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July 3, 2023

Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave.
Hillandale Building, 4th Floor
Silver Spring, MD 20993–0002.

Re: **Docket No. FDA–2023–D–0026** "Patient-Focused Drug Development (PFDD): Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making"

To Whom It May Concern,

On behalf of patients and families impacted by rare diseases, the EveryLife Foundation for Rare Diseases is pleased to offer the following comments to inform the U.S. Food and Drug Administration on the *"Patient-Focused Drug Development Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making".*

The EveryLife Foundation for Rare Diseases is a 501 (c)(3) nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments, and cures. EveryLife's establishment of a diverse coalition comprised of patient advocacy organizations, industry leaders, coalition groups, and other relevant stakeholders guides our policy efforts and provides advice and insight on urgent policy issues impacting the rare disease community.

As collaborative stakeholders, we have experienced a tremendous evolution of patient engagement and related areas since their infancy in PDUFA V -- to their continued development via 21st Century Cures and PDUFA VI -- and now their continued maturation today through the implementation of PDUFA VII. In this time, the landscape has shifted as the patient focused drug development movement evolved for the rare disease community. We've seen a deepened engagement and understanding of the patient perspective via numerous approaches such as the Patient Focused Drug Development meetings and the development of the FDA Benefit Risk Framework. We've had increased opportunities for meaningful participation in formal service on advisory committees, seen the formation of rare disease focused initiatives within CDER and CBER, seen the establishment of patient engagement advisory committees, and have benefited from reporting on the use of patient experience data within the regulatory review.

The PFDD Guidance Series, along with FDA's issuance of numerous other guidances that are informing the inclusion of patient experience data within clinical trial and patient-focused product development activities for drugs are resulting in lives changed and saved through products approved to treat rare conditions, especially those that have benefited from the inclusion of more robust patient insights and patient experience data as part of the review process. By instituting a structured approach to listen to the voice of the patient in a meaningful way, the FDA has demonstrated its commitment to science and to ensuring appropriate processes are in place to quantify the perspective of the patient or the caregiver.

The release of the fourth guidance in the patient focused drug development (PFDD) series marks a significant milestone that should be celebrated by all who have devoted countless hours to the work of integrating patient voices into the therapy development ecosystem. We are grateful for the opportunity to engage in the finalization of the fourth guidance and in line with the focus of this final guidance, we are eager to fully realize the potential of PFDD efforts through greater incorporation of patient experience data in regulatory decision making. To inform our engagement, the EveryLife Foundation convened a series of discussions with members of our Community Congress coalition partners focused on this Guidance, to include one session held in partnership with the National Health Council's Medical Innovation Action Group.

Underscoring the Importance of Guidance 4

Discovery, development and delivery of a new medical product is a complex, lengthy and resource-intensive undertaking that requires many different skill sets to execute well at every step along the way. In 2022, FDA approved 50 novel drugs and biologics (combined) and 41 innovative medical devices and technologies. Yet, for every medical product that succeeds to the approval stage, thousands of possible therapies don't progress. A substantial portion is abandoned in early phases of research before the compound or technology is ever tested in a human being. Even those that advance to clinical trials face formidable odds. For these reasons, our collective communities feel it critical to underscore the importance of utilizing all available data to inform the endpoints that will be utilized when assessing the safety and efficacy of products.

Integrate Additional Specificity and Examples to Help the Rare Disease Community Operationalize the Guidance

The EveryLife Foundation appreciates the need to ensure guidance is not overly prescriptive in nature while still providing stakeholders with actionable information, however, our conversations with rare disease stakeholders highlighted the need for FDA to provide additional context and specificity as it relates to very small patient populations. With 95% of rare diseases still lacking an approved treatment, there is tremendous opportunity to transform how patient experience data can be integrated into regulatory decision making to overcome historical barriers that have slowed or halted promising scientific advances. Guidance 4 makes great strides in addressing these issues, yet for this Guidance to be impactful in rare diseases with limited prevalence or extremely limited patient populations, sponsors and patient advocacy organizations need more guidance on how the agency will adjust expectations or its interpretation of meaningful patient involvement in COA development and use when done with limited populations.

One area that will benefit from enhanced specificity and examples is methods for establishing meaningfulness. The FDA recognized the challenges in establishing COA- based endpoints for smaller patient populations in the 2018 PFDD Guidance 3 regarding new endpoint and COA development. We urge the FDA to expand on this concern and provide more guidance for establishing meaningfulness in ultra small populations. Recently, the Expanding the Observer-Reported Communication Ability (ORCA) Measure Project, supported by the CDER Pilot Grant Program, began work to validate the ORCA Measurement as an effective COA for an additional 13 neurological disorders beyond the original rare Angelman Syndrome for which it was created based on a population of about 270 people. As more ultra rare therapies begin to arise, sponsors will need specific guidance on establishing measures of meaningfulness for their smaller patient populations. Additional specificity related to the use of within patient comparisons and the use of data demonstrating changes from baseline, trends from baseline, maintenance of function from baseline, within an individual patient and as related to significance for between group comparisons. We applaud the agency for broaching this area within this guidance and underscore how critical this detail is for rare disease study design.

Provide More Information on How and When to Engage with the Agency
A common theme that was present throughout stakeholder conversations since the draft Guidance 4 release was the need to enhance available details on how and when to navigate interaction with the FDA on PFDD related topics. While we appreciate that The Prescription Drug User Fee Agreement (PDUFA) Reauthorization VII outlines meeting types, scheduling timelines, and deliverable deadlines for sponsors to meet with the FDA, including new Type D meetings, these opportunities are highly structured and still limited in frequency. We encourage the Agency to provide further detail on all available opportunities for sponsors and patient advocacy organizations to engage with the Agency on PFDD related topics, especially the topics in Guidance 4. This detail should include when should meetings be scheduled, how should conversations be structured, what opportunities exist for engagement when measure development is being done in a collaborative space and outside of a specific company's program and clarity on the presence of patient advocacy organization partners in the interactions.

Build Linkages and Ties Throughout the Guidance Series and With Additional Relevant Guidances
The PFDD Guidance Series may be the designated home for content specifically dedicated to PFDD methods but the Agency has also made great strides in integrating concepts related to PFDD into adjacent guidance documents. As policy related to real-world evidence, digital health technology, decentralized clinical trials and other relevant topics continues to advance, we encourage the agency to intentionally integrate concepts and terminology from the PFDD series and to ensure that where applicable, elements of these existing Guidances are reflected and referenced within Guidance 4.

The PFDD Guidance Compendium Workshop Series was convened in 2021 to examine distinct phases of the medical product development process, from early-stage research through post-market integration into healthcare practice, and create alignment with the many Guidances and resources being generated by the agency. Led by the EveryLife Foundation in partnership with the National Health Council, BIO, PhRMA, and 88 subject matter experts from across our ecosystem, the product of our collective effort was "Guide to Patient Involvement in Rare Disease Therapy Development." It was intended to serve as a companion to the Guidances and expanding library of resources, as it references 20 FDA Guidances and 112 linked resources as a go-to navigational tool specific to rare diseases.
We encourage the FDA to continue to collaborate with us as we work to define regulatory research needs. We invite the FDA to continue to play an active role in the EveryLife Foundation's scientific workshop and look forward to utilizing this forum to convene community leaders to discuss opportunities to build evidence that leads to consensus around novel endpoints, statistical methods for within patient comparisons and for small patient sample sizes, and more. We additionally encourage FDA to conduct a review of the agency's existing PFDD glossary of terms to ensure it remains updated, consistent and relevant.

Ensure Terminology in Guidance is Aligned with Commonly Used Terms in the Scientific and Policy Community
We appreciate the efforts of the FDA to develop this series of Guidances to ensure patient-focused drug development truly keeps the patient experience and definitions of meaningfulness at the core of the guidance. This final guidance introduces a set of new terms into the guidance series. We would recommend a review of terminology used across the Guidances to ensure consistency for staff, sponsors, and other stakeholders involved in this process. Referencing outside sources, such as the DCT Guidances, the ICH addendum, and ISPOR Guidances and reviews on patient engagement to reflect terminology used by patient and sponsor communities.

Address Complexities of Using Multi-Component and Personalized Endpoints in Further Detail
In 2021, The EveryLife Foundation partnered with the National Health Council, BIO, and PhRMA to convene a four-part series to assess the Guidances informing the integration of patient experience data into clinical development through the lens of rare disease product development. During Workshop 2 of the series, which was held in July of 2021, significant discussion focused on the complexity of endpoint selection. Participants recognized the opportunity to utilize patient preference studies to help identify and prioritize endpoints; however, noted that the lack of guidance from CDER (at that time) for this approach added to the challenge of securing resources to conduct such studies.

Similarly, while novel endpoints such as personalized endpoints or comparisons with untreated patients might offer means to overcome some of the challenges for rare diseases, the regulatory expectations for acceptability of these approaches remains unknown. Workshop participants agreed that the qualification process for outcome measures has become onerous to the point of there being a widespread sense of futility. Patient advocacy representatives were frustrated by the lack of a clear pathway for their involvement, including ways for relevant data and/or expertise to be considered as part of the outcome review process. In general, there was a desire for the qualification process (at both the disease level and specific product level) to facilitate better understanding by reviewers of the dynamics of the disease itself, rather than being narrowly focused on one or more concepts of interest and an instrument's psychometric properties and performance.

Enhance Focus on Minimizing Patient Burden by Encouraging More Precompetitive Measure Development and Validation Collaborations

The PFDD Guidance Series and the Agency's commitment to more meaningful integration of patient experiences in regulatory decision making has resulted in a shift from PFDD activities being a "nice to have" to a "must do." While this is an incredibly welcome shift, the enhanced interest in conducting qualitative research and in collecting patient experience data could enhance the burden on patients and patient advocacy organizations if the right incentives and infrastructure are not in place. We are grateful for the Agency's references to the importance of minimizing patient burden within the Guidance but encourage the further strengthening of this section in the final document. Challenges related to patient burden are magnified in rare disease communities where limited populations are available to complete interviews, surveys and other qualitative research as well as to participate in all phases of clinical research. For these patients, there is an even greater imperative on sponsors and advocacy organizations to collaborate early and consistently on the precompetitive collection and analysis of PFDD related information. The FDA can encourage this collaboration within the Guidance and reinforce the Agency's commitment to such interactions throughout o the development process.

Additionally, we recommend the Agency consider including additional information and resources that address concerns related to patient burden and the impact this may have on the performance of the measure. In 2012, the Patient Centered Outcomes Research Institute (PCORI) released *The Design and Selection of Patient-Reported Outcomes Measures (PROMs) for Use in Patient Centered Outcomes Research*, highlighting patient burden considerations as one of the minimum standards for patient centered outcomes research. Specifically, PCORI highlighted the time, effort, and emotional strain on a patient by selecting the appropriate PROM, study design, and the patient and/or their proxy's disease state. PCORI has led the transformation of how the academic research community considers patient engagement in the design, conduct and dissemination of research. The lessons learned from PCORI and numerous other stakeholder collaborations can inform sponsors as they consider ways to lesson patient burden in both the development of measures as well as the burden associated with completing those assessments in a clinical trial environment.

Relatedly, decisions around endpoints and COAs are among the most challenging decisions in rare disease therapy development and take on added impact in today's environment since evidence generated in the clinical trial is often used by payers and others to determine coverage and reimbursement policies. Therefore, opportunities to engage multistakeholder initiatives that include patients, caregivers, clinicians, academic researchers, sponsors, regulators, payers and outcome assessment experts are optimal and ultimately reduce the overall burden on patients.

Ensure the Long-Term Success of PFDD Efforts Through Robust Dissemination and Transparency Related to Implementation Lessons

Patient advocacy organizations and sponsors have embraced the role patient experience should play in therapy development, spending precious resources on data collection and analysis, qualitative research and PFDD related engagements. The PFDD Guidance Series has contributed to a willingness for sponsors to think differently about what and how patient experience data is collected and used and Guidance 4 has the greatest potential of the four to solidify patient involvement in all aspects of therapy development as the norm moving forward.

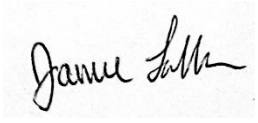
To maximize the uptake of the activities described throughout the PFDD Series, rare disease stakeholders have expressed a need for consistent and transparent operationalization of the Guidance, including a better understanding of how the Agency will approach the challenging task of learning and interpreting the patient experience data that is gathered. It is also important that intentional efforts are made to ensure advisory committee members who may discuss and use patient experience data to inform their recommendations are appropriately informed.

We encourage the FDA to commit to regular and robust sharing of information related to how patient experience data is being considered for regulatory decision making, including the sharing of best practices in the timing and structure of engagements with sponsors and patient advocacy organizations. We along with many others in the patient advocacy community are ready and willing to be a partner in these dissemination and implementation efforts to ensure PFDD is here to stay.

Conclusion

The EveryLife Foundation is enthusiastic about the progress represented within the Draft PFDD Guidance 4. We are grateful to all the community members who have worked tirelessly to ensure that the needs, priorities, opportunities, and urgency of our underrepresented rare disease community is strongly reflected in these recommendations. The foundation and its partners are eager to continue to weigh in and work with the agency, sponsors, and patient communities to ensure that the rare disease communities' patient experience continues to inform recommendations and decision-making all throughout the product development life cycle.
Thank you for the opportunity to provide comments and for your ongoing commitment to addressing the unmet needs of the rare disease population. If we can provide additional information to support your process, please contact Annie Kennedy, Chief of Policy, Advocacy and Patient Engagement akennedy@everylifefoundation.org.

Sincerely,



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