



October 28, 2021

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

Re: FDA-2021-N-0891: Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments

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 proposed recommendations for the reauthorization of the Prescription Drug User Fee Act (PDUFA). We are grateful for the Agency’s open and transparent opportunities for patient advocacy stakeholders to participate in this significant discussion.

MDA is the nation’s leading nonprofit organization dedicated to transforming the lives of individuals living with neuromuscular diseases through innovations in science and innovations in care. MDA fulfills its mission by funding biomedical research, providing access to expert clinical care and support through its national MDA Care Center Network, and by championing public policies and programs that benefit those we serve. Since inception, MDA has invested more than \$1 billion in research grants to accelerate treatments and cures for neuromuscular disorders, making MDA the largest source of neuromuscular disease funding in the U.S. outside of the federal government.

While substantial progress has been made in the research and development of therapies for NMDs, much need remains. Only a handful of the over forty NMDs under our umbrella have an FDA-approved treatment, leaving the remaining NMD communities still waiting for their first treatment. For those disorders where a therapy is currently available to patients, the treatment may be unsatisfactory, or limited to a subset of patients who demonstrate a specific genetic mutation that would be amenable to the intervention.

Consequently, FDA’s regulatory approach to neuromuscular disease therapeutic development is critical to the NMD community obtaining more and better treatments. PDUFA reauthorization offers MDA and the NMD community an opportunity to contribute our viewpoints to how FDA can better meet the needs of our community. Therefore, we are pleased to provide comments on the proposed recommendations for the reauthorization of the PDUFA program.

Overall, we are pleased with, and supportive of, the proposed recommendations as many of the proposals we put forward in August 2020 for consideration are reflected in the proposal.¹ Consequently, we support this proposal as we expect, if enacted, for it to meaningfully accelerate the development and review of better targeted treatments for NMDs. While supportive of the agreement, we also offer further suggestions for additional interventions to be included in final enactment of this reauthorization.

Our comments follow the structure of the proposed “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027” (Goals Letter) and provide MDA’s feedback and commentary on each of the proposals potentially most impactful to the neuromuscular disease community.

Split Real Time Application Review (STAR) Pilot Program

In our August 2020 comments to FDA, we called for “taking the ‘O’ out of Real-time Oncology Review (ROTR) and expanding this Oncology Center of Excellence (OCE) pilot program to all therapeutic areas, particularly neurology and rare diseases.

MDA is grateful to support the creation of the Split Real Time Application (STAR) Pilot Program, a new expedited review option modeled after OCE’s RTOR. While the program would likely only apply to a small minority of potential new treatments for neuromuscular diseases (the program is limited to only efficacy supplements for existing therapies, and the application must be comparatively straightforward and noncomplex), this pilot could substantially shorten the review time necessary to approve such new uses of existing medications.

We know there are multiple existing FDA-approved therapies that may be safe and effective in neuromuscular diseases but have not yet been approved for such uses by the Agency. Two FDA-approved treatments for non-neuromuscular diseases have been subsequently approved for the neuromuscular conditions myasthenia gravis and dermatomyositis. These are success stories of repurposing existing therapies into beneficial treatments for the neuromuscular community, but unfortunately, they are rare examples of such success.

Consequently, we hope the STAR program will remove unnecessary hurdles in reviewing and approving subsequent neuromuscular disease indications for existing safe and effective therapies. We thank the Agency and industry negotiators for the inclusion of this pilot program in the Goals Letter and look forward to the pilot’s success.

Expedited Approval Pathway Improvements

MDA is pleased to see several improvements and refinements to existing expedited approval pathways included within the Goals Letter. First, we are pleased to see the continued commitment to the Breakthrough Therapy Program. This program, which continues to find its

¹ “MDA Comments on PDUFA Reauthorization” (August 23, 2020), Retrieved October 28, 2021, from: <https://cqrcengage.com/mda/file/V8HnUH2T9P9/08.23.2020%20MDA%20Comments%20on%20PDUFA%20Reauthorization.pdf>

footing outside of Oncology, is instrumental to accelerating development and review of innovative neuromuscular disease treatments.

Second, we are particularly supportive of the greater attention paid towards early consultation on the use of innovative biomarkers as surrogate endpoints. Only a handful of neuromuscular diseases, such as Duchenne Muscular Dystrophy, have an established surrogate endpoint leaving nearly all neuromuscular diseases without a well-established biomarker to serve as a surrogate endpoint within clinical trials. Consequently, neuromuscular disease clinical programs are locked out of the accelerated approval pathway (as most are similarly unable to utilize an intermediate efficacy endpoint), leading most development programs to rely on antiquated and difficult-to-measure clinical endpoints.

Greater attention from the Agency on assisting sponsors in developing, establishing, and perhaps even validating innovative biomarkers as surrogate endpoints could greatly accelerate therapeutic development in neuromuscular diseases.

Advancing Development of Drugs for Rare Diseases

All neuromuscular diseases that fall under MDA's umbrella are rare diseases, many of which are considerably rare or "ultra-rare". Consequently, the provisions of the Goals Letter pertaining to programs for rare diseases are particularly salient to our community.

First, we support the continued dedication of the Rare Diseases Staff to training and educating reviewers across the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) on the unique issues and challenges of developing and approving a rare disease therapy. We also support their continued interaction and involvement with outside stakeholders, including the neuromuscular disease community.

Second, we are particularly pleased to support the creation of the Rare Disease Endpoint Advancement (RDEA) Pilot Program. This pilot program aims to address one of the greatest challenges in rare disease drug development: the lack of a well-established efficacy endpoint to use within clinical studies on small, heterogenous patient populations.

Perhaps nowhere else than in neuromuscular diseases is the lack of well-established and meaningful efficacy endpoints more apparent and deleterious to therapeutic development. For far too long, the antiquated six-minute walk test has been used in Duchenne Muscular Dystrophy, Pompe disease, and other neuromuscular diseases. Not only does this endpoint exclude non-ambulatory patients from these trials, but the community continues to decry the six-minute walk test as particularly poor in capturing truly meaningful outcomes. Similarly, the ALS community continues to emphasize the inadequacy and imprecision of the ALS Functional Rating Scale (ALSFRS) as a primary efficacy endpoint. The Charcot-Marie-Tooth, Limb-Girdle Muscular Dystrophy, and other communities similarly raise concerns with the inadequacy of the efficacy endpoints commonly used within their clinical trials.

We are hopeful that the RDEA Pilot Program, while limited, can present a first step towards better efficacy endpoints for neuromuscular diseases, particularly those who are non-ambulatory.

The pilot will only include a handful of rare diseases, so we are hopeful that at least one of these will be a neuromuscular disease with an antiquated endpoint. For those diseases that are not included in the pilot, we hope the three public workshops held by the program will help advance innovative efficacy endpoint development.

Advancing Real-World Evidence for Use in Regulatory Decision-Making

We support the Goals Letter provision that builds upon existing efforts to facilitate the use of real-world evidence (RWE) in regulatory decision making by expanding the Advancing RWE Program to grow FDA's role in the collection of regulatorily actionable RWE. FDA has already put forward guidances on how to collect RWE, and most recently, ensure the RWE is regulatorily actionable.

However, this pilot would take this effort even further by creating a partnership between FDA, regulated industry, and relevant stakeholders to collaborate on creating the appropriate structures and approaches to collecting regulatorily actionable RWE. While this pilot will be limited in scope, the lessons from the effort, plus the accompanying public workshops and updated draft guidances will hopefully bring clarity and direction to all stakeholders hoping to collect and submit RWE as part of a regulatory submission.

This could be particularly relevant to MDA as our Neuromuscular Disease Observational Research (MOVR) Data Hub is already collecting clinician-report outcomes (ClinRos) on seven neuromuscular diseases. If partnered with ongoing therapeutic efforts, MOVR could complement such efforts with RWE that could accompany regulatory submissions in ways instructed by the Advancing RWE program. We are particularly eager to partner with FDA and regulated industry to make this a reality, and we see this provision as taking us even closer to this possibility.

Enhancing the Incorporation of the Patient's Voice in Drug Development and Decision-Making

We are pleased to see the Patient-Focused Drug Development (PFDD) initiative continue to evolve and grow under this agreement. In our August 2020 comments, we asked that FDA 1) continue to expand its PFDD efforts, 2) allow externally-led PFDD meetings to continue, 3) consider funding mechanisms to lower the cost of collecting patient-experience data (PED) and patient preference information (PPI) for non-profit organizations, and 4) expand its clinical outcome assessment (COA) efforts. We are grateful to see several of these requests, and more, fulfilled within the Goals Letter.

First, the Goals Letter will allow for externally-led PFDD meetings to continue, an important opportunity for neuromuscular disease communities to educate the FDA on what its like to live with a neuromuscular disease. The effort to "develop a virtual catalog of standard core sets of Clinical Outcome Assessments (COAs) and Related Endpoints" will continue as well, hopefully including additional neuromuscular diseases not already included in the program.

Second, the Goals Letter details further efforts to make the PED and PPI collected as part of the PFDD initiative regulatorily submittable. As part of the agreement, FDA will publish "draft

guidance on use and submission of patient preference information to support regulatory decision making”. We hope this draft guidance will offer the clarity needed for outside stakeholders to ensure their efforts to quantify the patient voice can meaningfully inform regulatory decision making.

Finally, the Goals Letter also outlines the efforts FDA will undertake to ensure review staff are well-trained on methodologies for incorporating PPI and PED into regulatory decision making.

It has long been MDA’s goal for patient-derived data to meaningfully contribute to regulatory decision making in neuromuscular diseases, and we are hopeful that these provisions take us much closer to this reality. We are eager to participate in these programs if enacted.

Enhancing Capacity to Review Complex Innovative Designs

Therapeutic developers often must be creative when constructing clinical trial designs for rare, sometimes ultra-rare, severe heterogeneous neuromuscular diseases. The continuance and expansion of the Complex Innovative Trial Designs program will further facilitate the establishment of innovative Bayesian and other novel statistical approaches to measuring the safety and effectiveness of neuromuscular disease drugs in innovative trial designs.

We similarly support the expansion of the program, and the dissemination of lessons learned from the program to the stakeholder community in the form of case studies, public workshops, and draft guidances. We hope these program enhancements detailed in the Goals Letter will make the program more attractive to potential participants and will increase understanding and eventual usage of innovative clinical trial approaches.

Enhancing CBER’s Capacity to Support Development, Review, and Approval of Cell and Gene Therapies

Finally, our biggest priority for the PDUFA VII agreement was to ensure the CBER review staff responsible for gene and cell-based therapies had the requisite resources and expertise to keep up with the number and complexity of gene and cell-based therapies submitted for regulatory review and approval. We are pleased to see the needed investment to ensure gene therapies are reviewed thoroughly yet expeditiously provided within this agreement.

Gene and cell-based therapies represent the future of neuromuscular medicine. With one gene therapy already on the market for a neuromuscular disease (Zolgensma for spinal muscular atrophy), there are many more in the pipeline for Pompe disease, x-linked myotubular myopathy, limb girdle muscular dystrophy, Friedreich’s Ataxia, ALS, and more. The community routinely expresses excitement and anticipation for potential gene therapy advancements within their disease.

That being said, we will also hear uncertainty from our community about the potential adverse effects that can accompany gene therapy, often associated with immunogenicity concerns, off-target effects, and more. Consequently, the Patient Focused Drug Development meeting on gene therapy commissioned by this agreement will hopefully better instruct FDA on how to approach

the benefit/risk calculations those with neuromuscular diseases undertake when considering whether to pursue a gene therapy.

Further enhancements detailed in the Goals Letter are also welcome. The public/private partnerships formed to foster discussion and understanding of the novel aspects of gene and cell-based therapies will be instructive, as will the draft guidance on evaluating efficacy in small gene therapy clinical trials and the public meeting on post-approval long-term follow up using real-world evidence and data registries. We are grateful that regulatory approaches to individualized therapies are included as a focus of the public/private partnership.

In aggregate, we believe the provisions addressing gene and cell-based therapeutic development, review, and approval will accelerate the pace at which gene therapies reach our community.

Enhancing Use of Digital Health Technologies to Support Drug Development and Review

As a necessity brought about by the COVID-19 pandemic, many clinical trials had to alter their structure to adopt the features of decentralized clinical trials conducted from a participant's home or local clinic. Many in the neuromuscular disease community face immense difficulties traveling to and from academic medical centers and other often distant locations to participate in clinical trials. Decentralized clinical trials allow the neuromuscular disease community to contribute to ongoing clinical research while potentially improving their own health, all from the comfort of their own home or community.

We are pleased to see FDA and regulated industry agreeing to the next steps in the development and validation of digital health technologies. These tools are necessary to capture the requisite trial data from the home or community of the trial participant. We hope the enhancements in this area will further encourage the Agency and sponsors to employ decentralized clinical trials, particularly in the neuromuscular disease community.

Additional Proposals for Consideration:

While MDA is supportive of the agreement and many of the provisions within, we believe there are additional enhancements that could still be considered, either as part of the Goals Letter or added to the agreement as part of legislative consideration and enactment.

Incorporating the Patient Voice: First, we believe further efforts can be undertaken to incorporate the patient voice into regulatory decision making. We are still concerned about the lack of resources available to small, rare disease communities to collect PPI and PED in the rigorous ways suggested by FDA. With further efforts to actually incorporate such data into regulatory decision making, it is all the more important to increase efforts to assist these communities. We would ask for greater attention being paid towards ensuring the ongoing efforts in PFDD are reaching under resourced communities.

Furthermore, the FDA Patient Representative Program continues to play a key role in providing patient experts to review divisions and Advisory Committees. These patient experts are special government employees who can participate in product-specific, proprietary conversations that no

other patient or community member is able to attend. We need further investment in this program, and the PDUFA agreement is exactly where such an investment should be undertaken.

Disease-specific Guidances: Second, we ask for further enhancements in the process undertaken by FDA to review and publish disease-specific guidances. These guidances have been instrumental in accelerating drug development in Duchenne Muscular Dystrophy and ALS, and could be beneficial in additional neuromuscular diseases. However, we have observed that FDA often lacks the time and resources to subsequently review, edit, and publish draft guidances submitted by the community while simultaneously reviewing product submissions and completing other PDUFA requirements.

We hope the Agency and regulated industry consider adding enhancements to the process by which FDA reviews, edits, and publishes draft guidances for drug development in specific diseases or disease areas.

Project Facilitate: We are grateful that FDA and industry negotiators have agreed to take RTOR, an OCE pilot program, and expand it to all therapeutic areas. However, we see no reason why Project Facilitate, another OCE pilot program, could not similarly be expanded.

Launched in the summer of 2019, OCE's Project Facilitate streamlines the process of interacting with the Agency on requests for expanded access. Project Facilitate provides treating physicians with assistance in navigating the regulatory requirements of providing an investigational product through an expanded access program. Now over two years in existence, Project Facilitate has shown its utility in increasing the number of individuals successfully receiving a product through expanded access; in the program's first three months of existence, expanded access requests processed increased by 20 percent over previous time periods.

We see no reason why Project Facilitate could not be every bit as helpful in neurology, rare diseases, and other areas of the agency. Many individuals in the NMD community are facing life-threatening diseases without access to a clinical trial or alternative adequate treatment options. If made available by sponsors, expanded access can provide one of the best, albeit unproven, opportunities to treating these debilitating conditions. If expanded into other areas of the Agency, Project Facilitate could similarly increase the number of patients successfully utilizing expanded access programs. We strongly encourage FDA and industry negotiators to consider further enhancements to expand Project Facilitate into other areas of the Agency, particularly neurology and rare diseases.

Expedited Approval Pathways: MDA supports the enhancements to the expedited approval pathways included within the Goals Letter, including continued efforts to implement the Breakthrough Therapy Program, the investments in developing promising biomarkers to serve as surrogate endpoints, and the alignment of expedited approval pathways to cell and gene therapy development.

We believe the Agency and industry negotiators can go further by including additional enhancements. In November 2020, we joined with the Friends of Cancer Research and other

regulatory experts to publish a white paper on modernizing expedited development programs.² In the white paper, we called for 1) maximizing the intent of and modernizing expedited programs in the pre-NDA/BLA stage, 2) codifying a process for utilizing expedited programs, and 3) aligning the needs of emerging therapies and complex development programs with expedited approval pathways. Some of these proposals are indeed reflected in the Goals Letter, particularly aligning complex development programs with expedited approval pathways (as is reflected in the gene therapies section of the Goals Letter).

We encourage the Agency and regulated industry to consider further enhancements to the expedited approval programs focused on reducing redundancies across pathways, streamlining the use of multiple pathways at one time, and focusing on earlier use of the pathways in the pre-NDA/BLA stage.

In conclusion, we are grateful for FDA's invitation to offer our perspectives on the proposed enhancements to the PDUFA program as part of the PDUFA VII reauthorization. For questions regarding MDA or the above comments, please contact me at 202-253-2980 or pmelmeyer@mdausa.org.

Sincerely,

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

Paul Melmeyer, MPP
Vice President, Public Policy and Advocacy

² Friends of Cancer Research, “Modernizing Expedited Development Programs” November 2020, Retrieved October 28, 2021 from, https://friendsofcancerresearch.org/sites/default/files/2020-11/Modernizing_Expedited_Development_Programs-2020.pdf