



September 22, 2026

SUBMITTED ELECTRONICALLY

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Muscular Dystrophy Association Comments on “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products – Draft Guidance for Industry” - Docket No. FDA-2019-D-4964-0077

To Whom It May Concern;

In service of the neuromuscular disease (NMD) community, the Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or “Agency”) for the opportunity to comment on the Agency’s “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products – Draft Guidance for Industry”. Therapeutic development in rare and ultra-rare neuromuscular diseases has long been challenging, and the vast majority of neuromuscular diseases do not have any FDA-approved therapy. This is why ensuring that the Agency and the biopharmaceutical industry are utilizing the most efficient and patient-friendly methods of demonstrating substantial evidence of effectiveness is of critical importance to MDA.

MDA is the #1 voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 75 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of our community. MDA’s mission is to empower the people we serve to live longer, more independent lives.

Background on Neuromuscular Diseases Therapeutic Development:

Neuromuscular diseases, all of which are rare diseases, feature progressive muscle weakening, many severe enough to lead to significant morbidities and shortened lifespans. Most neuromuscular diseases are genetic, and decades of research investments have led to discoveries on disease underpinnings, etiology, progression, and potential therapeutic targets.

This has contributed to an advent of neuromuscular disease drug development where communities without any FDA-approved treatments just ten years ago now have several therapeutic options from which to choose. Still, progress has been uneven. The vast majority of

neuromuscular diseases still do not have any FDA-approved treatment, and ultra-rare and n-of-1 neuromuscular diseases frequently see little commercial interest in developing a treatment for their diseases.

Often one of the main impediments to successful neuromuscular disease therapeutic development is demonstrating substantial evidence of effectiveness in pivotal clinical trials. Neuromuscular diseases are heterogeneously progressive making it very difficult to present statistically significant evidence of effectiveness using traditional methods. Doing so may take a multi-year clinical trial and/or the elimination of unknown confounding variables. Furthermore, traditional methods of demonstrating substantial evidence of effectiveness may use archaic clinical outcome assessments or endpoints that do not align with our community's expectations for participation in clinical studies.

Consequently, approaching the demonstration of substantial evidence of effectiveness in a progressive, flexible, and patient-friendly manner is imperative to successful therapeutic development for our community. MDA believes this draft guidance is a step in that direction. Our below comments outline where we believe the Agency has meaningfully advanced the conversation on demonstrating substantial evidence of effectiveness as well as areas for further expansion, improvement, or refinement.

Factors Impacting the Strength of Evidence of Effectiveness

There are several parts of this section that raise concerns for neuromuscular disease drug development as well as other parts that represent positive steps in the right direction.

First, we appreciate the Agency's discussion on when external controls may be used in place of placebo controls (or other internal control approaches) in clinical trials. External controls are incredibly important in neuromuscular disease drug development as the use of placebos is often unethical due to the severe unmet need, lack of alternative treatments, and severely progressive and debilitating nature of the disease. We appreciate the Agency's listing of factors for the successful use of external controls, but are cautious about FDA stating that external controls should be used when "the estimated treatment effect based on the prespecified statistical analysis is so large that it is unlikely to be fully attributable to bias." For many neuromuscular diseases, large effects in slowly progressive diseases may not be captured under a realistic trial timeline. It may take years, perhaps a decade, to observe an effect "so large that it is unlikely to be fully attributable to bias". We worry that if this standard is applied to the use of external controls, many neuromuscular diseases will be locked out of the use of this method altogether.

We also call for the Agency to put greater emphasis on the benefits of "shorter or smaller studies" when using surrogate endpoints in clinical trials via the accelerated approval pathway, as discussed on pages 5 and 6. A shorter or smaller study can make all the difference in not only a successful clinical trial, but in the health and wellbeing of the trial participant and affected population at large. This benefit of using surrogate endpoints and accelerate approval, particularly in comparison to the weight given to the drawbacks of using surrogate endpoints and accelerate approval discussed later in the document, should be given much greater weight and attention.

We deeply appreciate the FDA stating that, “Eligibility criteria should be selected to reflect the intended-use population, including with respect to age, sex, race, ethnicity, and disease severity, with exclusion criteria used only if scientifically justified”. We wholeheartedly agree. This does raise several questions. First, will the Agency be encouraging sponsors to expand its inclusion criteria for participation when the sponsor may be inclined to choose enrichment strategies and select a narrow subset of the community instead? If a sponsor is concerned that doing so will confound the results, will the Agency approach this flexibly and allow for sub-cohort analysis? Will the Agency ask sponsors to use Diversity Action Plans (DAPs) to ensure the population of the clinical trial matches the intended-use population?

We similarly appreciate FDA stating that “even small effects may be clinically meaningful when the effect is on survival or irreversible morbidity”. Once again, we could not agree more. Still, this principle must carry the same if not greater weight in Agency decision-making as other points addressed in this section on statistical significance. We urge the Agency to prioritize these small but meaningful impacts on our community’s wellbeing over rigid adherence to p-value standards.

Approaches to Meeting the Substantial Evidence Standard

Within the section describing “Evidence from a Highly Persuasive Adequate and Well-Controlled Trial Plus Early-Phase Confirmatory Evidence” we again are supportive of certain FDA assertions while concerned about others. For example, we join FDA in supporting trial a structure that “enrolls a broad and representative population across multiple sites”. Similarly, we support the FDA when it encourages trials that “Generate results that are largely supportive across important trial subsets (e.g., across subgroups defined by concomitant or prior therapy, disease stage, age, sex, race, or geographic region in a global trial”. We will once again point out how salient Diversity Action Plans are in accomplishing these goals and encourage the Agency to ensure such plans are being used.

On the other hand, the assertion that “a single trial with hypothesis testing at the common one-sided 0.025 significance level may not adequately limit the probability of false positive” is discouraging given the myriad challenges neuromuscular disease clinical trials face in achieving statistical significance, and this statement reasserts a high bar for neuromuscular disease trials to overcome. Later in the document the FDA expresses flexibility on this standard, but we encourage FDA to mention that flexibility in this section as well so the reader gets the full picture.

Finally, the Agency lists factors that “FDA expects that a single highly persuasive trial will typically include”. We note the omission of a bullet that a trial should meaningfully fill an unmet need in an underserved patient population in a manner that is structured in a patient-focused way. FDA has routinely emphasized this expectation elsewhere, but in a list of FDA’s expectations for trial designs, we encourage FDA to include this expectation.

Regulatory Flexibility

We are broadly supportive of the “Regulatory Flexibility” section of the draft guidance as it includes several important flexibilities to ascertaining substantial evidence of effectiveness in neuromuscular disease clinical trials.

First and foremost, we support the general premise FDA outlines when it says “certain flexibilities might be more acceptable for a rare disease that is life-threatening and lacks available therapies than another rare disease with less severe consequences with multiple therapeutic options already available. Both of these scenarios, however, present a very different clinical context than a common, nonserious disease with several available treatment options”. Both of these scenarios are at play within the neuromuscular disease community with some ultra-rare communities still far away from a treatment while others are experiencing multiple FDA approvals each year. Nonetheless, the rarity, progressiveness, and heterogeneity across neuromuscular diseases remains resulting in needed flexibilities for the entire community.

We are incredibly grateful for FDA stating that “it may sometimes be possible to conclude that substantial evidence of effectiveness has been demonstrated despite residual uncertainty”. We could not agree more. Our community, particularly those still waiting for their very first FDA-approved treatment, understand such uncertainty when considering treatment options. While no community is monolithic, those who we serve generally are willing to accept such uncertainties in exchange for a chance at improved health and wellbeing.

We similarly support FDA when it says, “For example, in a trial relying on null hypothesis significance testing, a significance level higher than the common one-sided 0.025 level may be acceptable in some cases. The success criteria should be prespecified, justified, and agreed upon with the Agency.” Eschewing statistical rigidity in neuromuscular disease trials is critical to avoiding discarding effective therapies because the clinical trial results do not adhere to perfect statistical expectations. Nonetheless, we invite the Agency to consider times in which a significance level higher than the common approach but only found as the trial is ongoing may still be acceptable. FDA expecting that any departure from the norm must be “prespecified and justified” may not reflect the reality of the real world where sponsors and the Agency learn more about the disease and treatment in question as the trial continues. FDA should consider times in which alternative statistical analysis plans may be justified as a clinical trial(s) unfolds, so long as it is agreed upon with the Agency and occurs prior to unblinding.

The Agency also states that “mechanistic evidence of the drug’s treatment effect in a particular disease may be appropriate to use as confirmatory evidence” and cites an example of a genetic disease and a treatment that addresses the underlying genetic cause. This is particularly salient for genetic neuromuscular diseases, and we strongly encourage FDA to work with the biopharmaceutical industry and organizations like MDA to set the expectations for what mechanistic evidence can be used as confirmatory evidence, particularly within the recently announced Plausible Mechanism Framework. We similarly support the natural history data paragraph and call for similar collaboration on setting the minimally-acceptable standards for natural history data to serve as confirmatory evidence in establishing effectiveness.

We are grateful for the opportunity to comment on the FDA's draft guidance on Demonstrating Substantial Evidence of Effectiveness. For questions regarding MDA or the above comments, please contact me at pmelmeyer@mdausa.org

Sincerely,

A handwritten signature in black ink, appearing to read 'P. Melmeyer', with a long, sweeping horizontal line extending to the right.

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