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

RE: Docket No. FDA-2019-D-4964 for "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products"

To Whom It May Concern,

On behalf of the RARE Foundation, formerly the EveryLife Foundation for Rare Diseases, we appreciate the opportunity to comment on the updated draft guidance for determining substantial evidence of effectiveness.

The RARE Foundation is a 501(c)(3) nonprofit, nonpartisan organization 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. Our comments reflect the insights and experiences of our diverse coalition, Community Congress, comprised of patient organizations, industry leaders, and other relevant stakeholders who together inform our policy priorities.

Clear and up-to-date guidance from the FDA to therapy developers, researchers, patients, and others provides essential insight into the agency's views to inform the resource-intensive process of developing drugs and biologics. This is especially true with rare diseases, the vast majority of which lack any FDA-approved treatments. While additional clarity is important to the rare disease community, so too is recognition that rare disease therapy development and regulatory review often necessitate more adaptive approaches. We appreciate that the updated document recognizes this, including by seeking to clarify when the default posture should be one well-controlled trial with confirmatory evidence.

We also appreciate the recognition of disease rarity in the document, noting it as a factor that may warrant a more tailored review approach, including the use of adaptive tools that are fit-for-purpose for any particular rare disease. The larger rare disease community, especially rare disease therapy development programs, needs greater predictability from the FDA regarding how the agency approaches the use of regulatory flexibilities while concurrently empowering reviewers to apply the flexibilities warranted by the specifics of each application. This greater certainty or clarity about regulatory flexibilities would include, for example, greater confidence in understanding when evidence from a single trial will suffice; the expected source and strength of confirmatory evidence; and weighting given to disease-specific considerations such as unmet medical need, prevalence, and ethics of a well-controlled trial.

We appreciate that the guidance recognizes that there is neither a single set of clinical considerations nor a single definition of regulatory flexibility, but believe some additional clarity is necessary to prevent

unintended confusion and consequences, particularly among review divisions. As noted above, we believe it is possible to provide additional clarity while embracing adaptive tools in rare diseases.

Given the significant impact of updating the Substantial Evidence Guidance, we have identified several areas for clarification or recommended additions. These include:

- **Clarify the Agency's approach to applying the stated requirement that confirmatory evidence be 'highly persuasive' in rare disease programs.**
    - **Addressing how the highly persuasive criteria in the updated guidance will shift the Agency's current approach to rare diseases**, given that a single trial and confirmatory evidence are already largely the standard, and whether more than one of the listed criteria must be met to be considered highly persuasive.

- **Enhance the section describing 'how flexibility may be applied' with additional details on how the Agency will use patient experience data, patient preference information, and real-world evidence in its approach to determining whether the substantial evidence standard is met.**
    - Providing additional information on how the use of patient experience data, patient preference information, and real-world evidence will be factored into the regulatory review process.

- **Provide clarification on references to surrogate endpoints and commit to working with sponsors and patients to expedite the qualification of surrogate endpoints in rare diseases.**
    - **Clarifying the interpretation of the term feasibility in the context of this guidance,** ensuring that this interpretation is grounded in the realities of rare diseases, particularly as it relates to the use of surrogate endpoints.
    - **Acknowledging the validity of surrogate endpoints in rare disease product development and clarifying that their use is an accepted evaluation method,** rather than an "alternative approach," while also committing to work with sponsors and patient communities to expedite the qualification of new surrogate endpoints.

- **Optimize the role of the Rare Disease Innovation Hub to enhance the application of consistent, predictable approaches to substantial evidence determinations, including by providing additional resources that cross-reference how various guidances, pathways, and Agency programs interrelate in decision-making.**
    - Leveraging the expertise of the Rare Disease Innovation Hub to ensure all stakeholders understand how the Agency utilizes guidance documents to inform regulatory decision-making, and to inform further definitions of terminology used across guidance documents.

Clarify the Agency's approach to applying the stated requirement that confirmatory evidence be 'highly persuasive' in rare disease programs.

The guidance introduces a requirement that confirmatory evidence be "highly persuasive," and enumerates the elements of a highly persuasive trial. We are concerned that, in rare disease programs, not all of these criteria may be feasible or reasonable to meet, and that this terminology may raise the bar inappropriately for rare disease programs. For example, in rare diseases, particularly very rare conditions, traditional clinical trial statistical expectations may need to be adjusted to allow greater flexibility. Additionally, given the nature of several rare conditions that affect limited populations, meaningful subgroup analysis may be more limited. These realities necessitate that the agency further consider how a "highly persuasive" standard is met in rare disease.

Given the success of the Agency applying the regulatory tools authorized by Congress to make fit-for-purpose decisions in rare disease product evaluation, balanced with the community's concerns about the need for more predictable and consistent approaches to how these tools are applied, the Agency should provide more clarity about how the six criteria listed on page 11 will be applied in rare diseases[1]. In particular, the Agency should address how the highly persuasive criteria in the updated guidance will shift its current approach to rare diseases, given that a single trial and confirmatory evidence are already largely the standard, and whether more than one of the listed criteria must be met to be considered highly persuasive.

Enhance the section describing 'how flexibility may be applied' with additional details on how the Agency will use patient experience data, patient preference information, and real-world evidence in its approach to determining whether the substantial evidence standard is met.

The RARE Foundation is supportive of the Agency's recognition that in some rare disease product evaluations, additional uncertainty in statistical results is acceptable. Similarly, we are encouraged by the inclusion of references to natural history studies and real-world evidence as tools that can support effectiveness determinations.

Over the past 15 years, Congress and the FDA, via past user fee agreements and the 21st Century Cures Act, have incubated and evolved activities to deepen the role of patients and caregivers in the therapy development process. These actions have yielded meaningful progress through a variety of tools, including establishing methodological expectations for the collection and use of patient experience data, patient-informed benefit-risk assessments, community-initiated guidance documents, and multiple convenings that enable FDA to hear patients' experiences and perspectives directly.

Additionally, patient organizations are increasingly conducting regulatory-grade, pre-competitive development work, including the creation of natural history studies, disease registries, endpoint development, and post-market real-world data collection. Clear and up-to-date guidance documents are necessary to encourage this work to continue and to inform it, so that scarce resources can be directed toward actions that will have the greatest impact.

The cumulative effect of these developments is the availability of, or potential collection of, regulatory-grade information that can contribute to the totality of evidence used to satisfy the substantial evidence standard. Whether collected by patient organizations, academic collaborations, or sponsors, to be efficient, effective, and feasible, the Agency should provide additional information on how these tools will be factored into the regulatory review process. However, it is important that the Agency also recognizes the potential for these tools to themselves fill gaps in evidence and provide additional examples of scenarios in which patient

[1] U.S. Food and Drug Administration. (2026). *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry* [Draft guidance], 11. U.S. Department of Health and Human Services. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

experience data, patient preference information, natural history studies, and real-world evidence will be considered confirmatory evidence. The greatest possible clarity – including the expectations for any instruments – will be most helpful, especially to the patient advocacy community.

Provide clarification on references to surrogate endpoints and commit to working with sponsors and patients to expedite the qualification of surrogate endpoints in rare diseases.

The guidance notes a preference for the use of clinical endpoints 'when feasible' and suggests that surrogate endpoints should be an 'alternative approach' to clinical endpoints[2]. As noted earlier in our concerns about how FDA may define a highly persuasive trial, given the realities of rare disease therapy development, surrogate endpoints may be the only viable path to delivering safe and effective therapies to patients in a timely fashion. Rare disease patients wait lifetimes to access therapies, and the accelerated approval pathway has provided these communities with hope for a therapy.

For rare disease communities, the definition of "feasible" entails different ethical and trial-design considerations. For this reason, the Agency should clarify its interpretation of feasibility in the context of this guidance, ensuring that this interpretation is grounded in the realities of rare diseases. For example, how will the Agency factor in the extended period of time it would take to measure a clinical endpoint in different disease contexts, and how is this balanced with the ethical implications and the real-world realities of enrolling and resourcing the types of trials that may be necessary to make clinical endpoints 'feasible.'

Therapies that use surrogate endpoints and the accelerated approval (AA) pathway must meet the same safety and efficacy standards as therapies that use clinical endpoints. A 2024 study examining the use of AA found that by the end of 2022, 98% of the first 105 (approved in 2010 or earlier) AA had been converted to confirmed or withdrawn[3]. Of these 105 approvals, fewer than 10% were for non-oncology rare diseases, suggesting that this pathway is already underutilized by communities that could be best served by surrogate endpoints[4].

We acknowledge that the limited availability of qualified surrogate and intermediate clinical endpoints is a significant limitation in optimizing the use of AA for rare disease treatments. The same study found an average of 5.4 oncological accelerated approvals per surrogate marker, compared with 1.1 approvals per surrogate marker for all other accelerated approvals[5]. Given this reality and the promise of the Agency's renewed efforts to support rare disease product development across all sizes and types of rare diseases, expanded FDA efforts to expedite the qualification of surrogate endpoints in rare diseases are warranted. We also encourage the Agency to explore all possible options to prioritize the inclusion of surrogate endpoints in existing initiatives, such as the Rare Disease Endpoint Advancement Pilot, ensuring equitable opportunities for all disease communities to leverage this life-altering pathway.

The inclusion of content that signifies Agency preferences, such as referring to the use of surrogates as an 'alternative approach,' can have significant implications on sponsor and reviewer behavior. We encourage the agency to acknowledge the validity of surrogate endpoints in rare disease product development and clarify that their use is an accepted evaluation method, rather than an "alternative approach". This will be

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[2] U.S. Food and Drug Administration. (2026). *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry* [Draft guidance], 5, 163-166. U.S. Department of Health and Human Services. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

[3] Domike R, Raju GK, Sullivan J, Kennedy A. Expediting treatments in the 21st century: orphan drugs and accelerated approvals. Orphanet J Rare Dis. 2024 Nov 8;19(1):418. doi: 10.1186/s13023-024-03398-1. PMID: 39516878; PMCID: PMC11549740.

[4] *Ibid*

[5] Domike R, Raju GK, Sullivan J, Kennedy A. Expediting treatments in the 21st century: orphan drugs and accelerated approvals. Orphanet J Rare Dis. 2024 Nov 8;19(1):418. doi: 10.1186/s13023-024-03398-1. PMID: 39516878; PMCID: PMC11549740.

particularly impactful for communities, researchers, sponsors, and investors who may already view this pathway as inaccessible.

Optimize the role of the Rare Disease Innovation Hub to enhance the application of consistent, predictable approaches to substantial evidence determinations, including by providing additional resources that cross-reference how various guidances, pathways, and Agency programs interrelate in decision-making.

We commend the Agency for its efforts to improve resources for industry and patient advocates to better understand and engage in the product development process. The recent release of case studies using real-world evidence and the updated webpage of guidance that directly impacts rare disease therapy development will be particularly impactful for community engagement in this process.

The Rare Disease Innovation Hub, established in July 2024, has already begun driving cross-FDA knowledge-management initiatives to help reviewers apply consistent approaches. Since its creation, over 4,000 community members have engaged with the Hub through its RISE Workshop Series, and more than 100 organizations have connected directly with the Hub about its goals and FDA regulatory practices. The Hub's 2026 Strategic Agenda laid out an ambitious agenda to grow its role in facilitating the dissemination and update of rare disease best practices across the Agency, host three additional RISE Workshops on timely topics that can catalyze therapy development, create opportunities for rare disease patient organizations and experts to inform the therapy development and evaluation process, and streamline the navigation of FDA's rare disease resources[6].

The updates to the substantial evidence guidance highlighted the Hub's unique opportunity to ensure that sponsors, the broader community, and in some cases, reviewers, understand how the Agency uses guidance on relevant topics to provide advice and make decisions. The substantial evidence guidance directly or indirectly references numerous other guidances on relevant topics such as real-world evidence, confirmatory evidence, and the plausible mechanism framework. Community Congress members noted a need for technical details on guidance cross-references, as well as plain-language guidance summaries, visuals, and case studies that explain the connection between guidance advice and decision-making.

The Hub can also help further define several terms used in the updated guidance in ways that capture the unique realities of rare disease product development. For example, the guidance's references to "life-threatening" and "severely debilitating" refer to the general statutory definitions, but reviewers and sponsors would benefit from a more detailed understanding of how to apply these definitions in rare diseases. Additionally, clarifying that stabilizing or slowing irreversible loss of function in a slower-progressing disease should be factored into the definition of life-threatening, in the same way that expected survival time is for faster-progressing diseases.

Conclusion

The RARE Foundation is grateful to the Agency for reflecting many of the insights gained from its interactions with external stakeholders in the language and advice used in the guidance updates. With additional clarification and small adjustments to some terminology, the updated guidance can enhance the Agency's approach to ensuring that rare disease products are evaluated using rigorous, fit-for-purpose evidence that recognizes the unique characteristics of each program, disease, and patient experience.

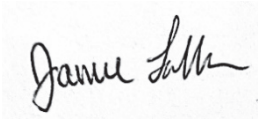
[6] Food and Drug Administration. (2026). *Rare Disease Innovation Hub: Strategic Agenda 2026*. https://www.fda.gov/media/185144/download?attachment

We urge the Agency to commit to regular assessments of how the updated guidance is understood and applied in decision-making, to communicate how the updated practices are evolving, and to ensure more rapid community understanding and uptake.

We look forward to continuing to partner with the Agency to ensure the lived experiences and regulatory learnings within the rare disease community are translated into improved policies and practices for the development and evaluation of rare disease treatments. If we can provide additional information on the above recommendations, please contact Jamie Sullivan, SVP of Policy & Advocacy, at jsullivan@rareadvocates.org.

Sincerely,

Annie Kennedy
Chief of Mission Officer
RARE Foundation



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