August 14, 2025

VIA ELECTRONIC DELIVERY

Center for Drug Evaluation and Research
Food and Drug Administration
Docket No: FDA-2025-N-0816
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Reauthorization of the Prescription Drug User Fee Act; Public Meeting [Docket No. FDA-2025-N-0816]

To Whom It May Concern,

On behalf of patients impacted by rare diseases, the EveryLife Foundation for Rare diseases is pleased to offer the following comments to inform the reauthorization of the Prescription Drug User Fee Act (PDUFA VIII).

The EveryLife Foundation for Rare Diseases is powered by the rare disease community to improve health outcomes by driving change through evidence-based policy, leading science-driven policy and regulatory research, activating the community to advocate for their rights and needs, and strengthening the rare disease community. We are an organization that understands that no disease is too rare to deserve treatment, and that rare disease therapies should be safe and effective. To that end, we convene a robust coalition comprised of patient advocacy organizations, biopharmaceutical partners, coalition groups, and other relevant stakeholders with a shared interest in policy focused on rare disease therapeutic development and regulatory infrastructure. We are pleased for the opportunity to engage within the PDUFA Reauthorization process and to offer input that reflects the engagements of our coalition around our community's shared PDFUA priorities.

More than 30 million Americans live with one or more of the 10,000 identified rare diseases[1]. While the majority of rare diseases (95%[2]) lack any FDA-approved disease-modifying therapies, we are grateful for recent breakthroughs that have extended the life expectancies of once-fatal conditions, and we are optimistic about the research that is ongoing to develop treatments for additional conditions. For more

[1] National Institutes of Health- National Center for Advancing Translational Sciences. (n.d.). Genetic and rare diseases information center. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/
[2] National Center for Advancing Translational Sciences. (2023, February 24). Delivering Hope for Rare Diseases. https://ncats.nih.gov/sites/default/files/NCATS_RareDiseasesFactSheet.pdf

than a decade, the rare disease patient community has played a significant role in the paradigm shifts and statutory changes that have occurred with respect to the inclusion of patients and patient experience data within clinical trial design and regulatory review.

Thanks to robust stakeholder engagement and strong commitments from the Agency, PDUFA VII included several commitments that directly support and advance rare disease drug development by strengthening regulatory science, patient engagement in the development and review of new therapies, and review predictability, consistency, and efficiency. These commitments built on the iterative progress made in each subsequent reauthorization of PDUFA and we hope that PDUFA VIII continues to include robust processes and regulatory science commitments relevant to rare disease therapy development.

Most recently, we are grateful to the agency for establishing the Rare Disease Innovation Hub to serve as the FDA's coordinating office for the optimization of rare disease expertise, processes, and engagement with rare disease stakeholders across all therapeutic areas, including drugs, cell and gene therapies, and medical devices.

Just as previous user fee agreements have yielded great strides that have led to positive therapeutic momentum for the rare disease community, we have identified five key areas of opportunity to advance rare disease therapy development as we look to PDUFA VIII.

1. Expanding PDUFA VII Pilot Programs

Thanks to the agency's swift implementation on pilot projects initiated in PDUFA VII such as the – Support for clinical Trials Advancing Rare disease Therapeutics (START) and the Rare Disease Endpoint Advancement (RDEA) pilot programs - improvements are occurring both in processes to advance innovative endpoints, and in the speed and structure of the review process.

The START Pilot Program aims to accelerate the development of treatments for rare diseases by providing enhanced, frequent, and iterative communication between sponsors and FDA review staff early in the drug development process. Four gene or cell therapy products to address serious rare conditions that are likely to lead to significant disability or death within the first decade of life and three products to address rare neurodegenerative conditions have been accepted into the Program since its initiation in 2023[3]. The START Program has already provided hope for novel therapy development for

[3] FDA. (2024, June 24). *Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program*. U.S. Food and Drug Administration. https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/support-clinical-trials-advancing-rare-disease-therapeutics-start-pilot-program

high unmet need communities such as NGLY1 Deficiency, Canavan Disease, Sanfilippo Syndrome, and more[4].

The RDEA Pilot Program supports up to three proposals per year for three years to help address endpoint development challenges in rare diseases. Innovation in endpoint development is a longstanding priority for the rare disease community and drug developers that are often forced to rely on novel clinical endpoints for each program or for whom surrogate endpoints are the only viable path forward. For example, surrogate biomarkers were used in an average of 5.4 diseases per marker for oncology accelerated approvals, compared to the 1.1 disease per marker for all other accelerated approvals[5]. The RDEA Pilot offers the chance for other rare conditions to advance the knowledge of surrogate endpoints and progress novel therapy development.

The RDEA pilot also offers an opportunity for the agency to provide more information and insight into the agency's viewpoints on topics such as the use of primary disease biomarkers and intermediate clinical endpoints. Clarifying the scientific framework to enable a clear and streamlined approach to use primary disease activity biomarkers as surrogate endpoints for accelerated approval will be a benefit to this program moving forward.

The RDEA can be a catalyst to improve the process by which novel endpoints are developed and incorporated into rare disease clinical studies with more predictable regulatory acceptance through robust internal education efforts, particularly those that aim to better familiarize review staff with novel surrogate considerations. Novel surrogates will be critical to continuing advancement of therapies for rare and ultra-rare diseases and could well be proposed as pilot projects if RDEA expands under PDUFA VII.

PDUFA VII also led to comprehensive National Academies of Medicine and Government Accountability Office studies that provided learnings and opportunities for action in advancing FDA's rare disease regulatory processes and informing how patient and expert voices are incorporated. PDUFA VIII stakeholder engagement should include attention to the findings of these studies that have relevance to the user fee commitment structure so that this timely opportunity to advance regulatory policy changes is not missed.

We hope that the opportunities stemming from these PDUFA VII investments will be applied to PDUFA VIII considerations. Furthermore, we urge the dissemination of data, case studies, and other learnings resulting from the PDUFA VII FDA pilots. We also encourage FDA to identify specific ways that patient advocacy organizations can engage in the strategy creation and implementation of pilot programs created in PDUFA VIII and we urge you to ensure that any program selected for participation in these

[4] *Ibid*

[5] Domike, R., Raju, G.K., Sullivan, J. et al. Expediting treatments in the 21st century: orphan drugs and accelerated approvals. Orphanet J Rare Dis 19, 418 (2024). https://doi.org/10.1186/s13023-024-03398-1

pilots has provided strong evidence of their intent to incorporate meaningful patient focused drug development activities.

2. Evolving Patient Focused Drug Development

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 conduction of more than one hundred Patient Focused Drug Development meetings, the development of the FDA Benefit Risk Framework, and the implementation of the Patient Experience Data Checklist. 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 the patient engagement advisory committee (CDRH), and have benefited from reporting on the use of patient experience data within the regulatory review.

FDA's issuance of numerous guidances that are informing the inclusion of patient experience data within clinical trial and patient-focused product development activities 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 and caregiver.

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 contributed to a willingness for sponsors to think differently about what and how patient experience data is collected, used and transformed patient involvement in all aspects of therapy development. To maximize the uptake of the activities described throughout the FDA Guidances, rare disease stakeholders have expressed a need for more consistent and transparent operationalization of the Guidances, including a better understanding of how the Agency will approach the challenging task of learning and interpreting the patient experience data that is gathered. A recent study by Jewell Martin and colleagues found that only 30% of applications included patient experience data in the benefit-risk framework, and just 27% included PED in labeling[6].

[6] Martin JD, Frear D, Roberts SA, Dohnal VA, Kieffer C, Morin SL, Lock I, Balogun A, Chhina N. Patient Experience Data (PED) in 2019-2023 US FDA NME Drug Approvals: Analysis and Recommendations. Ther Innov Regul Sci. 2025 Jul;59(4):859-870. doi: 10.1007/s43441-025-00788-w. Epub 2025 May 9. PMID: 40346376.

The evolution of PFDD within PDUFA VIII, marked by more transparency and consistency are required in the consideration and utilization of PED in the regulatory space to optimize and grow the commitment to collecting PED and its incorporation into clinical and payer decision-making. 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.

3. Establishment of the Science Focused Drug Development meeting mechanism

Building on the strides in patient engagement and the success of the externally led PFDD Workshop model, the establishment of a new mechanism for community engagement around scientific and regulatory challenges would provide an opportunity for developers, regulators, scientific experts, and patient advocates to systematically discuss specific development considerations in particular rare diseases.

The establishment of the Rare Disease Innovation Hub provides an opportunity to further evolve the processes for community engagement around key scientific and regulatory challenges. With appropriate resources, The Hub can facilitate the creation of a mechanism to convene medical experts, drug sponsors, scientific organizations, and patient organizations to align on novel approaches for development of products, including considerations around clinical trial design, patient populations, endpoints, the use of biomarkers and surrogate endpoints, the use of natural history as a control, and more, with a goal of expediting rare disease therapy development. Such meetings would include FDA participation and can be convened by developers or FDA in collaboration with key stakeholders.

We recommend implementing this new initiative as part of PDUFA VIII commitments to provide an opportunity for developers, regulators, scientific and academic experts, and patient advocates, to proactively and systematically discuss drug development considerations in particular rare diseases or groups of rare diseases that share a specific drug development challenge (e.g. study design, study duration, intended population, endpoints). Such an initiative would be distinct from existing mechanisms such as the Critical Path Innovation Meetings and INTERACT meetings which are more likely to occur between specific companies or organizations and the FDA and focus on general scientific innovation (CPIM) or be specific to early product regulatory advice (INTERACT).

4. Establishing opportunities for earlier payer engagement

By co-creating processes that build upon the impact of the PFDD movement –we can transform PFDD meetings from a single point in time, to a pathway for ongoing engagement as the ecosystem shifts, thereby enhancing the transparency of how patient experience data is used in regulatory decision making. PDUFA VIII could be transformative by establishing opportunities for earlier payer engagement to reduce barriers to access to life-alerting therapies once approved, learning from CDRH's Early Payor Feedback Program.

We encourage the agency to seek opportunities for engagement with stakeholders within the access ecosystem earlier in the approval process. This communication can help to better ensure that the measures being collected for inclusion within clinical trials and regulatory review will also be feasible for collection within the post-market environment. Only recently have patient communities begun to apply a remarkable level of engagement to the access environment; engagement that often begins when patients learn that long-awaited FDA approved products have launched into unfavorable access environments. For patients, these access barriers and delays translate into irreversible disease progression and – in some instances – pediatric patients aging beyond the labeling requirements before life-saving access is granted. Potentially transformative new therapies, such as gene and cell therapies, promise life-altering improvements in patient health. But these innovative therapies have also presented complex new challenges for payers, and for patients and their families related to coverage decisions. These challenges represent the need for opportunities for earlier and innovative engagement within the therapeutic development process.

5. Innovations in Post-Market Data Collection

More than 250 drugs have been approved through the accelerated approval pathway[7]. Still, for many rare disease communities, the pathway remains out of reach with only 23% of approvals having been for non-oncology rare diseases, despite being one of the only viable routes of bringing a treatment to market[8].

To better achieve the intent behind the accelerated approval pathway, and to ensure we learn from real-world applications of a treatment, we must innovate regarding how FDA uses post-market data. We commend the FDA for recognizing that the incorporation of patient perspective sits at the core of any post-market data collection[9]. Including the patient perspective will enhance the collection and application of real-world evidence within the post-market environment, including the include deployment of digital tools and technologies.

When the *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry* was released, we were encouraged to see the inclusion of the forms of real-world evidence and data considered acceptable when comparing data from externally controlled and treatment arms of clinical trials. As we expand upon these learnings in PDUFA VIII, we encourage more specificity around how to compare data for externally controlled trials utilizing real

[7] Domike, R., Raju, G.K., Sullivan, J. et al. Expediting treatments in the 21st century: orphan drugs and accelerated approvals. Orphanet J Rare Dis 19, 418 (2024). https://doi.org/10.1186/s13023-024-03398-1
[8] *Ibid*
[9] Center for Drug Evaluation and Research. (n.d.-b). *Patient-focused Drug Development Guidance Series*. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

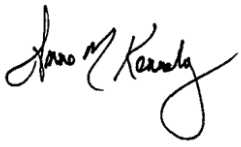
world data for a small disease populations[10]. Ensuring data compatibility for small disease populations includes additional complexities and merits additional consideration in regulatory guidance.

Similarly, the release of the guidances related to digital health technologies and confirmatory trials which addressing important issues such as data integrity, alternative study design, and special considerations required for rare diseases when designing confirmatory trials have been critical to the rare disease community[11, 12]. As we look to PDUFA VIII, we encourage building upon these foundations to reflect opportunities for FDA to work with the patient community to identify innovative study designs for confirmatory trials that utilize digital health technologies.

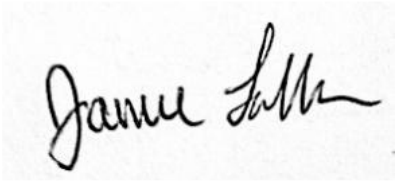
Conclusion

The EveryLife Foundation and our collective patient community organization partners are eager to continue to lean in and work with the agency, sponsors, and patient communities to ensure that the rare disease communities' patient experiences continue to inform considerations and decision-making all throughout the product development life-cycle. We would be happy to serve as a resource or to continue to help facilitate engagement with rare disease community partners; please contact Annie Kennedy, Chief of Policy, Advocacy and Patient Engagement at akennedy@everylifefoundation.org.

Sincerely,



Annie Kennedy
Chief of Policy, Advocacy, & Patient Engagement
EveryLife Foundation for Rare Diseases



Jamie Sullivan, MPH
Vice President of Policy
EveryLife Foundation for Rare Diseases

CC: Michael Pearlmutter, Chief Executive Officer
Frank Sasinowski, Chairman, Board of Directors

[10] FDA. (2023, February). *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

[11] FDA. (2023b, December). Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations

[12] FDA. (2025, January). *Accelerated approval confirmatory underway*. U.S. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-and-considerations-determining-whether-confirmatory-trial-underway