March 5, 2025

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. FDA-2024-D-2033, "Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics Guidance for Industry"

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 "Expedited Program for Serious Conditions – Accelerated Approval of Drugs and Biologics Guidance for Industry".

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. These comments reflect the engagements of this coalition around our shared experiences with the FDA's approach to accelerated approval.

There are over 30 million Americans living with rare diseases, a disproportionate percentage of whom are children. Of the estimated more than 10,000 rare diseases, fewer than 5% have an FDA-approved therapy[1]. For over a decade, the EveryLife Foundation and the patient community have worked to advance the science for the use of biomarkers in rare disease therapy development, to optimize the use of accelerated approval pathway for novel rare disease therapies, and to build congressional and public awareness about the challenges of rare disease drug development.

Thanks in large part to advances in science and technology, investments in rare disease research, the unwavering dedication of the patient community, and the leadership of the FDA in embracing regulatory science innovation rare disease product evaluation, over 1200 orphan designated approvals are now changing

[1] *Delivering Hope for Rare Diseases*. National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH). (2023).

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health outcomes for patients and families[2]. The accelerated approval pathway has played a significant role in allowing patients to access the full benefit of these orphan products.

To date, over 250 therapies have been approved through the accelerated approval pathway, improving the lives of patients with cancer, rare diseases, and other conditions with unmet needs[3]. Of those approved therapies, 58% of accelerated approvals have been converted within 5 years[4]. In fact, 98% of the first 105 accelerated approval therapies had been converted or withdrawn by 2022[5].

The accelerated approval pathway is working as intended: delivering better health to those in dire need. Since its inception, nine cancers, HIV, inhalation anthrax, and chronic iron overload had 5 or more products approved via the accelerated approval pathway[6]. Unfortunately, non-oncology rare diseases are nowhere near that milestone and account for just 23% of all products approved using the accelerated approval pathway[7].

We applaud FDA for recognizing in the guidance document the challenges associated with developing therapies for rare diseases and the need for a more flexible approach that considers the totality of information as part of the regulatory review process. This approach must include the full array of rare disease perspectives, inputs, and expertise available within and throughout the FDA and outside the agency. We believe that the accelerated approval pathway can be more effectively utilized to meet the needs of the rare disease community through specific points of enhanced community engagement to include enhancements in the following areas:

- Identifying the explicit role of the Rare Disease Innovation Hub in supporting the use of the accelerated approval pathway in rare disease;
- Emphasizing consistency, along with early and sustained engagement;
- Consultation with external experts prior to regulatory review;
- Inclusion of Patient Experience Data to inform endpoint selection;
- Withdrawal procedures; and
- Accelerated Approval Council status and activity update

Rare Disease Innovation Hub Opportunities

The agency's launch of the Rare Disease Innovation Hub in July 2024 provides the rare disease community with a new and invaluable asset that can help support FDA's assessment of key data points, such as the pathway's evidentiary criteria[8]. We recommend that the FDA include explicit references to the role the Rare Disease Innovation Hub can play in this work within a final guidance document.

As an example, to improve the development efficiency for accelerated approval candidates, we urge the FDA to seek dramatic improvement in the timeliness and throughput of such compounds via renewed

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[2] Food and Drug Administration. (n.d.). *Search orphan drug designations and approvals*. Orphan Drug Product Designation Database. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm

[3] 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

[4] Ibid

[5] Ibid

[6] Ibid

[7] Ibid

[8] Rare Disease Innovation Hub, Rare Disease Innovation Hub Strategic Agenda (2025).

attention to the qualification of drug development tools, especially the processes for qualifying biomarkers and intermediate clinical endpoints.

Collaboration with the Rare Disease Innovation Hub would also be useful when answering challenging questions, such as the options available to rare disease sponsors if a confirmatory trial is deemed infeasible. Additional clarity and the use of examples that illustrate how the FDA will approach different scenarios mentioned in the guidance will support efficient and effective rare disease therapy development.

Emphasizing consistency, along with early and sustained engagement.

We also recommend that the guidance encourage a consistent approach to facilitating early communications between sponsors and the FDA to determine if a candidate therapy is eligible for this pathway. While the document mentions the importance of early engagement and consultation with the FDA on multiple occasions, we encourage updating it to speak to consistency in this process to provide greater predictability to sponsors and other stakeholders. Specifically, we encourage the FDA to consider if elements of the *previously withdrawn* Target Product Profile guidance could be used to bring multiple stakeholders together with regulators to achieve agreement on endpoints and related outcome measures.

Consultation with external experts prior to regulatory review

We appreciate the FDA's stated interest in consulting with external experts, including advisory committees, on endpoint selection. While we appreciate the FDA's receptivity to engaging external parties, we are concerned that engaging advisory committees under current practice comes too late in the therapy development process to impact endpoint selection. If the FDA envisions advisory committees informing endpoint selection, the guidance should offer a process to enable such engagement far earlier than the typical use of advisory committees.

Inclusion of Patient Experience Data

We commend the FDA for recognizing the importance of incorporating patients' perspectives into the design of confirmatory trials, particularly within rare disease populations and trials. Including patient perspectives in a meaningful way in trial designs is indispensable in securing adequate participation rates, achieving milestones, and completing confirmatory trials. We are pleased that this issue is recognized in the guidance.

We also recommend that the FDA consider expanding this section to include the consideration of patient preference studies, benefit-risk assessments, and other scientifically rigorous tools to inform endpoint selection. Explicit references to such tools would complement additional FDA guidances as well as laws, policies, and projects intended to advance the use of patient experience data throughout the therapy development process. Such a reference would send a signal as to how the agency views such tools and could further support their development and refinement.

Withdrawal Procedures

We understand that while we hope products approved under the accelerated approval pathway will meet their intended outcomes, there will be instances in which the withdrawal of a product from the market will be necessary. Any such actions must be carefully considered and well-justified, and the FDA

must be transparent in its rationale and justification for any such actions. We are concerned that the proposed 30-day window for public comment on proposed withdrawals via the Federal Register is insufficient to enable adequate levels of engagement. As such, we request that you modify the guidance to change this to a 60-day window.

Additionally, we suggest that communications explaining a product's withdrawal include content understandable to lay (non-medical/non-scientist) audiences. Clear communication is necessary to engender trust and confidence in the system and process. In addition to explaining the reasons for the withdrawal, this communication must also include clear guidance for patient communities regarding their options.

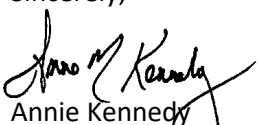
Accelerated Approval Council status and activity update

Under FDORA, an intra-agency coordinating council centered around accelerated approval was required to be established by the FDA within one year of enactment[9]. FDORA included specifications on council membership and tasked the AA Council with ensuring consistent and appropriate use of accelerated approval across the agency through direct engagement with product review teams, as well as the publication of annual reporting of the Council's activities on the FDA website[10].

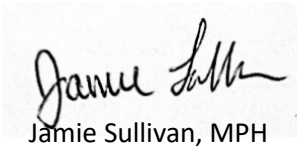
The community seeks clarity on the accelerated approval council's role, authorities, membership, and engagement as established by FDORA.

Thank you for the opportunity to provide input on this critical guidance and for your ongoing efforts to ensure that the accelerated approval pathway results in safe and effective therapies for patients with rare diseases. For further information, please contact Annie Kennedy, Chief of Policy, Advocacy, and Patient Engagement, at akennedy@everylifefoundation.org.

Sincerely,



Annie Kennedy
Chief of Policy, Advocacy & Patient Engagement



Jamie Sullivan, MPH
Vice President of Policy

CC: Michael Pearlmutter, Chief Executive Officer
Vicki Seyfert – Margolis, Board Chair

[9] Food and Drug Omnibus Reform Act of 2022 (2022).
[10] Ibid