LEADING THE FIGHT TO END DUCHENNE

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave, Bldg 51, Rm 1146
Silver Spring, MD 20993-0002
Docket No. FDA-2010-N-0128
RE: Prescription Drug User Fee Act; Reopening of Comment Period

April 25, 2016

To Whom It May Concern,

On behalf of Parent Project Muscular Dystrophy (PPMD), we are most grateful to the Food and Drug Administration for the commitment to integrating patient perspectives within the drug development lifecycle through the implementation of PDUFA V and for the opportunity to reflect on our experiences and to share our ideas to work collaboratively to build upon the patient focused drug development foundation within PDUFA VI.

PPMD is the world's largest organization focused on ending Duchenne muscular dystrophy. Duchenne is a progressive disease diagnosed in early childhood that affects skeletal muscle and the cardiac and pulmonary systems. There currently are no FDA-approved disease-modifying treatments, and children diagnosed with Duchenne typically live only into their 20s. In short, Duchenne is 100% fatal.

Though treatments have eluded us to date, PPMD and our partners have worked tirelessly to build a robust therapeutic pipeline and regulatory infrastructure. The FDA Safety & Innovation Act (FDASIA) and PDUFA V aligned perfectly with the dawning of a new day for our Duchenne community – one in which basic laboratory breakthroughs had developed into clinical trials, enabling the Duchenne pipeline of experimental therapies to become more robust than ever. We immediately embraced the opportunities presented to us through PDUFA V and have worked over the past few years to evolve the science of patient input and advance the field of Patient-Focused Drug Development.

Specifically, PPMD conducted the first-ever scientifically rigorous survey of parents of Duchenne patients to obtain quantitative evidence as to their views on benefit-risk. Today, we are expanding our patient-preferences studies to include a broader caregiver demographic and young people living with Duchenne, work that will add to this body of evidence and hopefully be factored into agency decision-making.

We have published a series of white papers analyzing PDUFA through the lens of the Duchenne community, including *PPMD's Putting Patient's First* and *PPMD's Patient's Are Waiting* publications. These publications highlight our Duchenne community's policy priorities around the use of adaptive approval, limiting exposure to placebo, and the regulatory importance of a benefit-risk framework specific to each product. They also include narratives that speak to the urgency and unmet need within our patient community.

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We have also led a comprehensive and multi-stakeholder effort to prepare the first ever patient initiated draft guidance to industry developing Duchenne therapies. This PPMD-led guidance, *"Guidance for Industry Duchenne Muscular Dystrophy Developing Drugs for Treatment over the Spectrum of Disease"* was submitted to FDA in June 2014. Our guidance - along with a Duchenne Community Policy Forum convened by PPMD in December of 2013 - was the foundation used by the agency to develop its own draft guidance on the same topic issued in June of this year entitled, *"Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment".*

We are encouraged by these tremendous developments and are eager to work with FDA and other stakeholders to continue advancing PFDD and the evolution of the Science of Patient Input to inform and shape the forthcoming user fee package.

As we look ahead to PDUFA VI, PPMD is focused specifically on two areas:

1. **The need for a mechanism to measure how PFDD tools are being used by the agency and impacting the drug development and review process; and**

2. **The need to build upon the PFDD foundation of Benefit Risk within FDASIA with additional process, definition, and structure.**

1. Related to a mechanism to measure how PFDD tools are being used and impacting the drug development process:

FDASIA and the corresponding industry agreement contained several provisions focused on greater patient engagement in the review process. These provisions included the strengthening of existing tools and creation of new ones needed to fill gaps, policies to allow for greater engagement of external experts in the review process, and a requirement for FDA to engage in multiple stakeholder meetings on benefit/risk and related issues with the goal of developing a structured benefit risk framework.

PPMD and others patient groups have developed novel and innovative ways of collecting patient data and information for industry and the FDA. We've done this not only in light of the law but in order to better educate ourselves, FDA and companies about things such as the unmet medical need, patients' risk tolerance, treatment preferences and priorities, and what qualifies as meaningful benefit to our populations.

While patient stakeholders strongly supported these reforms and are working to compile critical information to aid drug review and development, concerns exist as to whether or not - and, if so, how - these new tools are being used by the FDA.

To address this concern, we are proposing the development of a patient engagement assessment tool, the results of which would be included in the publicly disclosed safety and effectiveness data package of any approved drug.

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So how does it work?

Essentially we are asking for a checklist that reviewers would fill out indicating what tools were available for a given application and how those tools were used in the review process.

The list of tools would include:

- ✓ Benefit/risk data for the indicated populations
- ✓ Draft or final guidance produced by a patient group
- ✓ Patient-preference data
- ✓ Patient-reported outcomes data
- ✓ Qualitative reports from patient and experts in the community

This simple check list would provide a helpful feedback loop to patients groups who are spending time and resources on these tools. We need a way of knowing whether or not the tools we are creating are useful to review. If they are not being used or used as desired, this feedback is needed so the community can develop instruments that meet the needs of the agency.

This concept builds upon the success in recent years to strengthen the patient voice in the medical product development process.

2. Building upon the PFDD foundation of Benefit Risk within FDASIA with additional process, definition, and structure.

As you well know, each and every family within the patient community has their own personal story. And within our community, each family has a unique story about Duchenne. Each and every family is able to relate a story of loss, the 'little deaths' experienced as their loved one loses function. But we recognize that regulatory agencies make decisions based on rigorous data, and to that end, we, the patient community believe it would be critical to the FDA's decision making process if we were able to provide data related to caregiver and patient preferences. So, we as a community set out to 'quantify the tears', in an attempt to turn the voice of the patient into accessible data.

In order to accurately measure opinions or preferences we used scientifically validated approaches to ensure that whatever we did we did correctly. We partnered with social scientists and health economists from Johns Hopkins University. These partners helped us develop an appropriate instrument that we used to survey nearly 120 Duchenne parents, the first-ever quantitative survey of Duchenne community preferences on potential benefits and corresponding risks of candidate therapies. Specifically, we used the best-worst scaling (BWS) method that measured respondents' views on six relevant and understandable benefit or risk scenarios such stopping or slowing progression of muscle weakness, longer lifespan, nausea,

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and risks of bleeding. In addition, we collected the narrative stories of our families and found that the stories provided qualitative data in support of the quantitative data collected.

The primary study objective was to explore how parents/guardians of individuals with Duchenne prioritize risk and benefit in the context of new therapies.

In the survey, participants were provided with sets of simulated treatment scenarios and asked to choose the best and worst of each treatment scenario; later, participants were provided with sets of Duchenne-related concerns and asked to choose the one they worried about the most in the past seven days and the one they worried about the least. Thus, participants evaluated and compared their preferences toward the attribute levels and selected the pair of attribute levels that they perceive to be furthest apart.

Overall, we have found that parent participants prioritized protection of muscle function over any other attribute, including longer lifespan two serious risks, nausea, and having more information about the drug's risk and benefits. Participants' most significant worries were related to disease progression and care needs. The study suggests a parent population that is highly concerned about Duchenne's effect on their child's strength, and that is willing to accept risk and uncertainty for a treatment that would slow or stop muscle weakness.

In response to requests from FDA, PPMD has been working to expand this work further to capture a larger segment of the Duchenne community population.

Most recently, we partnered with an industry collaborator to understand patient preferences regarding a specific pulmonary candidate therapy. Through this work, involving more than 130 patients and caregivers, we again found that patients are willing to accept risks and burdens to achieve pulmonary benefits, notably improvement in cough strength. In this case, respondents chose to accept a strong benefit with an accompanying high risk more than two-thirds of the time, and the majority of respondents assigned low perceived burdens to three side-effects of taking medication, sustaining blood draws, and diarrhea.

Development of Best Practices for Disease – Specific Patient Preference Studies

In response to the overwhelming energy and interest in PFDD from both the patient advocacy community and industry to conduct rigorous benefit-risk studies – and to ensure that the lessons that have been learned to date are shared broadly -- the Biotechnology Industry Organization (BIO) and Parent Project Muscular Dystrophy (PPMD) have come together to launch of a new initiative designed to share best practices for the development of disease-specific patient preference studies. Through this effort, BIO and PPMD are producing a document outlining key considerations to help guide stakeholders on the development of patient preference studies, which can be used for multiple purposes, including informing the drug development and regulatory processes.

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To help guide this initiative, BIO and PPMD have assembled an Expert Review Committee (ERC) of thought leaders representing the patient community, academia, and the biopharmaceutical industry. The ERC is providing insights individually and as a group to shape and inform the output of this project. This initiative is examining key considerations related to patient

preference study development and implementation, interaction with the regulatory process, utilization of patient preference data, and model collaborations among the stakeholder groups, including patient organizations, academia, and industry.

PDUFA VI – Evolving the Building of the Foundation of Patient-Preference and Establishing A Permanent Place for Benefit-Risk within the Regulatory Framework

Informed by ongoing developments including a recent advisory committee meeting on a Duchenne candidate therapy, PPMD has been struck by the need to establish a designated forum for the review and discussion of patient preference and related data within the regulatory framework that places no additional burden on either the sponsor or the patient community.

Thanks to the leadership of FDA, we are seeing Benefit-Risk considerations incorporated throughout the drug-development life cycle and sponsors who are actively engaging with patient communities during pre-clinical development and protocol design, not just when looking to move products into the clinic. BIO, CTTI, and many others have brought thought leaders together to systematically build upon the existing benefit-risk frameworks and the National Health Council, together with Genetic Alliance are working to develop draft guidance around the incorporation of patient perspectives into the drug development process.

We at PPMD are proud to be a part of all of these efforts and to see that the incorporation of patient preferences into regulatory decision-making is not a trend, but rather a paradigm shift that is being carefully and thoughtfully undertaken.

To that end, as we look ahead to PDUFA VI – and PFDD 2.0 – and build upon the tremendous foundation of patient preference work that has been laid to date, we see an opportunity to address questions that have arisen over the past few months as to where and how this information fits into the overall application and review process.

As noted earlier, we would like to see transparency in how FDA reviewers are or are not using such information. Beyond this reporting, we would like to see the following:

- Clarity and guidance from FDA as to how, exactly, such data can be entered into the review process of a specific application, including instances where such information is supported by the sponsor and situations where it is not product-specific yet highly relevant to the issues being considered.

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- Requiring that FDA complete a benefit/risk evaluation for every candidate therapy, even in situations where the agency may question the overall benefit or efficacy of a candidate therapy. If this is the case, such views can still be noted but should be done as part of a defined benefit/risk assessment.

- Related to the point above, require that patient preference and related information be reviewed at a designated point during any advisory committee meeting on a candidate therapy where such information is applicable to the decisions to be made. Current procedures place the burden on either the sponsor or the patient community to relegate time during respective Advisory Committee review presentations or Open Public Hearing to allow for the presentation of such data, and we believe there must be a clear time and place for such a discussion.

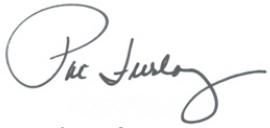
Formalization of the processes for review and discussion of applicable and scientifically rigorous patient-preference studies relevant to a product review throughout the drug development cycle and product review is a critical next step in the evolution of the implementation of the PFDD tools that are being invested in and developed.

In Closing
PDUFA V transformed the landscape – and has changed the way that patient communities, academia, clinicians, industry, and federal partners engage on another. The Duchenne community now stands at a hopeful time – with more than 30 companies working on potentially life changing therapies – and 2 new drug applications filed with the FDA this year alone.

The Duchenne community, like so many of our partners in the rare disease community, has come a long way, but we know that we still have far to go. We at PPMD believe that the patient voice is the blockbuster drug of the century for rare diseases.

We are grateful to the FDA for your leadership and continued commitment to placing patients at the heart of product development – and we look forward to continuing to collaborate and innovate alongside you.

Sincerely,



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