Duke | MARGOLIS CENTER *for* Health Policy

February 28, 2022

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

RE: FDA-2021-D-1146 Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

To Whom it May Concern:

The Robert J. Margolis, MD Center for Health Policy at Duke University ("Duke-Margolis" or the "Center") appreciates the opportunity to comment on the Food and Drug Administration's "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products" (the "draft guidance"). We are encouraged by the FDA's commitment to advancing real-world data (RWD) and real-world evidence (RWE).

Established in January 2016, Duke-Margolis is both an academic research center and a policy laboratory where stakeholders can come together to analyze, propose, and evaluate ways to improve health in the United States (U.S.) and beyond. The Center's mission is to improve health and health care value through practical, innovative, and evidence-based policy solutions. By catalyzing Duke University's leading capabilities, we research and convene activities focused on biomedical innovation and regulatory policy. Thought leadership on the regulatory acceptability of RWD and RWE is a dedicated goal for our team.

Duke-Margolis has two complementary programs dedicated to advancing RWD and RWE science and policy for regulatory use. First, under a cooperative agreement with the FDA's Center for Drug Evaluation and Research (CDER), Duke-Margolis has held several expert workshops and public conferences related to RWE and RWD regulatory acceptability. Second, the Center has formed a multi-stakeholder collaborative ("RWE Collaborative") with the intent and goal to strengthen the development and potential applications of RWD and RWE (member organizations and representative experts are listed in Appendix I). The RWE Collaborative is guided by an advisory group comprised of leaders from healthcare industries, academia, and others who are developing practical approaches to support the generation and use of regulatory-grade RWE. To date, Duke-Margolis' RWD and RWE activities have spanned several public and private meetings, the convening of multiple working groups, and the publication of six major white papers available on our website.

Through this work, Duke-Margolis aims to support collaborative strategies that advance the effective development and use of RWD and RWE. The comments and considerations below represent the thinking and recommendations of expert Center faculty and staff, which have been informed by RWE Collaborative activities and expertise. Duke-Margolis looks forward to continuing our work with the FDA, the RWE Collaborative, and other stakeholders to move RWE policy development forward. We hope that our work in this space will continue to be useful and informative to the FDA.

Duke-Margolis, as part of Duke University, honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the

individual members are free to speak their minds and express their opinions regarding important and pertinent issues. The Center's comments herein are informed by RWE Collaborative members but may not represent the opinions of every RWE Collaborative member. This comment letter is not intended to limit the ability of RWE Collaborative members to provide their own comments on behalf of their independent organizations.

We are pleased to observe and comment on how the FDA is thinking about issues surrounding the use of registries as a RWD source for regulatory decision making. Overall, we encourage stakeholders developing registries to review the Registries for Evaluating Patient Outcomes: A User's Guide (Fourth Edition)[1] as it goes into depth on many of the areas raised in this letter. We have a few areas of comments, organized by the categories listed below where we think more clarity from the FDA would be beneficial.

- **Delineating existing registries and purpose-built registries**
- **Facilitating and prioritizing the collection of outcomes data that are important to patients.**
- **Clarifying the roles and responsibilities of sponsors and registry managers.**
- **Developing consistent definitions for key terms or note where consensus is lacking.**
- **Building multi-stakeholder support for well-funded, multi-purpose registries.**

With these areas in mind, we suggest the FDA and other relevant stakeholders act in the near-term on the following steps as this guidance document is revised and implemented:

- **The FDA should work with stakeholders to formalize and advance patient-level or -reported endpoints that are capturable in well-designed registries.**
- **Stakeholders in the RWD/RWE space should continue to develop and refine consistent definitions for key terms, concepts, and endpoints.**
- **The FDA should engage in the conceptualization and development of multi-stakeholder registries that would appeal to diverse health care stakeholders with a range of disease interests, like cell and gene, Alzheimer's disease, and rare disease therapies.**

Delineating existing registries and purpose-built registries.

The FDA acknowledges in the draft guidance that a registry designed to answer a specific research question can have advantages over a repurposed existing registry. While this is true, the guidance document could benefit from greater delineation between the roles of existing registries and those that are specifically built to address a specific regulatory or research question. Registries have been developed and extensively used to understand disease progression and natural history. Though product-specific registries have been developed with regulatory uses in mind, registries are not typically built for regulatory purposes yet can still provide valuable data for evidence generation and, in some cases, support or guide regulatory decision-making. When possible, efforts should be made to leverage registry data to inform decision making, particularly in rare and life-threatening diseases where registries may provide vital additions to the totality of evidence.

[1] Richard E. Gliklich, Michelle B. Leavy, and Nancy A. Dreyer, "Registries for Evaluating Patient Outcomes: A User's Guide," Fourth edition (Agency for Healthcare Research and Quality (AHRQ), September 21, 2020), https://doi.org/10.23970/AHRQEPCREGISTRIES4.

Given the critical differences between existing and purpose-built registries, in its final guidance, the FDA should identify and describe the unique benefits and limitations to leveraging existing registries. Doing so would assist those attempting to leverage existing registries to support regulatory decision-making. Deriving examples from product approvals that were supported by registry data, like the recent tacrolimus approval[2], can help clarify the benefits and limitations of registry data.

Despite limitations to the use of existing registries to support regulatory decision-making, the FDA should consider convening a broad range of stakeholders who can help level-set around strategies to overcome those limitations. Additionally, further clarification on what should be included in a purpose-built registry designed to answer regulatory questions would be welcome. Outlining criteria for regulatory-grade registry data will better equip stakeholders to leverage registries as a RWD source. The FDA has an opportunity to provide such criteria in their final guidance.

Facilitating and prioritizing the collection of outcomes that are important to patients.

Many RWD sources play a crucial role in supporting the collection of patient-centered outcomes, which might include but is not limited to patient-reported outcomes, patient-generated health data, and patient-driven outcome measures. Registries, in particular, can play an important role in collecting this information. Yet, in real-world practice, clinical endpoints important to patients may become lost or drowned out in debates among and across health care systems. Regulators can help ensure that the patient perspective and voice is not lost when building or considering regulatory-grade registries. The FDA should emphasize the benefits of partnering with patient-level stakeholders to harmonize patient-driven endpoints with objective endpoints that are important to inform regulatory decision-making . We recommend the FDA offer additional considerations on the reliability and validity of patient-centered outcomes within registries to the extent they are appropriate to support regulatory decision making.

Explaining the roles and responsibilities of sponsors and registry managers.

While sponsors are ultimately responsible for the content of their submissions, they may have limited ability to influence or control certain operational aspects of registries. This is especially true for many, if not most, existing registries. We recommend that the final guidance acknowledge that the governance and management of existing registries is usually outside of sponsor control. We also recommend that the final guidance offer considerations for sponsors and owners of existing registries to explore adapting operational aspects or policies of those registries to make them useful for research and regulatory decision-making. Beyond that, the guidance might also suggest how to leverage other RWD sources in the event certain management practices for existing registries might create challenges to addressing a regulatory question or issue.

The guidance should also clarify how registry managers should ensure the privacy of patient-level data within a registry. To the extent the agency is able, the FDA should consider leveraging its existing legal authority to help protect the privacy of registry data undergoing regulatory review. This is especially

[2] Center for Drug Evaluation and Research, "FDA Approval Demonstrates the Role of Real-World Evidence in Regulatory Decision-Making on Drug Effectiveness," *FDA*, August 4, 2021, https://www.fda.gov/drugs/news-events-human-drugs/fda-approval-demonstrates-role-real-world-evidence-regulatory-decision-making-drug-effectiveness.

important for rare disease registry data, where the inherently small patient populations may increase the risk of reidentification.

We also ask that the FDA provide guidance on any unique considerations for the use of global or non-U.S. registries versus U.S.-based registries. Differences in privacy regulations and laws within, across, and outside of the U.S. may complicate consistent data collection across different patient populations. These regulatory differences may also impact access to non-U.S. registries housing U.S. patient data (e.g., non-U.S.-based, international rare disease registries) and the ability of sponsors to include such data in FDA submissions.

Ultimately, any submission to the FDA utilizing registry data should clearly describe the registry, how the data was collected, the nature of the data, and important evidence it can provide. Accomplishing this will require clear communication between sponsor and registry manager.

Developing consistent definitions for key terms or note where consensus is lacking.

We appreciate the FDA's effort to clearly define terms in RWE-related guidance, however, the registries guidance contains key terms that still lack consistent definitions. These include "interoperability," "missing data," and "registry" itself. The guidance discusses how a sponsor can demonstrate interoperability across data sources, but we advocate for this to be elaborated upon in greater detail. In doing so, the FDA can assign a definition to "interoperability." When defining this key term, it must be kept in mind that interoperability includes a two-way flow of data. Lack of consensus over "missing data" creates rifts in how health care stakeholders look at registries. Additionally, as we discussed in our comments on the FDA's "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision- Making for Drug and Biological Products," the FDA should further clarify what they mean by missing data and what evaluations of missing data they expect to see in submissions.

Crucially, the FDA should consider making a distinction between a registry and a registry-based study. For example, the European Medicines Agency (EMA) defines a registry-based study as an "investigation of a research question using the data collection infrastructure or patient population of one or several patient registries. A registry-based study is either a clinical trial or a non-interventional study...[3]." Meanwhile, the same EMA guidance defines "registry," or, synonymously, "patient registry," as an "[organized] system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure..." A critical difference between the two being that registry-based studies must seek to answer a pre-determined research question and not simply collect and parse through patient data. Furthermore, EMA delineates categories of registries and registry studies by defining "disease registry," "registry-based study," and "registry database" among other related terms. We encourage FDA to define terms in sync with EMA's definitions. Alignment across international regulatory bodies will facilitate the creation of broadly usable registries with applications not limited by international boundaries.

Building multi-stakeholder support for well-funded, multi-purpose registries.

While not strictly within the scope of this guidance document, FDA regulations and guidance should support the creation and maintenance of multi-purpose registries that can help answer vital questions about the safety and efficacy of products throughout the product life cycle. Industry, regulators, and

[3] "Guideline on Registry-Based Studies," n.d., 35.

academia do not always have the same inquiries, but creating data registries that can be applied broadly may help garner support and resources from more key stakeholders.

EMA's Patient Registries Initiative[4] that brings together a variety of stakeholders for collaboration is one approach for FDA to consider. One of the programs explicit aims is to support promoting and creating new registries where suitable registries do not exist, and, while developing them, plan for the registry to have wide applicability downstream. For example, a workshop on CAR T-cell therapies[5] brought together registry groups like the European Society for Blood and Marrow Transplantation (EBMT) as well as clinicians. They discussed challenges of using existing registries to support CAR T-cell therapy, and it was shared that EBMT was moving to a new registry platform to enable better post-authorization safety studies. These types of workshops aimed at making registries more useful for research and development and for regulatory decision-making could potentially be adapted to the U.S.

To maximize RWD's impact on health care, useful data must be accessible to more stakeholders. FDA guidance can help improve accessibility by incentivizing diverse groups of health care stakeholders to pool resources and contribute to innovation. Multi-stakeholder registries are a particularly attractive approach in settings like cell and gene therapies, Alzheimer's disease, and rare disease therapies that remain of interest to the FDA. Such settings will likely require combined efforts to have a sufficient and representative sample size to track both regulatory-and patient-reported outcomes. Axiomatically, rare diseases have few patients that can participate in trials or contribute to registries. Thus academics, vendors, and sponsors compete to enroll this limited group of individuals, and individual industry-sponsored registries can experience challenges with enrollment and fail to enroll sufficient numbers of patients to answer the research question. Therefore, a multi-stakeholder approach for collecting registry data may help address multiple research questions. Overall, FDA policy should encourage the use of registries as a RWD source that can be leveraged to foster meaningful innovation in patient care.

Duke-Margolis hopes to work with sponsors, data curators, and the FDA to advance the development of standards for providing the information the FDA asks for in this guidance document and any future guidance that will be released by the FDA. We look forward to working with the FDA and stakeholders across the field to continue advancing RWE. We thank the FDA again for the opportunity to offer comments on this draft guidance. Please send any follow-up questions to Rachele Hendricks-Sturrup. (rachele.hendricks.sturrup@duke.edu).

Sincerely,

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[4] EMA, "Patient Registries," Text, European Medicines Agency, September 17, 2018, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries.
[5] Patient Registries Initiative, "Report on CAR T-Cell Therapy Registries Workshop 9 February 2018," May 15, 2018, https://www.ema.europa.eu/en/documents/report/report-car-t-cell-therapy-registries-workshop_en.pdf.

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Appendix

Real World Evidence Collaborative Advisory Group Representatives and their member organizations:

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Elise Berliner -- Cerner Enviza

Barbara Bierer -- The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

Mac Bonafede -- Veradigm Health

India Bowman -- PatientsLikeMe

Brian Bradbury -- Amgen

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Adrian Cassidy -- Novartis

William Crown -- The Heller School for Social Policy and Management at Brandeis University

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Nancy Dreyer -- IQVIA

Andrew Emmet -- Pfizer Inc.

John Graham -- GlaxoSmithKline

Ceri Hirst – Bayer

Stacy Holdsworth -- Eli Lilly and Company

Solomon Iyasu -- Merck & Co.

Brad Jordan -- Flatiron Health

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