September 4, 2025

VIA ELECTRONIC DELIVERY

Center for Devices and Radiological Health
Food and Drug Administration
Docket No: FDA-2025-N-1157
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: No. FDA-2025-N-1157

To Whom It May Concern,

On behalf of patients living with rare diseases, the EveryLife Foundation for Rare Diseases is pleased to offer the following comments to inform the reauthorization of the Medical Device User Fee Act (MDUFA VI).

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. The mission and work of the Center for Device and Radiological Health (CDRH) remain critical to the rare disease community, supporting the development of medical devices that address diagnosis, treatment, and quality of life, slowing disease progression, and preserving precious time in the face of a life-threatening diagnosis.

The National Economic Burden of Rare Disease Study, led by the EveryLife Foundation, estimated that in 2019 the overall annual economic impact of rare diseases in the United States exceeded $966 billion. Of the total health economic assessment, indirect costs from productivity losses comprised the most significant economic impact at $437 million, followed by direct medical costs at $418 billion, and the non-medical and uncovered healthcare costs absorbed directly by families living with rare diseases at $111 billion[1].. The study also found that the mean diagnostic odyssey was 6.3 years and included more than 17 clinical providers[2]. In a follow-up study led by the EveryLife Foundation, the Cost of Delayed Diagnosis: A Health Economic Study found that the diagnostic odyssey leads to over $220,000 in avoidable medical costs and lost income per person[3].

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[1] Yang, G., Cintina, I., Pariser, A. et al. The national economic burden of rare disease in the United States in 2019. Orphanet J Rare Dis 17, 163 (2022). https://doi.org/10.1186/s13023-022-02299-5
[2] *Ibid*
[3] The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study, EveryLife Foundation for Rare Diseases, The Lewin Group, The Rare Disease Community, 2023. https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

Thanks to robust stakeholder engagement and strong commitments from the Food and Drug Administration (FDA), MDUFA V included several commitments that directly support and advance rare disease device development by strengthening regulatory science and enhancing patient engagement in the total product life-cycle.

In particular, notable advances that have led to CDRH's status as a leader in patient engagement in regulatory policy, thanks to MDUFA V have included:

- The continued growth of expertise on how to include patient preference information in submissions, including multiple guidance documents that illuminated new avenues from which stakeholders could meaningfully capture patient insights throughout medical product development and regulatory review.
- The establishment of the TAP Pilot – which was once again marked by CDRH's commitment to innovative approaches to advancing innovation – and convening experts.
- The further expansion of staff understanding of patient community engagement through increased training, direct exposure to communities, and the inclusion of a wide array of patient community perspectives

Just as previous user fee agreements have yielded great strides that have led to positive device momentum for the rare disease community, we have identified three key areas of opportunity to advance rare disease device development as we look to MDUFA VI.

1. Evolving CDRH Programs to Include Patient Advocacy Groups as More Formal Partners

Patient Preference Information
Since 2012, when CDRH first issued guidance on the inclusion of patient preference information (PPI) as scientific evidence within the benefit-risk regulatory submission[4] The CDRH has set the standard for incorporating PPI into the evaluation of medical devices. An important deliverable from MDUFA V was the *Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle* guidance[5]. The guidance was a comprehensive document that directs the field on how to collect PPI best, explains why it is important, and how it can benefit a sponsor's submission. The guidance highlighted the impact that PPI can have on the rare disease community, recognizing the importance of natural history studies, the patient perspective in benefit-risk assessments, and the need to engage the patient community throughout the entire development process. The guidance is encouraging and should be expanded on to ensure that PPI becomes a more systematic feature of regulatory submissions.

One example of guidance expansion is to address PPI and RWE in labeling. We urge the agency to provide more clarity on when and how PPI can be used in labeling, ensuring that patients and healthcare professionals receive the best information to guide their decision-making process.

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[4] Food and Drug Administration. (2012, March). Guidance for Industry and Food and Drug Administration Staff; Factors To Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and de Novo Classifications; Availability. https://www.federalregister.gov/documents/2012/03/28/2012-7418/guidance-for-industry-and-food-and-drug-administration-staff-factors-to-consider-when-making
[5] Food and Drug Administration (2024, September). Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/incorporating-voluntary-patient-preference-information-over-total-product-life-cycle

More Formalized Involvement of Patient Advocacy Organizations
Our community was pleased to see the FDA's continued commitment to advancing the field of patient engagement in the implementation of MDUFA V.

The CDRH Innovation Program maintains several innovative models for engagement aimed at accelerating patient access by bringing innovators together with regulators and payors early and often.

As we look to MDUFA VI, we recommend including patient advocacy organizations among the partners formally involved in collaborations formed through the CDRH Innovation Activities, specifically the Payor Communication Task Force and the Early Payor Feedback Programs.

Patient advocacy organizations maintain natural history datasets; global – regulatory grade – registries; are developing outcome measures based on patient and caregiver reported outcome assessments; funding studies in digital health technologies, wearables, and robotic solutions; supporting global clinical networks; qualitative and quantitative studies to inform clinical and regulatory decisions; and so much more.

Additionally, patient advocacy organizations are gaining extensive experience working with payors in external environments, navigating dynamic market access environments and adoption considerations, and continuously building learnings into ongoing data collection efforts. The formalized inclusion of patient communities would enable CDRH to apply lessons learned within a rapidly changing environment as innovation and payor programs further evolve.

A major success coming out of MDUFA V has been the TAP program[6], offering an opportunity for the agency to provide more information and insight into the agency's viewpoints on topics such as post-market surveillance, improving clinical uptake, and improving rapid development of innovative medical devices. The program has worked hard to increase predictability and reduce the time from concept to commercialization. As it continues to meet the MDUFA V goals and move into MDUFA VI, we encourage FDA to ensure that devices applicable to rare diseases are enrolled in the program and the organizations representing the relevant patient communities are formally incorporated as partners. The FDA should consider incorporating elements of The National Center for Advancing Translational Sciences' (NCATS) approach to the inclusion of patient advocacy organizations in the Rare Disease Clinical Research Network (RDCRN). The RDCRN includes the Coalition of Patient Advocacy Organizations (CPAG), a formal mechanism for incorporating patient advocacy partners in the operations, governance, and strategy of the RDCRN. In addition, each consortium operating under the RDCRN is required to include at least one patient advocacy organization as a formal partner, enabling meaningful participation and enhancing the program's productivity in enhancing rare disease research over the last two decades.[7]

2. Combination Products

Combination products play an important role in the treatment of many rare diseases. These innovative products can significantly enhance treatment outcomes and improve the quality of life for patients with rare diseases by providing more targeted and efficient delivery mechanisms, thereby reducing the

[6] Center for Devices and Radiological Health. (n.d.). *Total product life cycle advisory program (TAP)*. U.S. Food and Drug Administration. https://www.fda.gov/medical-devices/how-study-and-market-your-device/total-product-life-cycle-advisory-program-tap
[7] https://www.rarediseasesnetwork.org/about/our-network

burden of managing therapy delivery. Enabling optimized patient outcomes through improved drug delivery, enhanced diagnostic capabilities, and more localized drug release are just some of the potential enabling capabilities of innovations in combination therapies in rare diseases.

As the Office of Combination Products (OCP) has worked to increase transparency into the regulatory process for combination products, additional opportunities for improvement remain. Given the potential for combination products to improve patient outcomes, a dedicated combination product innovation program should be considered as part of MDUFA VI. Such an effort could include an enhanced consultation process for innovative products, and regulatory science-focused initiatives to integrate real-world evidence, patient experience data, and evolving digital health technology use into guidances and other processes.

3. Opportunities in Rare Disease Innovation

While 95% of rare diseases have no FDA-approved treatment, many benefit from medical devices such as implantable, assistive, wearable, and surgical devices[8]. Despite the small patient populations, programs such as the Humanitarian Device Exemption (HDE) program and custom device exemptions make it possible to develop devices for the rarest diseases. Unfortunately, these programs, most notably the HDE program, are underutilized, in part due to the strict eligibility requirements that differ significantly from the definition of an orphan disease (8,000 vs 200,000), complex oversight requirements, and financial restrictions.[9].

Given the extent of the unmet need that exists in the rare disease community and the financial constraints placed on companies willing to develop devices for our most vulnerable communities, we should commit to collaborative conversations with device makers, academic scientists, patient communities, and the agency team's tasked with administering the HDE program to identify strategies that can optimize the program within the agency's statutory authority.

The establishment of the Rare Disease Innovation Hub (RDIH), housed within CDER and CBER, with representation from CDRH in certain activities, presents an opportunity for greater cross-center collaboration that takes a holistic approach to maximizing drug, biologic, and device innovation for rare diseases. Close integration in RDIH activities will enable experiences from CDRH's approaches to patient engagement and the integration of PPI to be efficiently translated to applicable drug and biologic strategies.

It could also be an ideal avenue to identify opportunities for more efficient approaches to drug/device combo product reviews, post-market safety and efficacy monitoring, and other regulatory policy challenges. We urge you to convene these conversations throughout the MDUFA process so that promising opportunities for collaboration, such as pilot initiatives, can be integrated into MDUFA VI.

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[8] 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/

[9] Lottes AE, Cavanaugh KJ, Chan YY, Devlin VJ, Goergen CJ, Jean R, Linnes JC, Malone M, Peat R, Reuter DG, Taylor K, Wodicka GR. Navigating the Regulatory Pathway for Medical Devices-a Conversation with the FDA, Clinicians, Researchers, and Industry Experts. J Cardiovasc Transl Res. 2022 Oct;15(5):927-943. doi: 10.1007/s12265-022-10232-1.

Lastly, the RDIH strategic goals include the establishment of the Rare Disease Innovation, Science, and Exploration (RISE) Workshop series to address challenges common to multiple diseases or a class of diseases, for which evolving science offers innovative solutions[10]. The first workshop will focus on Controls in Rare Disease Clinical Trials for Small and Diminishing Populations. The EveryLife Foundation, along with other patient advocacy organizations, has submitted a proposal for a RISE Workshop to collectively optimize risk assessment and mitigation strategies, including rapid exchange of shared learning across the durable cell and gene therapy community. The RISE Workshop model presents an opportunity for MDUFA VI to advance rare disease regulatory science and propel innovation that can address issues that cut across device and drug development.

Conclusion

The EveryLife Foundation and our collective patient community organization partners are eager to continue leaning in and working with the agency, sponsors, and patient communities to ensure that the patient experiences of rare disease communities continue to inform considerations and decision-making throughout the product development life cycle. We would be happy to serve as a resource or 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.

[10] Food and Drug Administration. *FDA Rare Disease Innovation Hub*. U.S. Food and Drug Administration. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/fda-rare-disease-innovation-hub