July 23, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2024-N-1809:
Listening Session: Optimizing FDA's Use of and Processes for Advisory Committees

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 Food and Drug Administration's efforts to optimize the use of its advisory committees.

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 FDA advisory committees.

We are a community that feel an intense sense of urgency on behalf of the more than 30 million Americans living with rare diseases, a disproportionate percentage of whom are children. And as most are aware, fewer than 5% of the estimated 10,000 rare diseases have an FDA-approved therapy[1].

Thanks in large part to remarkable advances in science and technology, investments in rare disease research, heroic efforts by patient communities and importantly, the leadership of the FDA in embracing regulatory science innovation and the application of appropriate flexibility in rare disease product evaluation, over 1120 orphan designated approvals are changing lives of the patients and families affected[2].

Our optimism is balanced by the staggering extent of unmet need that remains and the recognition that in some cases, it is process and policy hurdles preventing scientific possibility from reaching patients. We are grateful for FDA's efforts to examine the role of its advisory committees and believe that some reform is necessary to ensure their use is serving the agency, patients, and the goal of safe and effective therapies reaching patients at the earliest opportunity.

Advisory committee reform is particularly relevant to rare disease product development which occurs in every center and across every division in CDER. A brief look at the use of advisory committees in novel, non-

[1] https://ncats.nih.gov/sites/default/files/NCATS_RareDiseasesFactSheet.pdf
[2] https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm

oncological rare disease therapies approved by CDER or CBER shows, over the span of 2022-2023, advisory committees were convened for 7 out of 36 approvals[3]. Rare disease products often target symptoms of diseases that affect multiple organ symptoms, have heterogeneous presentations and in about 70% of the time, begin in childhood[4]. There is no separate, lower or lesser legal or regulatory standard for approval of orphan products. Researchers, product developers, and FDA alike must confront these issues throughout all phases of development and employ creative approaches to product development and review. Optimizing the use of advisory committees will enable the FDA to better handle these and other complexities in rare disease product development.

Today's topic is also timely, as numerous efforts are well underway that can inform the agency's approaches to advisory committee reform. These include provisions in FDORA requiring a GAO study on how FDA incorporates rare disease external experts in the regulatory review process, a National Academies of Sciences and Medicine Study with an emphasis on improving consistency in decision making for rare disease product evaluations and provisions in the FY2023 appropriations report explanatory statement that encourage the FDA to work to include no less than two expert members on each advisory committee when that committee is reviewing an orphan designated drug.

The need for more consistency and transparency are key themes throughout rare disease regulatory policy initiatives. The sensitive rare disease development ecosystem and the high stakes for patients who, in most cases, lack any existing treatments, demand that attention be paid to appropriate composition of committees, greater clarity in expectations for when and what will occur in an advisory committee and a high level of transparency into how and why the agency uses advisory committee discussions in their decisions.

Categories of expertise, viewpoints or voices that are important for representation on advisory committees

Specific to the expertise that is included in any given advisory committee – there are a few categories of expertise that are particularly important for any orphan product review. Rare disease therapy development complexities demand a high level of expertise in innovative trial designs, thus including expertise specific to small-population clinical trials in an advisory committee is critical. Numerous global initiatives have recognized the complexities involved in conducting and analyzing clinical trials when population numbers are limited and put forward consensus recommendations to support novel statistical methodology in small populations. Ensuring there are experts on an advisory committee who fully understand how to design and interpret results from small population trials will help to produce meaningful conversations to guide FDA's approach.

Similarly, as the field of patient focused drug development and the use of patient experience data has advanced, experts in social sciences, patient preference studies and interpreting the use of patient experience data, are often absent from advisory committee discussions. CDRH's embrace of patient preference studies and The PFDD Guidance series are just two of the initiatives that enabled broader collection and use of patient experience data in developing and evaluating rare disease medical products, however the transformative potential of these initiatives is limited when advisory committee members are not provided with appropriate training on how to consider PED, especially when no expert is present on the committee to fill in the gaps.

Two additional stakeholders are essential to add to any advisory committee considering rare disease medical products or regulatory science related questions, a clinician who is an expert in the condition for which the product is intended, and a patient community representative. In instances in which it is a pediatric disease, the perspective of a caregiver may serve as proxy. And in instances where the condition being treated is a pediatric

[3] https://pink.citeline.com/datasets/advisory-committees

[4] Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020). https://doi.org/10.1038/s41431-019-0508-0

onset condition where individuals are now serving into adulthood, the FDA is urged to consider including both a patient representative and a caregiver representative, when possible. All these expert perspectives are especially critical to provide context to the complexities and nuances inherent in rare disease product reviews.

Ensuring diverse perspectives are heard and meaningfully incorporated into advisory committee discussions.

Adjusting Conflict of Interest Policies

To enhance meaningful advisory committee discussions and appropriately compose a committee that will review rare disease products, it is necessary to reconsider how conflicts of interest are determined. Patients and clinicians depend on the FDA's thorough and independent decision-making processes, and it is understandable that the agency upholds strict conflict of interest procedures in most cases. However, as many FDA leaders, including Commissioner Califf and center leaders have recognized, there is rarely an expert in a rare disease that does not spend time working on therapy development programs or educating others in the scientific and clinical community about the disease. In some cases, you can count the number of qualified experts in a given rare disease on one hand. It is these experts who can contribute the most to the tough questions FDA reviewers are wrestling with as they evaluate rare disease products. There must be processes in place to allow these experts to contribute, with reasonable guardrails in place to manage any potential for conflict of interest.

Similarly, to facilitate meaningful participation from a patient and/or caregiver representative, reconsideration of the process to determine conflicts is required. Patient representatives assume immense responsibility and the burden that comes along with participating in such high stakes conversations as advisory committees are for the patients and families waiting for hope. Increasingly, patient advocacy organizations are driving rare disease product development through investments, conduct of research and collection of patient experience data. These organizations and the engaged patients and families that lead them are well suited to identify and support experts who can meaningfully participate in nuanced advisory committee discussions; however, current processes lead to many of the most appropriate patients being ruled out due to their roles in the community.

Rare Disease Advisory Committee

Facilitating the appropriate composition of committees evaluating rare disease products is challenging, especially when dealing with ultra rare diseases with few patients and scientific experts. While impractical to ensure there are experts in every rare disease on standing committees, one alternative to ensure consistent rare disease expertise is meaningfully incorporated into advisory committee discussions, in addition to including temporary scientific, clinical and patient expertise, is to establish a standing Rare Disease Advisory Committee.

There is precedent for this approach. The pediatric, and risk communications panels, advise FDA on a broader set of issues within their remit. The recent establishment of the Advisory Committee for Genetic Metabolic Disease Treatments highlights the growing need to convene subject matter experts in focused areas to ensure accurate representation of community expertise and values. FDA has also convened joint meetings that involve two advisory committees to advise on an issue. A rare disease advisory committee can provide counsel to FDA on issues of importance in rare disease as well as possibly being convened jointly, as needed, with a human drug or device committee for the purposes of advising on a candidate therapy.

The committee could also be called to provide guidance on emerging issues of importance to the field of rare disease, such as new approaches to conducting and reviewing small population trials, qualifying biomarkers, or establishing new or modified pathways. Members would be selected from among authorities knowledgeable and experienced in rare disease research and development, statisticians with expertise in rare diseases, researchers with expertise in conducting trials for rare diseases (even if the expertise is in a different rare

disease than the one under discussion), geneticists with rare disease expertise, and rare disease patient advocates, including caregivers.

Advisory Committee Member Engagement Process Enhancements

Consistent and transparent use of advisory committees will enhance the public's trust in FDA's decision making and enable innovations to translate to better outcomes for patients. Enhancing current processes must include tweaks to the training processes for members, the agenda and facilitation of the meetings themselves.

Advisory committee members are chosen for their individual expertise, but many members lack a thorough understanding of the parameters that FDA operates in when considering rare disease products. As agency leaders embrace the need for applying appropriate regulatory flexibility to rare disease reviews, advisory committee members need to be given more insight into the factors that influence how FDA will approach flexibility. With more understanding of how FDA considers regulatory flexibility on issues such as endpoint selection, clinical trial design and evidence evaluation, advisory committee members will be able to provide more meaningful insights.

Additionally, advisory committee members' contributions can be enhanced by providing them, in advance, with available information on the patient population, impacts of living with the disease, patient preferences and risk tolerance and other information commonly available in official documents like a previous Voice of the Patient Report or readouts from listening sessions.

Preparation alone will not be sufficient to optimize advisory committee use, however. These suggestions are speaking specifically about meetings to inform product reviews, rather than previously suggested meetings that would tackle tough rare disease regulatory science issues. In line with comments from FDA leaders, we encourage changes to the advisory committee meetings that will facilitate more in-depth discussions on the tough issues in rare disease product development for a given disease and program.

One such change could be to identify a distinct time in the agenda to hear and discuss available patient experience data, including relevant evidence collected by credible organizations such as patient advocacy organizations. In the current format, sponsors are forced to decide if they will dedicate some of the limited time in presentation to cover patient experience data. As a result, typically only data collected by the sponsor is discussed, if any. Patient experience data is now being collected and curated by patient advocacy organizations. If there was dedicated time for this discussion when data is available, it will only serve to enhance pre-competitive collaborations to build on the knowledge base in a particular disease.

Consideration should also be given to the benefits of having a neutral facilitator in charge of advisory committee meetings, a role currently filled by the chairperson, typically an expert scientist, not an expert in generating fair and meaningful conversation for informing regulatory decisions. In numerous instances, we heard from community members who have witnessed advisory committee discussions dominated by one member's perspective or be derailed by less than accurate concerns that point discussions in one direction without opportunity for others to step in and ensure a full picture of the issue is painted. Expert facilitators are used in settings across public and private life to manage conversations, pull out key points and ensure objectives of the meeting are met. The FDA should consider the merits of deploying them for advisory committee discussions too.

Incorporating the consumer or patient voice into advisory committee meetings

In addition to seeking input on changes to the composition of committees and the processes for engaging members, the agency has also asked for suggestions on how you can incorporate the consumer or patient voice into advisory committee meetings in a more meaningful way. There are opportunities to enhance how public views are incorporated through changes to the Open Public Hearing (OPH) process. The OPH is the only

time that patients who participated in the trial, patients and families living with the disease, patient organizations, and others can weigh in with context that can support agency decision making. The limited time afforded to such comments results in the agency conducting a lottery to award speaking slots.

The lottery approach, while understandable, does not result in a diverse and representative array of speakers who can cover the universe of perspectives relevant to regulatory decisions. A more targeted approach would be to consider a hybrid process that identifies key stakeholder categories for each meeting and allots a reasonable time for each. In cases where demand outstrips availability for those spots, then a lottery approach can be initiated. This, along with providing additional clarity to the public on the rules for the OPH, how speakers are selected and guardrails for how advisory committee members should consider such testimony, will go a long way towards public trust and understanding of the agency's decisions.

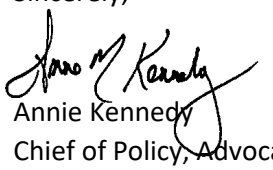
Additional areas of focus for advisory committee optimization

We encourage the agency to broaden their inquiry into the tough questions that have been raised by FDA leaders and regulatory experts in public remarks but were absent from the listening session and register notice. That is, what are the questions and topics that advisory committees should be weighing in on in the first place, and when is their input most useful? As Dr. Califf said in a 2023 interview, "We have these big societal issues and the decision about an individual product is like the tip of the spear of something that needs context and I think the best use of advisory committees is to get context, not the specifics on that particular product."[5]

Lastly, as you consider additional topics related to public education and understanding of the role of advisory committees, we again emphasize the importance of transparency, not just for ensuring public trust in the FDA, but also so that patients, sponsors, investors and others understand the rationale behind any decisions that are not in line with advisory committee discussions and can learn and adapt in future efforts. The stakes are too high, and time can be the most precious commodity for the rare disease community.

We are grateful for the opportunity to touch on issues of advisory committee composition and how tweaks to advisory committee member and public engagement can support rare disease product evaluation and overall rare disease development considerations.

Sincerely,



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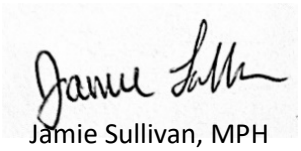

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[5] Gingery, D. (2022, April 29). US FDA's Califf Expects Advisory Committee Reform Talk "about a year from now." Pink Sheet. https://pink.citeline.com/PS146109/US-FDAs-Califf-Expects-Advisory-Committee-Reform-Talk-About-A-Year-From-Now