Rare Disease Company Coalition

BY ELECTRONIC DELIVERY

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Center for Biologics Evaluation and Research (CBER)
10903 New Hampshire Avenue, Silver Spring, MD 20993-0002

Director Patrizia Cavazzoni, M.D.
Center for Drug Evaluation and Research (CDER)
10001 New Hampshire Ave, Silver Spring, MD 20903

Re: Advancing Rare Disease Therapies Through a Food and Drug Administration Rare Disease Innovation Hub [Docket No. FDA-2024-N-3528]

Dear Director Marks and Director Cavazzoni,

The Rare Disease Company Coalition (RDCC) thanks you for your leadership on rare disease issues and applauds the establishment of the Rare Disease Innovation Hub. With so much at stake for the 1 in 10 Americans living with a rare disease, this new model for coordination and collaboration has the potential to spur the development of new innovations for the 95 percent of rare diseases with no FDA-approved treatment.

The RDCC represents innovative life science companies committed to discovering, developing, and delivering treatments for patients living with a rare disease. Our goal is to share the unique challenges—and promises—for companies who take these rare disease drugs from research through development, approval, manufacturing, and ultimately, to delivery to patients. Collectively, RDCC members invest more than $17 billion in R&D annually, and on average, invest nearly 60 percent of their annual expenditures back into R&D. Coalition members have brought over 50 treatments to market to date, many which are first-to-market therapies; and are currently working on more than 200 rare disease development programs.

We are optimistic that, alongside stakeholders across the rare disease community, the Hub will increase collaboration with patients, leverage cross-agency expertise and advance regulatory science on behalf of individuals living with rare diseases. We appreciate the opportunity to provide feedback and look forward to continuing to work with FDA and other stakeholders to support the Hub in fulfilling its mission and promise.

To that end, RDCC respectfully recommends that the Hub prioritize the following activities:

- Establish a Centralized Rare Disease Training Program
- Coordinate with the Office of Chief Scientist to ensure advisory committees are used effectively in rare diseases
- Facilitate inclusion of patient experience data in assessment of benefit and risk throughout the product lifecycle

- Ensure transparency of, and FDA's participation in, Externally Led Science Focused Drug Development meetings
- Participate in the Accelerated Approval Coordinating Council and ensure that review staff are equipped to use all available tools when appropriate to speed access to treatments for serious or life-threatening conditions with high unmet need
- Assess FDA's existing rare disease programs to identify impact and opportunities for improvement
- Develop a strategic roadmap with identified long and short-term priorities and quantifiable metrics for success
- Host biannual public meetings to share updates and progress toward the goals outlined in the strategic roadmap
- Submit annual reports to Congress on the successes, challenges, and learnings from the Hub

The above recommendations are described in greater detail below:

I. What specific rare disease-related scientific, regulatory, or policy issues should be prioritized for consideration by the Rare Disease Innovation Hub?

A. <u>Promote use of statutory authorities via coordination of training within and across FDA to ensure that safe and effective rare disease products are available to patients in a timely manner.</u>

For rare disease drug development, one size does not fit all. Rare diseases involve unique challenges, such as small, heterogeneous patient populations; diagnostic delays; and slow rates of progression for some diseases. Over the past several decades, Congress has enacted laws and FDA has issued regulations and policies that together comprise a rare disease "toolkit." However, the authorities provided in this toolkit are not always fully explored or appropriately applied. The Agency should be encouraged to exercise its existing authorities that is contained in this toolkit – including innovative trial designs, use of real-world evidence, and the accelerated approval pathway – to the fullest extent, and as appropriate, throughout the development and review of rare disease treatments.

RDCC commends the FDA for its commitment to advancing regulatory science through focused efforts on novel endpoints, biomarker development and assays, innovative trial design, real-world evidence, and statistical methodologies. RDCC recommends that FDA build upon this progress and leverage the Rare Disease Innovation Hub to strengthen FDA's existing rare disease training activities towards the goal of increasing knowledge, awareness, and implementation of FDA's rare disease "toolkit."

Recommendation: Establish a centralized Rare Disease Training Program through the Rare Disease Innovation Hub. The Hub should be responsible to develop educational materials and train review staff on rare disease issues, and the regulatory tools that are available to address them and provide a publicly available report summarizing training activities conducted. The Hub should leverage the educational materials to increase public awareness regarding FDA's rare disease "toolkit" and to educate advisory

committee participants.

B. Ensure the advisory committee process harnesses appropriate expertise for rare disease deliberations.

Advisory committees can play a critical role in guiding the FDA's decision-making. We applaud FDA for its efforts, including through the recent listening session[1], to improve the advisory committee process to ensure the incorporation of relevant expertise. However, there is an opportunity to optimize the composition of advisory committees to ensure that decision-making is informed by disease-specific context and includes robust consultation with rare disease experts. For a given rare disease, there may only be a handful of academic, scientific, or medical experts across the country. The current conflict of interest rules often disqualify these experts from participating in an advisory committee meeting, thereby limiting the availability of disease-specific expertise. Advisory committees should instead encourage the inclusion of enhanced expertise in the given disease or condition through greater use of existing waiver authorities.

The RDCC thanks the FDA for its initiatives focused on conflict-of-interest policies, including the listening session and public comment opportunities, as well as the ongoing policy development efforts being led by the Office of the Chief Scientist, aimed at enhancing the functionality and processes of advisory committees. RDCC strongly encourages the Hub to be involved in this assessment to ensure that FDA's efforts to optimize the composition of advisory committees consider the unique challenges of rare diseases.

Recommendation: The Rare Disease Innovation Hub should coordinate with the Office of the Chief Scientist to identify and implement solutions that increase the effectiveness of advisory committees for use in rare diseases.

C. Include patient experience data in the assessment of benefit and risk throughout the rare disease product lifecycle.

The RDCC appreciates FDA's efforts, including through recent guidance, to clarify the use of patient experience data (PED) in regulatory decision-making. However, due to the challenges associated with rare disease drug development, PED and real-world evidence (RWE) are generally used to provide supporting information to rare disease product applications, rather than informing benefit and risk.[2] FDA should be encouraged to apply a "totality of evidence" approach to drug development and review - including all endpoints that are met, patient experience data and real-world evidence – in the assessment of benefit and risk throughout the rare disease product lifecycle. In line with the aim of advancing regulatory science for rare diseases, the Hub should explore opportunities to engage stakeholders and share information on best practices for collecting and integrating PED and RWE in regulatory decision-making.

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[1] Food and Drug Administration. Public Meeting: Optimizing FDA's Use of and Processes for Advisory Committees. June 2024. Available: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/public-meeting-optimizing-fdas-use-and-processes-advisory-committees-06132024

[2] Food and Drug Administration. FDA Assessment of Use of Patient Experience Data in Regulatory Decision-Making. June 2021. Available: https://www.fda.gov/media/150405/download?attachment

Recommendation: The Rare Disease Innovation Hub should facilitate a public meeting and comment period to inform development of guidance on the use of PED and RWE in regulatory decision-making, including the threshold for incorporation in the benefit-risk assessment and product label. Further, FDA should be encouraged to finalize the existing suite of on patient-focused drug development draft guidances.

D. Ensure FDA's access to clinical and scientific expertise and timely scientific exchange through Externally Led Science Focused Drug Development (SFDD) meetings.
It is critical that FDA reviewers have access to the latest advancements in rapidly evolving science behind specific rare diseases to make timely and informed regulatory decisions. However, with10,000+ identified rare diseases and counting, we recognize that today, there are limited opportunities for co-education between FDA reviewers and experts in the field about the science underlying specific rare diseases. While there are meetings that bring together experts and regulators, they are happening today in an ad-hoc fashion, which leads to inconsistencies in replicability and accessibility.

Consistent with the goal of the Hub to serve as a single point of connection with the rare disease community, the Hub is best positioned to tackle the issue of co-education. Furthermore, the Hub's function of enhancing alignment across FDA's centers can be achieved through co-education by providing opportunities for visibility and information sharing across the Agency.

The Externally Led Science Focused Drug Development (EL-SFDD) meeting represents a new forum to facilitate earlier discussion and education about specific rare diseases or groupings of rare diseases between FDA leaders, reviewers, scientific & medical experts, industry, and patient representatives. While helpful forums exist among FDA's current suite of meeting types, gaps remain in ability to ensure FDA leadership and reviewers have maximal expertise on scientific and development considerations for specific rare diseases. EL-SFDD meetings could promote cross-training of Agency and sponsor teams and provide a meaningful opportunity for collaboration, knowledge sharing, and scientific alignment earlier in the development process. A recent policy proposal, the Scientific External Process for Educated Review of Therapeutics (Scientific EXPERT) Act of 2024, would codify the EL-SFDD meeting to ensure that regulatory approaches keep pace with rapidly evolving science.

Recommendation: The Hub should be responsible to ensure participation from review teams and other FDA staff as appropriate and ensure that EL-SFDD learnings are included in the centralized Rare Disease Training Program as described above in (A). Importantly, the Hub should be responsible to ensure transparency regarding the selection of participants to ensure the participation of appropriate stakeholders including patients, disease experts, and industry representatives.

E. Advance regulatory science regarding accelerated approval therapies.
For 30 years, the accelerated approval pathway (AAP) has served as a critical lifeline for

rare disease patients, leading to significant advances in the treatment of serious, life-threatening diseases. The AAP is a critical tool that can address the unique challenges of rare disease drug development and provide rare disease patients with earlier access to treatment based initial evidence of safety and effectiveness, while confirmatory studies required to verify clinical benefit are ongoing. In many cases, this pathway may be the only option to evaluate treatments for small populations with slowly progressive diseases, because the amount of time needed to establish clinical benefit makes running a clinical trial nearly impossible. However, use of the AAP is inconsistent across the Agency. Some areas, such as the Oncology Center of Excellence, have vast experience and success using the AAP to bring about new treatments. At the same time, the program is underutilized in other areas, including rare diseases. RDCC applauds FDA for its efforts to support the use of the AAP, including through the establishment of the Accelerated Approval Coordinating Council (AACC), to ensure the consistent and appropriate use of the pathway.

Recommendation: The Director of Strategic Coalitions should be a standing member of the Accelerated Approval Coordinating Council and participate in all AACC meetings. Additionally, since the Hub aims to advance regulatory science with dedicated workstreams for consideration of novel endpoints and biomarker development, the Hub should develop a resource (to be included in the Rare Disease Training Program described above) to ensure that review staff are equipped to use all available tools when appropriate, including surrogate endpoints reasonably likely to predict clinical benefit, to speed access to treatments for serious or life-threatening conditions with high unmet need.

II. *To the extent the issues identified in response to Question 1 are related to specific types of rare diseases or conditions, please explain.*

As described above, there are common challenges and opportunities associated with rare disease drug development, and in the environment for rare disease drug development. At the same time, each rare disease (and rare disease subset) is characterized by unique features and circumstances. It is important that FDA, in addressing the issues identified in the response to Question 1, collaborate with rare disease stakeholders and experts to maximize the benefit and impact of the Agency's rare disease activities and programs.

III. *What specific types of rare disease-related activities do you believe would benefit from enhanced collaboration, focused attention, or increased transparency (to the extent legally permissible) under the Rare Disease Innovation Hub? Please identify in your comments rare disease-related activities or initiatives currently being undertaken by CDER or CBER that you believe would benefit from being undertaken by the Rare Disease Innovation Hub as a joint endeavor.*

The Rare Disease Innovation Hub should prioritize an assessment of FDA's existing rare disease programs to identify impact and opportunities for improvement. The assessment should include an opportunity for stakeholders - including drug sponsors and patients - to

provide feedback. Further, the Hub should consider providing regular updates on all the rare disease programs.

IV. *Please comment on approaches that the Rare Disease Innovation Hub should follow for engagement with patients and caregiver groups, industry organizations, and scientific/academic organizations (including different approaches for different types of engagement, as appropriate).*

A. Develop a strategic roadmap with quantifiable metrics for success.
The Director of Strategic Coalitions should develop a strategic roadmap with identified long and short-term priorities and quantifiable metrics for success. This roadmap should be developed in collaboration with the rare disease stakeholder community via public comment opportunities (such as this docket), and remain flexible to adapt to new challenges, opportunities, and innovations.

B. Increase communication and collaboration with rare disease stakeholders.
The Hub should host biannual public meetings to share updates and progress toward the goals outlined in the strategic roadmap.

C. Submit annual reports to Congress to monitor progress and outline need for additional resourcing.
Hub leadership should submit annual reports to Congress on the successes, challenges, and learnings from the Hub. FDA should also submit an appropriations request to expand the Hub's footprint and capabilities.

We appreciate the opportunity to provide feedback on the establishment of the Rare Disease Innovation Hub, and we thank Directors Marks and Cavazzoni for their continued commitment to improving the lives of Americans living with rare diseases. Should you have any questions, please feel free to contact me at stacey@rarecoalition.com. We look forward to working with you.

Sincerely,

Stacey Frisk
Executive Director
Rare Disease Company Coalition