VIA ELECTRONIC DELIVERY

June 14, 2019

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

Re: Characterizing FDA’s Approach to Benefit-Risk Assessment Throughout the Medical Product Life Cycle; Public Meeting; Request for Comments (Docket No. FDA-2019-N-1468)

Dear Madam or Sir:

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 the fifth and sixth versions of the Prescription Drug User Free Act (PDUFA V & VI) and the 21st Century Cures Act. We appreciated the opportunity to participate in the public meeting convened by FDA on this topic on May 16, 2019 and are grateful for the opportunity to further reflect on our experiences and share our ideas as to how patient experience data and related information can inform the benefit risk assessment and regulatory decision making.

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. Children diagnosed with Duchenne typically live only into their 20s. In short, Duchenne is 100% fatal.

Though curative treatments have eluded us to date, PPMD and our partners have worked tirelessly to build and support a 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 progressed 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 PFDD field. That engagement continued throughout the PDUFA VI discussions as we worked to apply our ‘regulatory learnings’ and experiences to help innovate pathways and processes for continued meaningful engagement to further advance the science of patient input for the benefit of all rare disease communities.
PPMD’s Commitment to the Science of Patient Preference

In 2014, PPMD conducted the first-ever scientifically rigorous survey of parents of Duchenne patients to obtain quantitative evidence as to their views on benefit-risk. Since that time, we have expanded our patient-preference studies to include a broader caregiver demographic and people living with Duchenne, exploration of the preferences of providers, symptom treatment prioritization, a product-specific study, and an expansive recently completed patient preference study around gene therapy. Our intent is that this growing body of evidence will be factored into industry and agency decision-making.

As you well know, each and every family within the patient community has their own 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 more data related to caregiver and patient preferences. So, we, as a community, set out to turn the voice of the patient into accessible, impactful data.

In order to accurately measure opinions or preferences we used scientifically validated approaches including stated preference methods commonly used in social science research, but infrequently used in rare diseases. We partnered with social scientists and health economists from Johns Hopkins University. These partners helped us develop an appropriate instrument 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 as stopping or slowing progression of muscle weakness, longer lifespan, nausea, 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 emerging therapies.

In the survey, participants were provided 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

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compared their preferences toward the attribute levels and selected the pair of attribute levels that they perceived to be furthest apart.

Overall, we have found that parent participants prioritized protection of muscle function over any other attribute, including longer lifespan and serious risks such as bleeding or heart arrhythmia. Participants’ most significant worries were related to disease progression and getting the best care. 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, especially which could preserve ambulation or other critical bodily functions.

In response to requests from FDA, PPMD expanded this work to capture a larger segment of the Duchenne population. Through partnering with an industry collaborator, we set out to understand patient preferences regarding a specific pulmonary candidate therapy. As a result of 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 which participants perceived to be a meaningful benefit. 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 the three side-effects of taking medication, sustaining blood draws, and diarrhea. During this survey, respondents also prioritized treatment development for non-motor symptoms of Duchenne treatment using the BWS approach. Symptoms closely tied to morbidity and mortality, such as ‘weaker heart pumping’ and ‘lung infection’ were prioritized above other non-skeletal muscle symptoms among both adults with Duchenne and their parents.

The successful implementation of previous preference surveys inspired us to apply the advanced preference method of discrete choice experiment (DCE) to explore tradeoffs around more complex attributes faced by the Duchenne community, including risk of fracture, kidney damage and chance of drug failure. A ‘research as an event’ approach was used to survey over 160 adults, parents, physicians, researchers, and members of industry at PPMD’s Annual Connect Conference. Consistent with our earlier work, participants were willing to accept chance of kidney damage, fracture, and drug failure in exchange for improved muscle function.

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The ‘research as an event’ study has led to an expansive international effort in collaboration with global advocacy partners to examine patient preferences in Duchenne across six countries (Australia, Belgium, Canada, Netherlands, United Kingdom, United States) and is currently underway. Patients, parents, advocates, and researchers have worked together to adapt the previously-validated DCE to have greater internationally applicability. We have finished pilot testing the survey, and the first stages of recruitment with a target of 360 respondents in total. The successful completion of this study will represent the first-ever international study of preferences for Duchenne treatments.

Finally, PPMD recently completed an extensive patient preference study over the last two years exploring risk tolerance and preferences within gene therapy. This study was in partnership with two Industry partners in the pre-competitive space and, as with all our studies, employed community engaged approach and was led by a community advisory board. This process has included informal engagement with personnel within the Center for Biologics Evaluation and Research (CBER) and a series of qualitative interviews and pilot studies to inform the quantitative portion of the study. Gene therapy represented a unique opportunity to measure preferences with a potential time limited benefit profile, general uncertainty around benefit and risk, and the one time administration without possibility of re-administration condition of the therapy. We used a BWS approach to measure what patients and caregivers cared most about when deciding to join a clinical trial. We found, similar to other studies, that the potential to impact muscle function and secondary symptoms linked to morbidity and mortality were prioritized over risks, burdens and uncertainties. In a second experiment, we assessed patients’ and caregivers’ maximum acceptable risk (MAR) of mortality for gene therapy at different timepoints in disease progression, using a threshold technique. Our data showed heterogeneity in risk tolerance, however we did find that risk tolerance increased with progression of disease. We found little difference between caregivers and patients’ preferences. A subset of participants was willing to accept quite high risks; about 35% of both caregiver and adult respondents would accept a risk of death of ≥ 200/2000 in the last year of being able to bring arms to mouth.

Overall, with our growing body of patient preference research, we are encouraged and eager to work with FDA and other stakeholders to continue advancing the integration of patient preferences within the drug development life cycle and regulatory decision-making.

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5 Holly Landrum Peay, Ryan Fischer, Janice P. Tzeng, Sharon E. Hesterlee, Carl Morris, Amy Strong Martin, Colin Rensch, Edward Smith, Valeria Ricotti, Katherine Beaverson, Hannah Wand, Carol. Gene therapy as a potential therapeutic option for Duchenne muscular dystrophy: A qualitative preference study of patients and parents
MansfieldPublished: May 1, 2019 https://doi.org/10.1371/journal.pone.0213649

Priorities when deciding on participation in early-phase gene therapy trials for Duchenne muscular dystrophy: a best–worst scaling experiment in caregivers and adult patients
As we look ahead to how patient experience data and related information can further serve to inform the benefit risk assessment and regulatory decision making, PPMD is focused on the following:

1. **The need for reliable integration of patient preference data within the Benefit Risk Framework itself for use in both premarket and post-market processes.**

2. **The need for clarity - and inclusion in the Guidance – as to processes for incorporation of relevant patient preference data within regulatory submissions and reviews.**

3. **The need to establish a designated forum within the Advisory Committee review process for the review of the completed Benefit/Risk Framework and introduction of relevant patient experience data, independent of, and complementary to, sponsor presentations and the Open Public Hearing.**

Our discussion of each area follows.

1. **The need for reliable integration of patient preference data within the Benefit Risk Framework itself for use in both premarket and post-market processes.**

FDA has a number of programs and policies in place to evaluate the benefits and risks of potential therapies and to gather and assess the patient perspectives. But, while much progress has been made, some significant gaps remain. One such gap is that the FDA does not yet include any patient experience or preference data as part of its risk-benefit framework. This means that the agency’s signature tool for evaluating risk-benefit is not currently required to include data from the patient perspective that could be critical to informing the agency’s evaluation and, ultimately, its decision on whether or not to approve a product, how to properly label a product, or how to conduct post-market assessment.

We urge the agency to ensure that all relevant patient experience, or PFDD related data – including information developed by a product sponsor or a third party such as a patient advocacy organization or academic institution – be formally included and considered as part of the risk-benefit assessment by specifically integrating PFDD data within the Benefit Risk Framework. This action will send an important signal to all stakeholders that patient experience and PFDD data will be fully incorporated into the agency’s review process and will encourage such entities to develop scientifically rigorous and meaningful tools and data.
2. The need for clarity -- and inclusion in the Guidance – as to processes for incorporation of relevant patient preference data within regulatory submissions and reviews.

Clarity and guidance from FDA is needed as to how, exactly, such patient-preference 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.

3. The need to establish a designated forum within the Advisory Committee review process for the review of the completed Benefit/Risk Framework and introduction of relevant patient experience data, independent of, and complementary to, sponsor presentations and the Open Public Hearing.

Related to the point above, we recommend that the implementation of the enhancements of the Benefit Risk Framework under PDUFA VI include an opportunity for the Benefit/Risk Framework and relevant patient experience data and related information to be reviewed at a designated point during any advisory committee meeting on a candidate therapy. Current procedures place the burden on either the sponsor or the patient community to dedicate time during respective Advisory Committee review presentations or the Open Public Hearing portion to allow for the presentation of such data. We believe there must be a clear and separate time and place for such a discussion.

In Conclusion

PDUFA VI embraces the potential for a positively transformed therapy development landscape – and a deep commitment from the FDA to patient engagement. Patient-Focused Drug Development has deeply changed the way that patient communities, academia, clinicians, industry, and federal partners engage one another. We are grateful to the FDA for your leadership and continued commitment to placing patients at the heart of product development. We look forward to continuing to collaborate and innovate alongside you.

Sincerely,

[Signature]

Founding President & CEO
Parent Project Muscular Dystrophy
ADDENDUM

This addendum contains references to key Patient-Focused Drug Development and other patient experience initiatives undertaken to date by Parent Project Muscular Dystrophy and its partners.


A D D E N D U M (CONT.)


