August 23, 2020

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

Re: FDA-2010-N-0128: 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 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 eight of the over 43 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 our priorities for the PDUFA reauthorization.

Ensuring Robust Resources for Gene and Cell Based Therapeutic Reviews

One of our greatest priorities for PDUFA reauthorization is ensuring the negotiated agreement between the FDA and regulated industry adequately funds the Center for Biologics Evaluation

and Research's (CBER) gene and cell-based therapeutic regulatory reviews. Gene therapies represent the greatest hope and possibility for truly transformative therapeutic interventions that significantly slow, perhaps halt, or even "cure" neuromuscular diseases. Already one gene therapy has been approved for an NMD (Zolgensma for SMA) and many more are in the pipeline, including for Duchenne muscular dystrophy (DMD), facioscapulohumeral muscular dystrophy (FSHD), Pompe disease, and more.

While many challenges remain in gene therapy development, including immunogenicity challenges, viral vector manufacturing bottlenecks, and more, limited FDA capacity and resources is a surmountable challenge that can be successfully addressed by a robust investment included within PDUFA. Without such an investment, regulatory review of gene therapies, as well as additional critical advice and guidance offered by FDA experts throughout gene therapy development, could be substantially slowed. Recent estimates by FDA leaders are that the Office of Tissues and Advanced Therapeutics, the FDA office largely responsible for gene therapy reviews, is facing a substantial staffing shortage of medical experts needed to review the upcoming surge in gene therapy development and regulatory reviews.[1]

Consequently, we strongly encourage the FDA and regulated industry negotiators to include a substantial increase in PDUFA-negotiated dollars going towards gene and cell-based therapy reviews to ensure FDA review does not serve as a bottleneck to life-changing, perhaps life-saving, treatments and cures reaching the NMD community.

Expanding Regulatory Guidance and Acceptance of Decentralized Clinical Trials

Traveling to clinical trial sites often far away from home has always been a challenge for those in the neuromuscular disease community. Many individuals with an NMD have mobility challenges that make it very difficult to travel, especially by plane. Many patients have even stopped flying altogether due to the lack of accessible accommodations on airplanes. Many other individuals with neuromuscular diseases are children, making long-distance travel to clinical trial sites even more costly and time intensive as generally the whole family is involved.

Traveling to clinical trial sites has served as a deterrent to participation for many in the NMD community. In a recent survey of the NMD community, when asked about the main impediments to participating in a clinical trial, 29 percent of respondents said that trial sites were too far to travel to.[2] If 29 percent of a rare disease patient population chooses to not participate in a clinical trial due to distance, recruitment for the trial could be severely impacted, potentially substantially delaying trial initiation.

These challenges have only been exacerbated by the COVID-19 pandemic as travel is even more difficult and dangerous for the NMD community, and clinical trial sites may similarly be unsafe

[1] Alliance for a Stronger FDA, Alliance Learns About CBER Priorities for 2020 and Beyond (2020, January 25). Retrieved August 23, 2020, from https://strengthenfda.org/2020/01/25/alliance-learns-about-cber-priorities-for-2020-and-beyond/

[2] ONEVoice: Insights and Observations from a National Survey of Adults and Families Living with Neuromuscular Disease (2018, December 9). Retrieved August 19, 2020, from https://www.mda.org/sites/default/files/2018/12/MDA_OneVoice_Whitepaper.pdf

for high-risk patients to visit. Sites may also close due to focuses on COVID-19 and engaging in high-cost travel is even more difficult to uncompensated patients who may be facing greater financial constraints due to the economic recession.

Consequently, we urge the FDA and industry negotiators to include regulatory approaches to decentralized clinical trials within PDUFA reauthorization. We are aware that policy and regulatory conversations continue within the Agency on establishing more concrete regulatory approaches to decentralized clinical trials, and we are hopeful that FDA guidance may be released prior to PDUFA VII codification. Nonetheless, with an infusion of resources and the power of statutory codification, we believe regulatory approaches to decentralized trials can be more impactfully included within the PDUFA reauthorization process.

The Patient Voice in FDA Programs and Regulatory Approaches

The reauthorization of PDUFA offers stakeholders the opportunity to examine closely the utility of current patient involvement programs at FDA, many of which are operating as intended and others that could be further strengthened. MDA believes patient involvement at the FDA could be further enhanced in the following programs:

Patient-Focused Drug Development: First created as part of the fifth iteration of PDUFA, the Patient Focused Drug Development (PFDD) program has several key facets, all of which have increased the voice of the patient in therapeutic development and regulatory review. We believe each core tenet should continue, and in some cases be developed further, in the next PDUFA reauthorization.

We strongly encourage FDA to allow and facilitate the continuance of PFDD meetings and related efforts over the next PDUFA cycle. Several neuromuscular disease communities have held externally-led PFDD meetings, all of whom have spoken favorably on their experience and the positive effects the meetings had on congregating the community and amplifying patient voices. MDA has also led an externally-led PFDD meeting for Pompe disease and found the experience, as well as the patient viewpoints and data collected, enriching and educational. We hope externally-led meetings will continue under the next reauthorization of PDUFA.

Second, we thank and congratulate FDA on the continued development and dissemination of guidances for the stakeholder community focused on collecting patient experience data (PED) and patient preference information (PPI). These guidances, once disseminated and finalized, will prove invaluable to stakeholders seeking to collect PED and PPI salient to therapeutic development and review.

With these guidances in hand, patient organizations will have a useful toolkit on collecting PED and PPI: yet impediments will remain. Rare disease patient organizations have so many promising efforts to pursue but often scarce resources to pursue them. Therefore, while knowledge and instruction should no longer be a limiting factor, lack of resources will likely remain so. Consequently, under the next PDUFA reauthorization, we encourage FDA and industry negotiators to consider creating an FDA grant program that funds patient organizations, particularly rare disease patient organizations, to collect PED and PPI in accordance with the

published FDA guidance series. Data collected will be unbiased as it will not be tied to any particular therapy's development and will prove invaluable as FDA and other stakeholders seek to understand the disease through quantified patient viewpoints. We urge FDA and industry negotiators to consider such a grant program as part of PDUFA negotiations.

Finally, we encourage FDA to expand its funding efforts in clinical outcome assessments (COAs) in rare diseases. Currently FDA has awarded grants to several efforts seeking to develop COAs in rare diseases, and the program could be expanded to further fund such efforts, particularly in neglected rare diseases and underserved minority populations.

Patient Representative Program: The FDA Patient Representative Program (PRP) provides a unique benefit to the Agency and therapeutic development as patient experts are able to serve as special government employees (SGEs) and, once vetted and approved, consult on proprietary drug development matters other patients are disallowed from advising on due to confidentiality laws.

Unfortunately, the PRP is under-resourced and underutilized. While patient representatives still serve on Advisory Committees providing salient expertise, patient representatives could be much more engaged and participatory in assisting review divisions on divisional assignments with product-specific issues. If able to consult early and often, product development could be substantially benefited by having a patient voice in the room. Furthermore, the PRP is currently staffed by only one full-time employee (FTE). This lack of resources adversely affects proactive recruitment for patient representatives.

We request that as part of PDUFA reauthorization, the FDA and stakeholders commit to an infusion of resources for the FDA Patient Representative Program to allow for the program to be as impactful as possible.

Disease-Specific Guidances: As mandated by the *21st Century Cures Act*, FDA published draft guidance on best practices in developing and submitting externally-submitted disease-specific draft guidances. In neuromuscular diseases, several draft guidances specific to therapeutic development in a neuromuscular disease have been published, most notably in Duchenne muscular dystrophy and amyotrophic lateral sclerosis (ALS).

We believe the FDA process and approach towards disease-specific guidances submitted by external stakeholders should be re-addressed as part of PDUFA reauthorization negotiations. We ask that FDA and industry put structure and resources behind FDA's response to disease-specific guidances. With additional resources in hand, FDA review divisions responsible for responding to such draft guidances will not have to decide between spending time and resources on product reviews and assessing and developing disease-specific guidances. Additionally, setting a timeline and structure around FDA responses to externally-submitted draft guidances would be welcome. Such structure will add predictability and certainty to the process FDA undertakes in digesting and responding to externally-submitted draft guidances.

Statement of Patient Experience: MDA would also welcome further discussion on how the use of the "Statement of Patient Experience" can be expanded. Currently, upon approval, FDA

releases a "Statement of Patient Experience" that identifies what kind of patient-derived data was considered during the product's consideration. While this is certainly a step in the right direction, there are several additional expansions we encourage the FDA and industry negotiators to consider.

First, the Statement of Patient Experience could be streamlined so stakeholders reviewing the Multi-disciplinary Review and Evaluation do not need to go searching through the document to find the referenced section listed in the Summary. Instead, this information could be included in the Statement of Patient Experience itself rather than just citing a section.

Second, while FDA cites what information was considered during the review, there is often little discussion or context on how this information impacted the review. We encourage FDA to consider including such context preferably in the Statement of Patient Experience itself, or at the very least in the relevant section. This will help stakeholders better understand how the PED or PPI they are collecting are impacting FDA reviews.

While minor in nature, we believe these expansions of the Statement of Patient Experience hold utility in better highlighting and understanding the impact of PED and PPI used as part of the evaluation.

Individualized Therapies Regulatory Pathway:

With the science of therapeutic development continuing to evolve, greater attention is being given to individualized or "n-of-1" therapies that are targeted to a specific person. Several examples of such therapies already exist, including Milasen for an individual with Batten's disease and another anti-sense oligonucleotide (ASO) for an individual with ALS. These therapies naturally stretch our regulatory system as the rules and regulations are ill-suited to therapeutic approvals for a single individual.

Currently, expanded access and perpetual INDs are used to allow for the experimental administration of an investigational product for a single individual. But to MDA, this approach does not represent an ethical long-term strategy that reflects the financial realities of developing complex treatments targeting individuals.

Consequently, we urge FDA and industry negotiators to consider including further development of a tailored regulatory approach to individualized therapies. As gene and cell-based therapies continue to accelerate in their evolution, a regulatory pathway for individualized therapies will only become more needed. We encourage FDA and industry negotiators to address these challenges as part of PDUFA VII negotiations.

Expansion of Oncology Center of Excellence Pilot Programs

The Oncology Center of Excellence (OCE) continues to be on the forefront of regulatory innovation by piloting programs to further accelerate and streamline regulatory review of oncology therapies. While there are several innovative pilots ongoing, we envision two particular

programs being ripe for expansion into other areas of the Agency; Real-time Oncology Review and Project Facilitate.

Real-time Oncology Review (RTOR): Launched within the past year, the RTOR program allows OCE to greatly expedite the review of oncology therapies that 1) offer substantial improvements over existing therapies, and 2) the study design is straightforward using well established endpoints. If a therapy qualifies for RTOR, the sponsor can submit data to OCE to consider prior to the submission of the actual new drug application (NDA) or biologics license application (BLA), thus allowing FDA to greatly expedite consideration of the therapy.

Several products have been approved by FDA using RTOR, many of which have taken under one month to conduct, an astoundingly expedited review timeline.[3] While many neuromuscular disease products would likely not qualify for an expanded real-time review program due to complex trial designs or less-established endpoints, we believe many others may, including some recently-approved transformative therapies. We encourage FDA and industry negotiators to consider expanding RTOR into other areas of the Agency, particularly neurology and rare diseases.

Project Facilitate: 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 a year 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.[4]

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 expanding Project Facilitate into other areas of the Agency, particularly neurology and rare diseases.

Rare Diseases Program:

[3] Real-Time Oncology Review (RTOR): First Drug Approval, (2020, June 25) Retrieved August 23, 2020, from, https://www.quanticate.com/blog/real-time-oncology-review-first-drug-approval#:~:text=The%20efficient%20real%2Dtime%20data,to%20address%20key%20regulatory%20questions.

[4] Kormanik, Natasha L, et. Al, Project facilitate: A review of the FDA oncology center of excellence expanded access pilot program, (2020, May 25) Journal of Clinical Oncology, Retrieved August 23, 2020, from, https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.7023

As part of PDUFA VI, the Rare Disease Program was further expanded to take on new roles, most notably being, "integrated into review teams for rare disease development programs and application review to provide their unique expertise on flexible and feasible approaches to studying and reviewing such drugs."[5] This new responsibility was added to the existing responsibilities of training review division staff on rare diseases as well as engaging with the rare disease stakeholder community.

With the re-organization of the Office of New Drugs (OND) within CDER, and in particular the creation of the Division of Rare Diseases and Medical Genetics (DRDMG) within the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, it is worth examining if any restructuring of the Rare Diseases Program in CDER is necessary in order to maintain the goals of this program under the new OND structure. We encourage FDA and industry negotiators to discuss the future of the Rare Diseases Program, and its optimal operations, as part of PDUFA VII negotiations.

Evolution of expedited review programs:

As the FDA and industry negotiators are considering the next five years of regulatory review under the PDUFA program, we encourage negotiators to think creatively about the current status of the expedited review programs and if or how they can be further improved. For example, the accelerated approval pathway could be considered underutilized due to a lack of validated (or at least well accepted) surrogate endpoints to use. Furthermore, Fast Track designation could be re-examined to ensure it is still providing the benefits intended especially in comparison to other expedited review pathways. MDA is looking forward to being part of this conversation on innovating expedited approval pathways for years to come.

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

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs

[5] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, Retrieved August 23, 2020, from, https://www.fda.gov/media/99140/download