May 2, 2023

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA-2022-D-2983: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry

Dear Sir or Madam,

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or "Agency") for the opportunity to comment on the Agency's Draft Guidance entitled, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry". We are grateful for the Agency's efforts to guide the stakeholder community on how best to construct externally controlled clinical trials.

MDA is the #1 voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 70 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of our families. MDA's mission is to empower the people we serve to live longer, more independent lives.

Neuromuscular diseases are a group of rare, serious, progressive, mostly irreversible conditions that, while each unique, are collectively defined by progressive muscle weakening and degeneration leading to physical disabilities and, for many, early mortality. Innovative treatments for NMDs are particularly difficult to test within traditionally structured clinical trials for several reasons. First, it may be unethical, perhaps even impossible, to use placebos in certain ultra-rare, life-threatening diseases where no existing treatments halt or delay the progression of the disease. Second, NMDs are often very heterogeneous, making it difficult to ascertain statistically significant differences between a small placebo group and an experimental arm. Finally, many NMDs are slowly progressing, thus causing challenges in ascertaining a treatment effect in a clinical trial that lasts a handful of months, maybe even one year. Consequently, alternative clinical trial designs, such as the use of external controls, are particularly important to accelerating therapeutic development within neuromuscular diseases.

Overall, we are grateful for, and encouraged by, FDA's efforts to bring greater information and clarity to the stakeholder community to potentially facilitate a greater use of external controls through the issuance of this Draft Guidance. As the Agency works to finalize this guidance, we ask the FDA to take an encouraging, helpful, and facilitating approach towards the biopharmaceutical industry using external controls rather than an approach of discouragement and skepticism. It is important that industry sees FDA as a collaborator and partner as external

controls are being considered and not as a skeptic or barrier. This Draft Guidance often took a tone of "here's all the ways external controls can go wrong", rather than "here's all the ways external controls go right". We ask the Agency to be mindful of this as it approaches the potential increase in use of external controls in rare neuromuscular diseases.

In addition to this overall consideration, we ask the Agency to consider the following:

External Controls in Heterogeneous, Irreversible, Ultra-Rare Diseases

Within the Draft Guidance, FDA states that "Given that externally controlled trials do not involve randomization of the study population to the treatments being compared, the treatment and control arm populations should be as similar as possible regarding known factors that can affect the outcome being measured." This will be inherently difficult within rare neuromuscular diseases as often the progression and manifestation of symptoms heterogeneously occurs across a very small disease population. Consequently, as it is already difficult to craft highly similar placebo and experimental arms, so too will it be difficult to craft a highly similar external control and experimental arm. We ask FDA to be mindful of this reality and flexibly approach how best to construct external control arms in a heterogeneous population.

The Draft Guidance also states that, "Of note, if the natural history of a disease is well-defined and the disease is known not to improve in the absence of an intervention or with available therapies, historical information can potentially serve as the control group". We ask that FDA expand this example to diseases that "are not known to slow in progression absent an intervention or with available therapies." Many neuromuscular diseases cause irreversible muscle degeneration, and consequently effective therapies are those that halt or even just slow the progression of the disease. Many risk/benefit and patient preference studies, as well as Patient-focused Drug Development meetings, have reiterated the importance of slowing progression of disease. We request FDA to amend this sentence to include diseases that are known not to halt or slow progression without an intervention.

The Agency further states that "In many situations, however, the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low, and sponsors should choose a more suitable design, regardless of the prevalence of disease." We disagree with FDA's disregard of disease prevalence as still far too often we see treatment development efforts in ultra-rare neuromuscular diseases fail because FDA inflexibly layers approaches used in common or non-ultra-rare diseases onto ultra-rare diseases. FDA should never disregard the challenges unique to ultra-rare disease drug development.

Managing Confounding Variables:

We thank the Agency for offering guidance to sponsors on how to design externally-controlled trials. We ask that FDA address the following recommendations when finalizing this guidance.

First, many natural history cohorts that could potentially serve as an external control involve voluntary and self-selecting participation. For example, many individuals in the neuromuscular disease community have opportunities to participate in registries or natural history studies, but of

course their participation is voluntary and often impacted by whether they are attending a clinic that facilitates participation, and they have the time and means to participate. Further discussion on whether or how such natural history studies can avoid confounding variables due to self-selecting participants would be helpful.

One such potential confounding variable is the mode of data collection. FDA warns against the external control data being collected any differently than the data within the experimental arm of the clinical trial. For historical controls, this may be unavoidable as the data collection occurred prior to the trial, and perhaps in a manner that could not be mimicked within the trial. Furthermore, often it is patient organizations collecting the data within a historical control rather than a biopharmaceutical company let alone the sponsor. These data collected by patient organizations may be invaluable and the most comprehensive of any study available to serve as a historical control. How does FDA recommend these valuable data can still be used even if they were collected in a manner different than the clinical trial?

FDA concludes this section, stating "Given the challenges outlined, externally controlled trials are more likely to provide convincing results when the effect size on a well-characterized outcome of interest is anticipated to be large". Later, on page 14, FDA again states that "Especially when the anticipated effect size is modest, an externally controlled trial may not be an appropriate study design because of concerns for bias affecting the results". We remind the Agency that large effect sizes within rare neuromuscular disease clinical trials are often impossible over the time period in which a typical clinical trial is run. NMDs are often slowly progressive, and any "large effect" may occur over several years, perhaps even a decade. Consequently, we urge FDA to ensure NMDs are not locked out of using externally-controlled trials simply because large effect sizes are difficult, perhaps even impossible, to capture.

On page 7 of the Draft Guidance, FDA discusses how the use of alternative therapies can confound results. Given the severity of neuromuscular diseases, plus the lack of effective treatment options, many in the NMD community turn to anything that may be effective in alleviating symptoms of the disease. We ask that FDA is mindful of the desperation of living with an untreatable condition, and the medical experimentation that may result, when considering that participants in an external control group may have tried a variety of other treatment options.

The Agency also discusses how time differences in data collection could confound results. This may again disadvantage rare neuromuscular diseases, particularly ultra-rare diseases, as an extended amount of time may be required to collect the necessary amount of data to serve as an external control. We ask the FDA to not allow a longer data-collection period to become an inherent disadvantage for using external controls in rare diseases. Instead, perhaps it should be incumbent on the Agency and sponsor to show that a time difference did in fact confound results rather than requiring sponsors to prove a time difference does not affect results.

Use of Innovative Clinical Outcome Assessments and Decentralized Clinical Trials:

MDA encourages FDA to consider how the use of wearables, innovative clinical outcome assessments, and decentralized trials may address some of the concerns stated within the Draft

Guidance. On page 9, FDA expresses concerns with different modes and methods of data collection inside and outside of a trial setting, stating, "A similar consideration applies to the assessment of motor milestones, such as the ability to sit or walk, which are usually not recorded with the same rigor during routine clinical care compared to approaches used in clinical trials." This difference in assessment could be addressed through the use of wearables, thus facilitating assessments of motor milestones regardless of the location of data collection. Decentralized clinical trials that occur in the community setting could also obviate concerns over the rigor of assessments being conducted in the community versus the clinic. Afterall, within a decentralized clinical trial, the location of data collection in the external control arm may be identical to the experimental arm: in the home.

We encourage the Agency to consider how the ongoing efforts to further decentralize clinical trials, fund and validate new clinical outcome assessments, and accelerate the development of wearables can facilitate the use of external controls.

Submission of Patient-Level Data:

On page 16 of the Draft Guidance, FDA states that, "Sponsors must include in their marketing applications relevant patient-level data (i.e., data on each participant and patient in the externally controlled trial), as required under FDA regulations, for both the treatment and external control arms". This may prove impossible for any data that is not collected by the sponsor themselves, particularly if the data originates from a patient organization's natural history study. Many of these studies include a prohibition on patient-level data leaving the natural history study, and if it occurs, it would violate the informed consent document signed by participants.

We encourage FDA to consider how stringent this requirement is, and the consequences of adhering strictly to requiring patient-level data for external controls. In doing so, the Agency may be substantially limiting the amount of data available to potentially serve as a historical control.

In conclusion, we are grateful for the opportunity to comment on FDA's efforts to facilitate the use of external controls in clinical trials. For questions regarding MDA or the above comments, please contact me at 202-253-2980 or pmelmeyer@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Vice President, Public Policy and Advocacy
Muscular Dystrophy Association