Comment from Rare Disease Patient Organizations
February 28, 2022

Food and Drug Administration
U.S. Department of Health and Human Services
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

Re: FDA-2021-D-1146, *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry*

Dear Commissioner Califf, Dr. Cavazzoni, Dr. Marks, and Dr. Pazdur,

On behalf of the patient organizations signed below, we thank you for the opportunity to submit a comment in response to the FDA's draft guidance document *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products*.

We are a group of forty-two **rare disease patient organizations**, who have prepared this comment through a collaborative process to share our experiences with patient registries and natural history studies. We are part of the Rare As One Network and receive funding from the Chan Zuckerberg Initiative ("CZI"), but the views reflected herein are ours and do not necessarily represent the views of CZI. We are the sole authors of this comment, and the opinions and proposals are our own.

Each organization signed below is involved in a range of programs and research activities that support the development of new therapies, the improvement of clinical care, and the increase of basic knowledge about a rare disease. Many of us share our perspective as creators of patient registries and natural history studies, and we work closely with our patient communities to collect real-world data (RWD) and contribute to clinical research.

As key stakeholders in the collection of RWD, we are submitting this comment to share our experiences and suggestions for how regulators, patient organizations, and industry can work together to leverage the potential of RWD and translate into real-world evidence (RWE) in support of research and regulatory approval of rare disease therapies.

Patient organizations are vital to identifying and reaching rare disease patients and are increasingly building registries, designing natural history studies, and collecting real-world data.

Patient organizations typically spearhead the identification and engagement of a highly dispersed patient base, build collaborative research networks for their specific diseases, and fund basic, translational and clinical research efforts. Since there are fewer financial incentives for private industry to invest in foundational RWD for rare diseases, patient organizations often initiate urgently-needed RWD efforts in their disease areas, knowing that longitudinal data takes time to collect. As patient organizations, we are uniquely positioned to play a major role in the collection of RWD, particularly patient-generated data, as we have the trust and engagement of our patient communities.

While many patient organizations have made incredible progress in leading efforts to collect and share data within their disease areas, many have also learned difficult lessons along the way. In small, lean rare disease organizations, financial and human resources are limited. Many of us have faced huge losses in time and labor as we attempted to use RWD from existing registries and natural history studies to support regulatory approval processes. We know of experiences in the rare disease community where RWD were not accepted as RWE or not considered of sufficient quality for regulatory decision-making.

Without clear guidance from all end users of the data, including the FDA, we fear the unnecessary loss of precious resources and the resulting erosion of patient community trust. While recommendations currently exist for many individual RWD components, we are seeking early and holistic guidance, as well as consistent, systematic feedback on how patient groups design or refine their data collection capabilities. In addition, we are eager to share our collective learnings and work with all stakeholders to maximize the power and responsible use of RWD.

Those of us who attended the recent FDA Stakeholder Meeting on February 25th were thrilled to hear Dr. Theresa Mullin, CDER's Associate Director for Strategic Initiatives, discussing the potential for the FDA to use central coordination to maximize synergies, including:

1. Build out FDA bench including knowledge and understanding, including … real world data
2. Conduct rare disease-focused policy development
3. Coordinate rare disease-specific regulatory science initiatives and resource investments (*Dr. Theresa Mullin, February 25, 2022*)

Aligned with Dr. Mullin's ideas, our proposals below are suggested action steps for how the FDA can better support and engage with patient organizations, both those just beginning their efforts to collect patient-generated RWD as well as those who have already developed expertise in the area. Acceptance of these initiatives and proposals is critical to make progress towards urgently needed rare disease treatments and cures, and we encourage a collaborative and swift process to realize our shared goals.

PROPOSAL #1: Provide additional guidelines, resources, and training for patient organizations engaged in designing and operating registries and natural history studies

While the current guidance is a useful resource and starting point for industry, it is limited in providing concrete guidance to help patient organizations confidently design registries and natural history studies that yield usable data for research and regulatory decision-making. It discusses the *reliability* and *relevance* of registry data and how to improve both, but remains vague and falls short in providing clear direction and design guidelines for patient organizations that play a vital role in this area.

Whether data is "good enough" for regulatory review is a big question for patient organizations. Many of us feel that the process of converting RWD into regulatory-grade RWE has been insufficiently defined, making it difficult to plan how to use our RWD for many purposes, including serving as a control arm for a clinical trial sponsored by a pharmaceutical company. Before patient organizations put in the time, energy, and funding required for long-term longitudinal data collection, we seek a better understanding of specific data requirements and how to increase the quality and reliability of the data. We also seek better understanding of how to address the challenges associated with cleaning and structuring data for analysis and integration.

We need further guidelines, resources, and training specifically tailored for patient organizations. The current guidance document targets industry and does not address the unique considerations of "third parties" that are engaged in designing registries. Differences in objectives, timeframe of development and risk-benefit trade-offs typically exist between RWD efforts driven by industry and patient groups. Patient organizations' efforts often evolve over time—from outreach and community-building mechanisms; to tools for identifying patient and disease characteristics; to multi-purpose systems capable of capturing the burden of disease, disease progression and end points (or surrogate endpoints) useful to the clinical development process. In contrast, industry efforts may often be specifically built to address regulatory approval requirements.

We propose several ways that the FDA can provide necessary guidance on how RWD can best meet regulatory standards:

- ➔ Issue separate guidance for patient organizations: The FDA should issue guidance specifically for patient organizations who are undertaking the collection of RWD, registry data, and natural history data.[1]

- ➔ Institute public review sessions: The FDA should provide more guidance by hosting public review sessions that show examples from rare disease patient organizations that have successfully conducted natural history studies as well as examples of failures. This would help rare disease organizations better understand specific FDA requirements and allow rare disease organizations to learn from each other.

- ➔ Mandate and provide public access to relevant data: To the extent possible, the FDA should share the source and contact information for registries and natural history studies that have been used to support regulatory approvals. This would also be helpful in connecting interested parties to other organizations with successful RWD programs, and potentially enhance cross-organizational learning.

- ➔ Systematically codify the results of past drug submittals: The FDA should provide publicly-accessible summaries that codify the data elements and data approaches from prior natural history studies that were factors in the approval or disapproval of an application. By routinely sharing this type of information, patient organizations could continually assess the quality and relevance of their prospective data efforts to potential future submissions.

- ➔ Summarize minimum standards for "typical" individual data elements: This work has always created a burden for patient organizations, who do not typically have access to the experience that a CRO can provide for a pharmaceutical company in this area. Detailing minimum standards for data, where possible, would streamline and simplify the registry and natural history study design processes for many rare disease organizations.

We acknowledge that there are other stakeholders within the Department of Health and Human Services, such as the National Center for Advancing Translational Sciences (NCATS) and Rare Diseases Registry Program (RaDaR), that are working to support patient organizations creating registries, and so the FDA should not bear the sole or primary burden. Rather, there should be better coordination between agencies, and better harmonization between front-end data collection and back-end data use, to better facilitate eventual regulatory approval.

[1] The agency has another relevant draft guidance on *Rare Diseases: Natural History Studies for Drug Development* (March 2019), but it is similarly written for industry actors.

Implementation of these ideas would enhance the understanding of all users of RWD, including the FDA, since effectively using RWD to inform clinical endpoints and to create external control arms is new for all. While there is a rationale for approaching feedback on a case-by-case basis, the broad commonality among rare diseases calls for a more systematic approach. Furthermore, ethical considerations in the rare disease space create a vital imperative to move as quickly as possible. For example, a small group of us considered asking the FDA for a Critical Path Innovation Meeting (CPIM) to request natural history study guidance on issues including the use of quality-of-life proxies when no validated tools exist. However, we deferred a request for a CPIM meeting and are instead seeking a way of getting guidance from the FDA that can be disseminated to all rare disease organizations needing such guidance. These recommendations would also serve as touch points and opportunities for two-way communications between regulators and patient organizations—a structured way for patient organizations to tell the FDA what's important to registry creators and to patients.

PROPOSAL #2: Create a defined review pathway with a clear point of contact for patient organizations to receive input on the design and implementation of registries and natural history studies

Currently, industry has pathways for receiving input and feedback on the design of their clinical studies and trials. In fact, the current draft guidance, under the section *Considerations for Regulatory Review*, states:

> "*Sponsors interested in using a specific registry as a data source to support a regulatory decision should meet with the relevant FDA review division before conducting a study that will include registry data. Sponsors should confer with FDA regarding …*"

However, patient organizations, which are well positioned to collect this invaluable data, are without an analogous pathway to correspond with the FDA. As key stakeholders, patient organizations need a dedicated pathway to discuss and receive input from the FDA when creating registries—before expending significant resources and time to collect the data from their patient communities. By the time sponsors are "interested in using a specific registry," it is too late for patient organizations as "third parties"[2] to have the guidance necessary to ensure that their registries are set up to meet the regulatory data standards required by the FDA.

[2] Current draft guidance states: "*If the registry data are owned and controlled by third parties, sponsors should have agreements in place with those parties to ensure that all relevant patient-level data can be provided to FDA and that source records necessary to verify the RWD are made available for inspection as applicable.*"

Since patient organizations are involved in creating registries, they need a pathway for meeting with regulators, submitting protocols, and receiving feedback. Patient organizations should have the opportunity, similar to industry, to confer with the FDA and receive input on a range of topics, including:

- ➔ Protocol reviews
- ➔ Alignment of surveys questions with data that the FDA would accept when evaluating therapies for approval
- ➔ Applicability of previously designed natural history studies
- ➔ Recommendations of accepted common data elements across disease, specific organs/systems, or disease areas

When RWD—collected and maintained by a patient organization—are used for a regulatory filing, specific feedback regarding the ultimate usability of the data should be provided directly to the patient organization, separate from the determination provided to the industry sponsor.

Creating such a dedicated pathway with clear points of contact for early review of patient organization's data initiatives will also greatly streamline communications. Since the FDA is a large, complex organization, current channels of communication between patient organizations and the FDA can be very slow and inefficient. When one of our signatories tried to get a comment from the FDA on a natural history study, seeking clarification on an ethical issue in relation to industry conduct, it took 18 months to get a response. Other groups have spent years trying to identify the correct FDA representative for support and feedback, without any success.

We also believe that such a pathway for timely feedback and input will foster two-way communication that will benefit both patient organizations and regulators. Patient organizations have significant expertise and experience on registries and RWD, particularly as the burden to collect RWD often falls on patient communities. The unique experience and expertise of the rare disease community can bring great benefit to the FDA and pharmaceutical companies, as well as support the deeper integration of patient voices in the drug development process.

PROPOSAL #3: Commit to funding and resources, including setting aside a portion of user fees

The FDA needs resources to implement and operationalize the above proposals for providing concrete guidance, pathways and engagement mechanisms for patient organizations. The agency should commit to putting funding towards this type of infrastructure to incorporate patient input

as mandated by the 21st Century Cures Act.[3] **Furthermore, if industry is using registry data and natural history data to obtain regulatory approval of their therapeutics, they should also support patient organizations and regulators in ensuring the quality, relevance, and reliability of the data.** Consequently, we believe that the FDA should set aside a portion of user fees from industry to support patient organization efforts to design and manage registries and natural history studies—potentially as part of the reauthorization of the Prescription Drug User Fee Act (PDUFA) for fiscal years 2023 through 2027.

FINAL THOUGHTS AND INVITATION

The current draft guidance mentions that sponsors should have agreements in place when using "registry data [that are] owned and controlled by third parties". We ask the agency to think further about how to ensure that patient voices remain central to these efforts, especially where there may be imbalances of power. There are stark differences in approaches among academia, industry, and patient organizations when it comes to data sharing, ownership and collaboration. As typically small, lean teams operating in limited funding environments, rare disease patient organizations must be efficient in their use of both human and financial resources. Consequently, patient organizations typically want to learn from each other and "do things together and collectively." With our focus on driving improvements in treatments for our disease areas, we want to make our data available to all potential industry and academic partners, without compromising the stewardship of our communities' collective assets.[4]

Conversely, academia and industry are frequently much more focused on data ownership and exclusivity. Many of us have questioned the ethics of sponsors asking our community members to participate in clinical trials and then not making the clinical trial and control arm data accessible. It will take a larger effort for academics and industry to fully embrace data sharing, especially as the patient organizations pushing for more transparency increasingly become key players in this space. We recognize that research and commercial data need to be held for their intended purpose; FDA guidance on future data release and usage after that initial purpose is met will be transformative to the rare disease space.

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[3] The 21st Century Cures Act directs the FDA to issue new guidance to inform the development of patient engagement tools and advance patient-focused drug development, but the agency has not been set up to implement processes and structurally incorporate patient voices in the approval process. *FDA Plan for Issuance of Patient-Focused Drug Development Guidance Under 21st Century Cures Act Title III Section 3002* (May 2017).

[4] We applaud and support the National Institutes of Health (NIH) for its recent decision to issue a data-sharing mandate. Starting in January 2023, the NIH will require most researchers and institutions receiving NIH funding to include a data-management plan in their grant applications and to make their data publicly available.

Finally, in the spirit of sharing learnings and working collectively, as rare disease patient organizations, we invite the FDA to actively engage and collaborate with us. We believe such active engagement will help operationalize this guidance, enhance the substance and utility of the use of RWD, and foster more efficient and successful drug development for all rare diseases.

Thank you for your efforts on behalf of rare disease patients and for your attention to our comments. We look forward to working with you on rare disease drug development.

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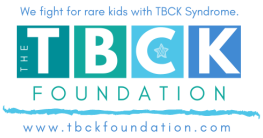

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