April 27, 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 "Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause; Draft Guidance for Industry" - Docket No. FDA-2026-D-1256-0002

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 "Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause; Draft Guidance for Industry".

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.

All neuromuscular diseases that fall under MDA's umbrella are rare diseases, and the vast majority are ultra-rare diseases with many affecting fewer than 100 people. Therapeutic development is incredibly challenging for these diseases due to regulatory misalignment and a lack of a commercial market. Consequently, only a handful of the hundreds of ultra-rare neuromuscular diseases currently have an FDA-approved treatment.

This is not a scientific problem. Many of these ultra-rare neuromuscular diseases, while scientifically complex and often heterogeneous in nature, are monogenic and likely excellent candidates for genetically-targeted cell and gene therapy. It is our regulatory and commercial market structures that prevent these potential treatments from reaching our community.

Consequently, we have led the neuromuscular disease community in trying to find ways to address these challenges. We launched the MDA Kickstart program that aims to overcome the lack of commercial incentive by bridging the translational gap between early academic science and commercial drug development and leveraging regulatory incentives like the Rare Pediatric Disease Priority Review Voucher program, to help to de-risk gene therapy programs enough to

bring them over the threshold for profitability.[1] Through our Advocacy Collaboration Grants Program we have funded collaborators to develop a roadmap for n-of-1 therapy coverage and reimbursement.[2] We have also actively participated in the Somatic Cell Gene Editing Consortium, which addresses key challenges in the development and access of next-generation genetic therapies for rare diseases.

It has become abundantly clear that a new FDA regulatory and approval framework for individualized therapies is sorely needed, and why a new pathway is welcomed. This Draft Guidance and the proposed Plausible Mechanism Framework is a big step in the right direction, and we are incredibly grateful to the Agency for proposing this approach. Still, rare disease resources are limited, so ambiguity can lead to sponsors overspending on unnecessary studies or delaying critical studies. We strongly support development efforts for individualized therapies for NMDs, but additional clarity is required to reduce development and regulatory uncertainties around operationalizing the framework and truly delivering on its promise to the ultra-rare neuromuscular disease community. Below are our suggestions to the Agency on ways to strengthen its proposed approach.

Background and General Considerations:

MDA requests the Agency consider the following additions and revisions to the Framework for it to better serve the ultra-rare neuromuscular disease community. First, FDA should clarify which diseases may qualify for this new pathway. While the draft guidance states that this pathway is intended to build upon existing rare disease approaches, public statements by FDA officials have expressed openness to this applying to common disease treatments as well.

Furthermore, many NMDs are monogenic but may not meet the severely debilitating or life threatening (SDLT) threshold (such as Charcot-Marie Tooth disease, facioscapulohumeral dystrophy, and certain myopathies). FDA should elaborate on how this framework can apply across the broader rare disease spectrum, including conditions with slower progression and substantial morbidity or how flexibility may vary across different disease severity tiers. Greater clarity on which diseases qualify for this framework and which do not is needed.

The Draft Guidance would also benefit from a discussion of how individualized therapies that may qualify for this pathway apply across heterogeneous populations of rare diseases, including whether scalability expectations differ between ultra-rare mutations versus mutation clusters within the same disease. We also ask the Agency to clarify how mechanistic certainty interacts with clinical uncertainty in small N trials, particularly where strong mechanistic evidence can compensate for low statistical power in clinical endpoints.

Regulatory:

We encourage greater clarity within the Draft Guidance on the expectations for demonstrating substantial evidence of effectiveness. The document discusses when one trial plus confirmatory evidence is warranted, and when external controls for the single trial may be appropriate. Still, in

[1] For more on MDA's Kickstart program, please visit: https://www.mda.org/research/kickstart
[2] For more, please visit: https://www.cureraredisease.org/archived/resources/whitepapers

truly n-of-1 diseases in which any trial may treat the entire population living with the disease thus fully obviating the promise of any commercialization, alternatives are necessary.

In the Draft Guidance, FDA states,

> "if the effect of a treatment is dramatic or self-evident, occurs rapidly following treatment, and is unlikely to have occurred spontaneously, it may be acceptable in some situations to compare a change from baseline to an estimate of what would have happened to the patient in the absence of the treatment with the intervention. This estimate may be based on available natural history data, general knowledge of the disease, or the baseline lead-in period."

This is one alternative approach that we envision will be critical to many SDLT ultra-rare neuromuscular diseases using this pathway. Greater discussion on when this approach can be used rather than a well-controlled clinical study would be helpful.

Nonclinical:

MDA recommends that the Agency consider several revisions and additions to the nonclinical discussion within this draft. First, greater clarity is needed on what constitutes sufficient nonclinical evidence to support human studies, including expectations around the effect (ex. editing efficiency, splicing correction, functional change) and reproducibility across independent systems. This clarity will be critical to efficient and affordable development in academic and other low-resource settings where many, if not most, n-of-1 therapeutic development is occurring.

We encourage FDA to further define whether nonclinical evidence should demonstrate biological activity, functional rescue, and/or disease-relevant phenotypic improvement, particularly in NMDs where full phenotypic correction may not be feasible. While much of this is understandably disease and product specific, those who are developing these nonclinical models will need greater clarity on what they are striving to demonstrate, and what is sufficient for the agency.

We appreciate the Agency's intentional move away from animal testing and towards new approach methodologies (NAMs). It is well known within neuromuscular diseases that animal models may not recapitulate human NMD pathology. However, NAMs (such as organoids and patient-derived cells) may have variability or limited physiological relevance. FDA should clarify how to prioritize or integrate evidence across systems when results are discordant (since literature can be used to establish mechanistic disease evidence). FDA should provide clearer guidance on when surrogate systems (ex. iPSC-derived muscle or neuronal cells) are sufficient versus when more physiologically relevant models are required—particularly for assessing potency, immunogenicity, and biodistribution. In addition, expectations for reproducibility should be defined, including consistency across platforms, laboratories, and donor samples, especially in the context of individualized therapies.

We similarly request greater clarification on suggested approaches to biomarkers particularly when indirect biomarkers (such as circulating plasma-based markers) are acceptable and how multi-modal biomarkers (molecular, imaging, functional, digital) can be integrated to support the plausible mechanism. This will further assist development efforts in neuromuscular diseases in which empirical and definitive clinical findings may be difficult to capture.

MDA envisions, at times, that nonclinical programs must be expanded to better capture the data and findings needed to move into the clinic. We request that the Agency identifies clear inflection points that will point to a need for additional toxicology studies based on emerging risk signals or mechanistic uncertainty. This guidance will help our researchers, clinicians, and biotechnology developers more independently predict when additional toxicology studies will be needed.

Finally, for scalable individualized therapies, FDA should clarify which attributes must be re-evaluated per variant, including off-target risk, potency, immunogenicity risk and biodistribution. This will be particularly important in the ultra-rare genetic neuromuscular diseases in which a platform delivery mechanism can be used carrying varying transgenes (or other genetic interventions) for different genetic subpopulations.

Clinical:

MDA is grateful for the Agency's guidance on the clinical expectations when utilizing the plausible mechanism framework. Similar to other sections of the Draft Guidance, we encourage FDA to offer prospective developers with greater guidance and clarity.

First, greater clarity from the Agency would be helpful on the evidentiary threshold at which biomarker-driven outcomes may substitute for or reduce reliance on traditional clinical endpoints in ultra-rare populations. While we now have decades of experience in applying this threshold under the accelerated approval pathway, additional information on if or how this may differ in the plausible mechanism framework would be helpful.

We also ask that the FDA consider the role of natural history data within using this pathway. Natural history data is critical to understanding and developing therapies for NMDs due to the slow, variable, and often age-dependent progression. Yet most of the ultra-rare n-of-1 populations for which the plausible mechanism framework may be most promising may not have the "well-characterized natural history in the untreated population" that the Agency may be looking for. FDA should offer greater clarity on what natural history data will be needed for a bespoke genetic therapy to use the plausible mechanism framework. FDA should also clarify how such data should be used to contextualize treatment effects and distinguish therapeutic impact from disease variability.

Long-term durability of potential interventions is particularly important in chronic NMDs. FDA should clarify expectations for duration of follow-up needed to establish durable molecular and functional effects. The Agency should also specify how the durability of biomarker or molecular correction should be weighted in benefit-risk assessments relative to short-term clinical

outcomes. These time-scale expectations, particularly on the long-term clinical, functional, biomarker, and molecular effects, deserve further exploration from the Agency.

Finally, we always encourage the Agency to utilize real-world evidence (RWE), patient experience data, and patient preference information in all its regulatory pathways. To what extent can these patient-derived data contribute meaningful evidence, including natural history evidence, to support a plausible mechanistic pathway, particularly in ultra-rare patient populations?

CMC:

The chemistry, manufacturing, and control (CMC) of prospective bespoke therapies approved via the plausible mechanism framework is critically important to the safety and effectiveness of the product. Given the unique nature in which these products may be approved and administered, the CMC aspects of this pathway deserve a unique approach as well.

MDA urges the Agency to consider flexibilities in how products approved through this pathway will be manufactured. FDA states, "multiple aspects of the commercial manufacturing process should be considered when developing the manufacturing process to support the initial IND (e.g. scale, validation, commercial feasibility, etc)". But commercial manufacturing may be out of reach for many individualized therapy development efforts. To begin with, most contract development management organizations (CDMOs) may only create 200 to 500 liter batches for cell and gene therapies. Some of the more specialized CDMOs that focus on these treatment modalities may make 50 liter batches, but for an n-of-1 therapy, only a liter or two of product may be warranted, and a 50 liter batch would be far too expensive and wasteful. This may place commercial manufacturing out of reach for most academic developers or small biotechnology companies, thus locking them out of the plausible mechanism framework.

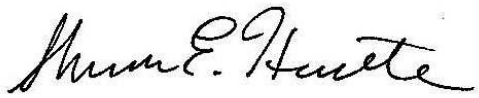
We encourage the FDA to approach this paradigm flexibly and consider ways in which academic developers can still meet FDA's manufacturing standards without requiring large commercial batches of product.

Other Considerations:

MDA strongly supports and is grateful for FDA's encouragement of data sharing within this Draft Guidance. Sharing data in ultra-rare NMDs is paramount to successfully developing treatments for these complex and understudied diseases. MDA is proud to share the data obtained through our NeuroMuscular ObserVational Research (MOVR) Hub with many partners in the neuromuscular disease space, and we appreciate the Agency's encouragement.

We are grateful for the opportunity to comment on the FDA's draft Plausible Mechanism Framework. For questions regarding MDA or the above comments, please contact Paul Melmeyer, Executive Vice President, Public Policy and Advocacy at pmelmeyer@mdausa.org

Sincerely,



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