



May 5, 2023

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

**Re: FDA-2023-N-1190-0001: Cellular, Tissue, and Gene Therapies Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments**

Dear Members of the Cellular, Tissue, and Gene Therapies Advisory Committee,

In service of the neuromuscular disease patient community, including individuals with Duchenne muscular dystrophy (DMD), the Muscular Dystrophy Association (MDA) thanks you for the opportunity to submit comments on the May 12<sup>th</sup>, 2023 proceedings of the Cellular, Tissue, and Gene Therapies Advisory Committee (the "Committee") as it discusses delandistrogene moxeparvovec intended for use by ambulatory individuals with DMD with a confirmed mutation in the DMD gene.

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. We serve all individuals with neuromuscular diseases, including DMD, in a variety of ways including advocating for the accelerated development of more and better therapies for the neuromuscular disease patient population.

MDA does not participate in product-specific advocacy, and thus will not make a specific recommendation on this treatment. With several therapies approved by the Food and Drug Administration (FDA or "Agency") each year for neuromuscular diseases, plus hundreds more in the therapeutic pipeline, MDA simply cannot evaluate the incredibly complex justifications for any specific regulatory action, including approval, for each of these therapies to make comprehensive endorsements on regulatory action.

Instead, MDA channels the neuromuscular disease community's desire for more and better therapies into recommendations for systemic cross-therapeutic approaches the Agency should employ when regulating the development and potential approval of neuromuscular disease therapies. The following outlines flexible regulatory approaches we expect the FDA and this Advisory Committee to utilize when considering this and all rare neuromuscular disease therapies.

## **Utilization of the Accelerated Approval Pathway:**

First, we encourage the FDA to liberally and flexibly utilize the accelerated approval pathway for neuromuscular disease treatments as NMDs are often slowly progressive diseases in which clinical benefit cannot be accurately captured within the traditional time period of a randomized, placebo-controlled clinical trial. Consequently, without the accelerated approval pathway, some treatments for NMDs, including gene therapies, may take years longer to prove clinical benefit, if pursued at all, thus delaying or denying effective treatments for serious, unmet needs for populations that desperately need them. Most neuromuscular diseases, including DMD, are irreversible in their progression (at least with the current science of muscle degeneration) and consequently the muscle damaged and lost while waiting for new therapeutic approvals cannot be regained upon later approval of the therapy.

As Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research (CBER) recently stated at MDA's Clinical and Scientific Conference, saying "For many rare diseases, we just won't get there in a timely manner using our current approach.....We can't be so careful about our approvals under accelerated approval that we prevent potentially lifesaving therapies from getting to market in a timely manner."<sup>1</sup> We fully agree with Dr. Mark's assertions and encourage the FDA and this Advisory Committee to consider this approach.

Furthermore, many neuromuscular diseases are caused by single-gene mutations resulting in the absence, dysfunction, or deficiency of key proteins necessary for neuromuscular functioning. Gene therapies hold the promise of the ability to supplement or replace these missing or dysfunctional proteins by increasing the amount of functional proteins within the cell. Already gene therapy has proven successful in spinal muscular atrophy, and MDA is confident that gene therapy will eventually prove safe and effective not only in Duchenne muscular dystrophy, but also limb-girdle muscular dystrophy, Pompe disease, Friedreich's Ataxia, and more.

If these gene therapies show increased levels of the key missing or dysfunctional proteins at the cause of these neuromuscular diseases, these protein levels are prime candidates to serve as surrogate endpoints that reasonably predict clinical efficacy within these neuromuscular diseases, thus opening the accelerated approval process to neuromuscular disease gene therapies and greatly accelerating access to life-altering, potentially life-saving treatments.

Finally, we understand many have expressed concerns that the accelerated approval pathway has been abused by companies that substantially delay or even avoid conducting confirmatory trials to confirm effectiveness. While we do not believe these concerns are entirely unfounded, we are confident that with the recent reforms to the accelerated approval pathway passed into law by Congress, FDA now has the authority to require confirmatory trials to occur in a much more timely manner, and MDA supports the FDA using this authority.

We encourage the FDA and this Advisory Committee to consider the liberal and flexible use of the accelerated approval pathway as it considers gene therapies for rare neuromuscular diseases.

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<sup>1</sup> Peter Marks, MD, PhD. (2023, March 20). Realizing the Promise of Gene Therapy. MDA Clinical and Scientific Conference. Dallas, Texas, U.S.A.

## **Regulatory Consistency Across the Agency:**

MDA urges the FDA and this Advisory Committee to be as consistent as possible on its regulatory decision making as they consider new treatments for rare neuromuscular diseases. Despite concerted efforts to create greater transparency, coordination, and consistency across review divisions and medical centers when implementing expedited approval pathways, assessing substantial evidence of effectiveness, and utilizing regulatory flexibility to consider approving new therapies, we still hear frustration from the biopharmaceutical industry and patient community that the same statutes, regulations, and guidances are implemented differently across divisions and centers.

We urge the FDA and this Advisory Committee to consider how flexible approval mechanisms have been used in DMD and all neuromuscular diseases as it considers approval of this therapy, and to strive for a consistent approach with decisions already made by the Agency.

## **Considering the Unique Risk/Benefit Calculus of the Community:**

As the FDA and this Advisory Committee considers the merits of this and any biologics licensing application (BLA) for a new treatment for a neuromuscular disease, we urge the FDA and this Advisory Committee to consider the unique risk/benefit calculus the DMD or any other neuromuscular disease community may use when weighing the risks and benefits of the treatment.

Perhaps most applicable, [recent studies have evaluated the risk tolerance of the DMD community when considering non-curative gene therapies](#).<sup>2</sup> We implore the FDA and this Advisory Committee to review the findings of this and other relevant publications to better understand the risk/benefit calculus of members of the DMD community.

Finally, several individuals with DMD, their loved ones, and their advocates (including MDA) will be testifying during the Open Public Hearing portion of the May 12<sup>th</sup> Advisory Committee hearing. We ask the FDA and Committee members to pay close attention to the thoughts and viewpoints of community members as they testify.

## **Flexible Approaches to Approving Rare Disease Treatments**

Finally, the FDA has a well-established record of approving treatments for serious and life-threatening rare diseases without the standard level of proof of effectiveness required in more common or less serious diseases. Analyses have shown that at least two-thirds of rare disease drug approvals are done so by the Agency flexibly considering whether the effectiveness evidence is adequate. These flexibilities have been reiterated by Congress in the three most recent user fee reauthorizations, and consistently supported by patients, their loved ones, the organizations that serve them, their clinicians, and their elected officials.

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<sup>2</sup> Peay HL, Fischer R, Mange B, Paquin RS, Smith EC, Sadosky A, Russo L, Ricotti V, Rensch C, Morris C, Martin AS, Ganot A, Beaverson K, Mansfield C. Patients' and caregivers' maximum acceptable risk of death for non-curative gene therapy to treat Duchenne muscular dystrophy. *Mol Genet Genomic Med*. 2021 May;9(5):e1664. doi: 10.1002/mgg3.1664. Epub 2021 Mar 23. PMID: 33755338; PMCID: PMC8172191.

Developing treatments for rare neuromuscular diseases presents unique challenges that must be addressed with the aforementioned flexibilities. Once again, we are asking the FDA reviewers and this Advisory Committee to remember these flexible approaches already put forward by the Agency when evaluating this and all new potential treatments for DMD and rare neuromuscular diseases.

We are grateful for the opportunity to comment on the Committee's May 12<sup>th</sup>, 2023 proceedings. For questions regarding MDA or the above comments, please contact me at 202-253-2980 or [pmelmeyer@mdausa.org](mailto:pmelmeyer@mdausa.org).

Sincerely,

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

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