April 3, 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 "Opportunity for Public Comment on Rare Disease Educational Materials from the Center for Drug Evaluation and Research's Accelerating Rare disease Cures Program and the Rare Disease Innovation Hub - Docket No. FDA-2026-N-1584-0001

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 "Rare Disease Educational Materials from the Center for Drug Evaluation and Research's Accelerating Rare disease Cures Program and the Rare Disease Innovation Hub".

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.

Neuromuscular disease therapeutic development is inherently challenging and complex. All neuromuscular diseases under MDA's umbrella are rare diseases with the vast majority ultra-rare diseases with zero FDA-approved therapies. FDA's LEADER 3D and Rare Disease Innovation Hub programs are particularly salient to accelerating therapeutic development and regulatory review for prospective NMD therapies. We are pleased to provide comments and feedback on the initiatives' existing programs and offer suggestions of other resources to consider when building these two programs.

Feedback on Existing LEADER 3D Educational Materials:

The relevance, clarity, and effectiveness of existing LEADER 3D educational materials: We believe the existing LEADER 3D educational materials are relevant, clear, and effective in delivering their message. The short and animated nature of the videos make them easy to digest and understand. One approach to strengthen all the videos to consider is to add FDA leadership voices to the videos to give their message greater weight.

We also suggest that FDA act quickly to update the videos if they potentially become out of date. For example, "Video 1: Challenges, Strategies, and Regulatory Considerations for the Design of Rare Disease Clinical Trials" highlights how two pivotal clinical trials are the standard approach to proving substantial evidence of effectiveness where recent FDA announcements have pivoted the default approach to one clinical trial plus confirmatory evidence.[1] "Video 1" could also be accompanied by a checklist for evaluating if your disease or prospective therapy may be able to rely on a single trial plus confirmatory evidence rather than two clinical trials. Finally, patient advocacy organizations would be well served to have a version of this video specifically tailored to them, including suggestions on who to approach within the Agency to commence conversations on this topic rather than offering a blanket "please talk to the FDA early" suggestion.

"Video 2: Understanding Endpoints in Rare Disease Drug Development" is very topical for rare disease patient advocacy organizations and would benefit from more information on how to validate a biomarker to become a surrogate endpoint, a challenge most patient advocacy organizations want to tackle but have difficulty knowing how to do so. Many programs are mentioned and cited within this video that could potentially benefit from their own video explainers. For example, the Rare Disease Endpoint Advancement (RDEA) pilot program could be well explained using a similar format.

Similar to Video 1, "Video 3: Considerations for Collecting/Using Natural History Data Fit for Use in the Regulatory Setting" would also benefit from a checklist on how to ensure natural history data can be later used as a historical control. One such suggestion could include ensuring the endpoints collected via natural history data collection align with current and potential future clinical trials.

Finally, the case studies are excellent and are very helpful in illustrating the FDA's thoughts and interpretations through the "FDA Guidance Corner" blurbs. Also very helpful are the "critical thinking questions" that assist the reader in looking at the issue at hand through their own disease or disease area's lense.

<u>Suggestions for additional topics or formats for potential future materials that would further support rare disease drug development:</u> There are several additional topics or formats we believe FDA should explore to grow the LEADER 3D program. These include:

1. Videos explaining specific guidance documents: For example, the recently published Plausible Mechanism Framework would greatly benefit from a 5-minute pithy video explanation such as the others published already.
2. Consider case studies of efforts that did not end up succeeding and what we can learn from those efforts.
3. An additional topic for future materials could be a decision tree (presented in video or other formats) on who a patient advocacy organization should contact within FDA regarding specific opportunities. For example, if a patient advocacy organization is interested in a pre-clinical meeting to discuss endpoints for their disease, or if they are

[1] Prasad V, Makary MA. One Pivotal Trial, the New Default Option for FDA Approval — Ending the Two-Trial Dogma. N Engl J Med. 2026 Feb 19;394(8):815-817. doi: 10.1056/NEJMsb2517623.

interested in convening an externally-led patient focused drug development meeting, a decision tree would be helpful in guiding the organization on who to approach.

4. Alternative formats such as regulatory path web tools or playbooks could be explored. A developer could input their particular modality (gene therapy, small molecule, etc), population size (n-of-1, ultra-rare, rare, etc), and other key factors, and then examples or outputs on the likely path towards approval with a checklist are generated.
5. An "ask the experts" or FAQ where therapeutic developers can ask questions and the FDA answers them could illustrate to the public some of the complexities of therapeutic development.

All of these options would broaden the Agency's educational programming for rare disease stakeholders, and would help fill gaps in knowledge currently existing in many communities.

Rare Disease Innovation Hub: Educational Resources for Patients and Patient Organizations

Existing educational resources intended for patients and patient organizations that relate to rare disease product development: Below is a short list of resources available to patients and patient organizations relating to rare disease drug development:

- The National Center for Advancing Translational Sciences (NCATS) has a toolkit for Patient-Focused Drug Development (https://ncats.nih.gov/research/research-resources/ncats-toolkit)
- The Critical Path Institute has collected a webinar series on Patient-Focused Drug Development – (https://c-path.org/category/webinars/)
- Global Genes has a RARE University – courses for understanding drug development / data (https://globalgenes.org/learn/rare-university/)

Areas of rare disease product development where desired educational resources for patients may not exist: The following are areas of rare disease drug development where greater educational resources are warranted:

- The Plausible Mechanism Framework – patient organizations and their communities need more plain language education on what this framework will entail
- Platform technologies and their role in drug development and regulatory approval
- Innovative trial designs: educational resources on basket trials, umbrella trials, platform trials, and more would be helpful
- Incorporating decentralized trial operations like digital health tools (DHTs) and data: educational resources on where and how DHTs can be incorporated would be helpful
- The difference between the U.S. regulatory scheme administered by the FDA and the schemes of other jurisdictions, such as Europe's EMA.

Rare Disease Innovation Hub: Educational Resources Intended to Support Developers Engaged in Rare Disease Biologics Development:

The Accelerating Medicines Partnerships (AMP) Bespoke Gene Therapy Consortium Regulatory Playbook (https://bgtcplaybook.document360.io/) is an excellent resource for gene therapy development. Further needs for educational resources in biologics development include;

- Resources on "N-of-1" or "N-of-few" – transitioning an individualized therapy to a commercial developer.
- Gene therapy and high-cost biologics – communicating with payors on an FDA approval, including the indication, the label, and how to interpret FDA's decision.
- Greater explanation on new approach methodologies (NAMS) – what is acceptable and what still may not be acceptable by the Agency?

We are grateful for the opportunity to comment on the FDA's LEADER 3D and Rare Disease Innovation Hub's educational offerings. 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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Muscular Dystrophy Association