on benefit risk where we state

> *"For a drug intended to treat a serious disease with unmet needs, FDA may accept greater uncertainties about benefit or risk at the time of approval…. FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met. FDA therefore often exercises greater regulatory flexibility in these cases…"*

FDA does not "modify" its benefit risk assessment specifically for ALS, but, as for serious diseases like ALS that have substantial unmet needs, the patient perspectives and needs, and the seriousness of this devastating disease are very much considered in our regulatory actions.

28. *Please describe how the FDA assesses risk-benefit when deciding how many ALS patients can participate in a Phase 1 safety/toxicity trial for a drug or biologic?*

Risk-benefit is considered throughout the course of a drug's development. However, early in development, there is typically limited information on the drug's benefits or risks. The typically short duration of Phase 1 studies (days to weeks) means that study patients with the disease have a limited likelihood of seeing benefit. However, these studies are critical in providing the initial safety and pharmacokinetic experience that can support further development; in addition, these studies can provide early information on drug response using pharmacodynamic endpoints—measures that can detect evidence of a drug response showing that the drug is "hitting" its target. The size of Phase 1 studies is determined by these study objectives to provide early assessments

`

of safety and tolerability information, and data on drug exposure. Since there is limited benefit and risk information early in development, smaller trials, not exposing large numbers of patients to the drug for longer durations, are appropriate. Such studies are very carefully monitored to detect—and if need be act on—any safety event that may occur. Often such studies include a modest number of patients: for example, 10-30 patients would a be typical size of a Phase 1 study. Because these studies are relatively small and short in duration and play a critical role in the stepwise development of a potentially valuable drug, the benefit risk balance is considered to be favorable.

29. *Given that ALS is plagued by small sample sizes as typified by many rare diseases and exacerbated by trial exclusions, how would you recommend the ALS research community increase sample size to make it easier to achieve the FDA specified p-value of .05 without killing Americans as each year passes?*

Although ALS is an orphan disease, unfortunately, there are thousands of individuals living with the disease in the US, and there are many centers that care for patients with this disease that are well qualified and capable of participating in clinical trials of promising drugs. FDA has worked with trial sites and trial networks to further increase site capability, expanding the number of sites that can support trials of therapeutics. In addition, trial networks are typically global so that trials can be conducted not just in the US, but in many regions where there is appropriate expertise and capable investigational sites. Such global participation can further accelerate recruitment and trial completion.

30. *It's my understanding that ALS trials are hampered by small trial sizes compared to other neurodegenerative diseases like Parkinson's, Alzheimer's, Huntington's Disease and MS. Can you please identify the average trial size in Phase 1, 2, and 3 trials for these 5 diseases?*

Since the question is focused on ALS, and barriers to trial conduct in this disease, we will focus our answer on trials for ALS. We note that although ALS is an uncommon disease, it is not, unfortunately, a very rare disease, occurring in approximately 2 per 100,000 individuals per year so that in a city of 1 million people, there are about 20 new cases per year. Referral centers in large catchment areas, therefore, may see as many as 10-50 new cases per year, and may care for several times that many patients with ALS at any one time. ALSFRS-R, the standard clinical endpoint in ALS trials, is reasonably sensitive, so that with trial durations of 6-12 months, and, depending on the anticipated extent of effect, with trial sizes of 100-200 patients, meaningful drug efficacy can be detected. For this reason, a network of sites, especially in a multinational development program, can recruit patients into a trial over a period of 6-12 months. By comparison, the two Phase 3 trials submitted for the approval of Aduhelm for Alzheimer's disease enrolled over 3,200 patients, and in the 2020 approval of opicapone for Parkinson's disease over 1,000 patients were enrolled in the two clinical trials supporting approval.

31. *Do you have any thoughts why it is easier for someone to schedule their own assisted suicide than it is to try an investigational drug in Phase 3 clinical trials?*

`

We understand that ALS is a devastating disease, and it saddens us that patients may feel they need to make decisions about assisted suicide. FDA does everything within its authority to facilitate Phase 3 clinical trials or expanded access for investigational drugs for ALS. The availability of investigational drugs in a Phase 3 trial is determined by the study size, location of investigations sites, timeline of trial enrollment, and trial enrollment criteria. Investigational drugs may also be available through expanded access programs—which are determined by sponsors; whether such programs are available typically relates to the status of their development program and availability of the drug to support both clinical trials and expanded access use. FDA's role in expanded access is to ensure that the potential for benefit exceeds risk to the patient, considering the seriousness of their disease and the lack of adequate therapeutic alternatives. In general, FDA bases its decisions regarding an expanded access IND request on the assessment of the patient's health care provider and therefore authorizes a very high proportion of such requests (~ 99%). Moreover, FDA handles emergency requests for expanded access drugs rapidly, typically within 24 hours (and often within hours of the request).

32. *Are you aware of how the suicide rate in ALS compares to the national suicide rate or the suicide rate for oncological diseases?*

Yes, we are aware of recent studies that have found higher rates of suicide rates for individuals with a diagnosed neurological disorder. FDA recognizes that ALS and other neurodegenerative diseases can be devastating to the patient and their family, and that the diseases are often associated with depression. Comprehensive care of patients with these diseases must include supportive care, including careful attention to the patient's mental health. The need for therapies in neurodegenerative diseases, including in ALS, is great and urgent, and FDA is fully committed to all efforts that our organization can make to support development efforts.

33. *The FDA has repeatedly acknowledged the "critical unmet need" in ALS. Please identify all regulatory pathways that speed up drug approval once an IND is submitted to the FDA and how many months or years, on average, that expedites approval for an ALS therapy vs a traditional pathway.*

There are a number of different pathways that are available to speed development of promising therapies for neurodegenerative diseases. Two programs that are available to accelerate the IND development stage of promising drug programs include fast track and breakthrough designation. Fast track designation may be given based upon preclinical data or even a strong hypothesis of possible benefit and supports greater interactions between FDA and sponsors, among other benefits. Breakthrough designation is provided when, based upon preliminary clinical data (often from earlier phase [referred to as "Phase 2 studies"] randomized controlled studies in patients) there is preliminary evidence that the drug may lead to a substantial improvement over available therapy on one or more clinically significant endpoints. This designation further supports increased interactions between FDA and sponsors, increased involvement of senior FDA staff, and indicates to all relevant FDA disciplines the importance of supporting expeditious drug development, such as moving up product manufacturing readiness. In addition to these two programs that can speed development, priority review designation reduces the timeframe for regulatory review once a new drug application or biological license application is received. Finally, accelerated approval is available to speed development by allowing approval based upon

`

either an earlier clinical endpoint (an intermediate endpoint) or a surrogate endpoint that is "reasonably likely" to predict benefit. Unfortunately, there is a lack of surrogate endpoints that are considered "reasonably likely" to predict benefit in many neurodegenerative diseases. This is due to the limitations of our understanding of the mechanisms of disease for many neurodegenerative diseases; such understanding serves to identify particular molecules ("biomarkers") that are altered in disease, and improved by drug, and therefore might predict drug benefit. Such biomarkers can then serve a number of important roles in drug development, including, when appropriate, as surrogate endpoints.

It is difficult to calculate the average time that such programs save for drug development as the drugs that receive these expedited development programs have shown early promise and are to meet an unmet need and are different than drugs that go through a traditional review process without one of these expedited review designations. AA should enable earlier approval as the goal of identifying the surrogate endpoint is to identify a disease modifying endpoint that precedes the ultimate clinical endpoint. The GAO found that the greater the number of expedited programs for which the NDA qualified, the shorter the time FDA took to complete the initial review.[17] A recent analysis noted that drugs with breakthrough designation reach the market approximately two years earlier than those drugs that do not have breakthrough designation, measuring the time between IND submission and approval.[18]

Although there are several applicable programs, discussed above, that can speed development of promising therapies for neurodegenerative diseases, FDA recognizes the critical unmet need for novel therapies for many of these diseases, and works closely—and interacts frequently—with sponsors regardless of whether their drug has a particular designation. If the clinical division that regulates a particular drug views the drug as promising, they will use an "all hands on-deck" approach and meet with sponsors as needed to provide all the support that we can. This enhanced interaction typically occurs in such situations regardless whether the drug has formally received fast track or breakthrough therapy designation.

34. *Using the Emergency Use Authorization pathway, vaccines for COVID came to fruition in approximately a year. Although the EUA isn't applicable to ALS therapies, is there an existing regulatory pathway that would enable an ALS therapy to come to market in a similar timeframe? Or is this something Congress needs to address for imminently life-threatening, rare diseases for which there are no disease modifying treatments?*

The remarkably rapid development and authorization of vaccines for prevention of COVID-19 as well as monoclonal antibodies and other antivirals for the treatment of COVID-19 reflects a concatenation of factors—factors that cannot be readily matched in the search for treatments of neurodegenerative diseases. These differences, and not the lack of an applicable regulatory pathway, underlie the much longer time frame for finding and approving a therapy for neurodegenerative diseases. The platforms leveraged to develop vaccines for COVID-19 and

[17] GAO, FDA Drug Approval: Application Review Times Largely Reflect Agency Goals, GAO 20-244/
[18] Pregelj, L. *et al. Clin. Pharmacol. Ther.*110, 1018–1024 (2021). While FDA staff did not agree with all of this analyses and the conclusions reached, the data on timing of approval seems accurate see Corrigan-Curay, J and Stein, P., FDA Breakthrough Therapy Designation-Trial Design and More- Commentary, *Clin. Pharmacol. Ther* 110 869-870 (2021).

`

other therapeutics have been developed over years[19], the course of COVID-19 is rapid, evolving over a matter of days, and the incidence of disease has been extremely high, so that therapies to prevent or treat this disease can be rapidly evaluated, with endpoints evaluated within weeks or at most months. Neurodegenerative diseases, in contrast, are uncommon and progress over months to years.

Indeed, the recent approval of Aduhelm reflects how years of research and learnings from earlier failed trials informed subsequent development and trials. Because our understanding of certain neurological diseases is more limited, surrogate endpoints that would predict drug benefit and speed drug development are often not yet available. These, not the lack of regulatory pathways, are the "headwinds" that slow development of treatments for neurodegenerative diseases. Indeed, when the science and the data support it, FDA has all of the regulatory tools to make development and regulatory review highly efficient and expeditious.

The Honorable Brett Guthrie (R-KY)

Dr. Cavazzoni, we continue to see challenges in developing drugs in the neuroscience space. The testimony from the second panel helped us understand the real-life consequences of failing to adequately address those challenges. The status quo is simply unacceptable; we must do better for patients and their families. To improve development in the neuroscience space, we need a stronger emphasis on patient-focused drug development at FDA, we need to improve the utilization of drug development tools at FDA, and we need to increase engagement between FDA and stakeholders. There is precedent for this. This is what is occurring at the Oncology Center of Excellence.

1. *Dr. Cavazzoni – can you discuss why the FDA's Oncology Center of Excellence has been a success, and what FDA has learned through its establishment*?

There has been a sea-change in the available treatments for patients with cancer. The first step in the dramatic and successful arc of how cancer treatment has evolved over the past decades was the rapidly growing understanding of the mechanisms of disease. Recognition of molecular "drivers" of cancers, and markedly enhanced understanding of the immunobiology of cancer, are advances that provided highly promising therapeutic targets. The advances in science, with recognition of a wealth of molecular targets, in the 1990s and early 2000s quickly translated to an exponential growth in new drug development programs, leading to treatments that often have provided dramatic responses to oncological diseases that previously had only very limited options. What this has taught us is that a concerted effort to support drug development must go hand-in-hand with a deep and thorough understanding of disease pathogenesis, providing promising drug targets. Basic science must, necessarily, precede drug development, but research and clinical development can then be mutually informative; clinical success validates the research approach and stimulates additional investment. The resources available to OCE, in terms of staff and operations, allow for more involvement by FDA in supporting key regulatory

[19] See for example, The tangled history of mRNA vaccines, Nature, 14 September 2021 https://www.nature.com/articles/d41586-021-02483-w

`

science initiatives, working with sponsors and other stakeholders. Comparable investments in staff working on neurologic conditions and other rare diseases may similarly accelerate progress.

The Honorable Michael C. Burgess, M.D. (R-TX)

1. *The Food and Drug Administration Advisory Committee is intended to provide an independent review of the product seeking approval from the agency. Although it is important to ensure conflicts of interest are avoided, often Members of the Advisory Committee are far removed from the complex conditions being considered. Would selecting Advisory Committee members with a specific and intricate knowledge of the disease or condition impacted by the product being reviewed lead to a deeper understanding of the safety and efficacy of the product?*

FDA agrees that it is essential to have individuals participating in an advisory committee (AC) meeting who have expertise directly relevant to the disease being targeted by the drug under review and FDA makes every effort to achieve that goal. Clinical divisions holding AC meetings typically supplement the committee with experts with this specific disease area knowledge if not already part of the committee. There are, however, challenges FDA divisions face when working to bring the right expertise to the panel. Often, subject matter experts in a particular disease have participated in either the development program of the drug under review or in competing drug development programs, leading to a conflict of interest precluding their serving on the panel for that meeting. Also important to note, however, is that panel members who may not be experts on the specific disease at issue, but who are specialists in the broader disease area—and have managed patients with the specific disease—may also provide important insights and input. And other discipline experts, such as statisticians, clinical trialists, or experts in pharmacology may also have important perspectives to contribute to the discussion. FDA agrees that participation by experts in the specific disease is important for a valuable AC discussion, recognizes the challenges, and works hard to populate AC panels with individuals who can provide useful input.

2. *How is real-world data and evidence improving FDA's ability to support product approval decisions for innovative treatments?*

FDA has been working extensively to gain experience in the use of real world data (RWD) and real world evidence (RWE) to support regulatory decision-making. Over the past years, FDA has sponsored or participated in many workshops and panel discussions and engaged in a wide range of research projects with different stakeholder groups intended to move the field of RWD/RWE forward. FDA has reviewed many submissions from drug sponsors with proposed RWE programs intended to support regulatory decisions. These proposals are reviewed in depth with the relevant clinical division and by an expert internal committee (called the RWE subcommittee of the Medical Policy and Program Review Council) that meets regularly. This experience gained over the past years has markedly enhanced our understanding of the strengths and limitations of studies using RWD intended to support regulatory decisions and expanded our ability to provide thoughtful and detailed advice to sponsors. Finally, FDA has been working on

`

a series of guidances[20] for industry and other stakeholders to provide detailed information on a wide range of critical aspects related to the design and analysis of studies using RWD. It is also worth noting that industry and FDA recently agreed on a new RWE pilot program (as part of the proposed PDUFA VII goals letter) that is intended to further enhance opportunities for collaboration between drug developers and FDA on the design of studies using RWD that may have a greater chance of success in providing the data FDA needs to approve new indications for drugs under applicable scientific and legal standards.

Despite all of these extensive efforts, there remain significant challenges to using RWE as the basis for regulatory decisions. FDA expects that the research, policy development, new guidances, and extensive experience will progressively lower barriers, support development of new approaches, and eventually expand the use of RWE to support regulatory decisions. However, it is important to note that RWE will remain one tool for drug developers to use and will not replace the need for double-blind randomized clinical trials to support drug approvals—especially for the initial approval of new drugs.

The Honorable Dan Crenshaw (R-TX)

Dr. Cavazzoni, over the last several months I have been asked by a number of individuals advocating on behalf of patients with ALS to support a proposal (H.R. 3537) that creates a federal grant program that creates a pathway for organizations to purchase non-FDA approved treatments for individuals with life-threatening diseases. The proposal requests these federal funds be used for individuals who are not enrolled in a phase 3 trial but are enrolled in an expanded access program.

1. *One reason given for supporting this proposal is that the advocates believe the data obtained from individuals who take the non-FDA approved medicine through an expanded access program can be used along with data obtained from the standard random controlled clinical trial to determine a medication's effectiveness. Is that likely?*

2. *I also understand random, controlled trials are just that – "controlled." Can a process outside the clinical trial be structured in such a way that the data obtained outside the clinical trial could be considered valid by FDA as they consider approval? If so, what are the major considerations that would have to be resolved in order for this data to be considered acceptable?*

The primary intent of expanded access (EA) is to provide access to potentially beneficial drugs for patients with limited other options, and who cannot participate in clinical trials, for example

[20] To date CDER has published three draft guidances for RWE: 1) Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products; 2)Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry and 3) Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. These guidances can be found at the following URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

`

due to trial enrollment criteria or proximity to trial investigational sites. Since the primary intent is treatment and not research, typically only limited information on outcomes and safety information is provided to FDA. Nonetheless, there are a number of instances where EA data has provided useful information on safety, especially when reasonably detailed information is collected, and even useful information on effectiveness, typically when the drug response is large and therefore even uncontrolled data can be interpretable. For example, for a disease with a rapidly downhill course, information from a series of patients receiving treatment under EA that shows no evidence of deterioration over a period during which essentially all patients have marked deterioration, can be convincing. For drugs that are not expected to provide a dramatic effect, uncontrolled experience information is challenging to interpret and provides very limited utility in establishing drug benefit. For diseases with heterogeneous presentations and variable natural histories, such as many neurodegenerative diseases, and where drugs in development are typically expected to provide a modest but not dramatic effect size, randomized trials are needed to identify those typically modest effects. These can provide well-matched treatment groups, and are capable of efficiently detecting modest, but meaningful, effect sizes.

With respect to data "outside" of a clinical trial, FDA has been working extensively on ways in which real-world data (RWD) and real-world evidence (RWE) can support regulatory decision-making. RWD is data emerging from the wide range of routine health care interactions, and RWE is based upon analyses of this data. The challenge is that this information is not available for initial approval of a drug, as the drug must be marketed for RWD to be generated. Therefore, RWE may be useful to generate data that may be considered, along with other data, in support of adding new indications or new populations, to the labels of approved drugs. The challenge of using data outside of a clinical trial, and generally the challenge of uncontrolled data, is that the selection of patients by their health care provider to take a particular treatment means that patients receiving this treatment may differ in important ways from patients who receive other treatments—ways that are associated with different outcomes. Randomization balances treatment groups so that patients in the active treatment and placebo groups have generally similar characteristics—and can be expected to have similar outcomes, so that when outcomes are better in the active treatment group, one can conclude that the drug provided benefit.

`