October 10, 2023

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

RE: FDA-2022-D-2629 Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs 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 "Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products" ("the draft guidance") document. 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 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 conduct 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 collaboration ("RWE Collaborative") with the intent and goal of strengthening the development and potential applications of RWD and RWE. RWE Collaborative Advisory Group members and their respective organizations are listed the Appendix and are comprised of leaders from health care 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 eleven major white papers available on our website.

Through this work, Duke-Margolis aims to support collaborative strategies to 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 forward.

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.

Our comments herein focus on the potential role of RWD in generating postmarket evidence for populations that may have been underrepresented in clinical trials. As FDA noted in this draft guidance document, several guidance documents have been recently released by the agency outlining key considerations for the use of RWD and evidence to inform regulatory decision making and, relatedly, draft guidance on clinical trial diversity action plans. We support any notion suggesting that these guidance documents, both draft and final, and early conversations with the relevant review divisions at FDA should form the basis around uses of RWD/E to answer research questions in postmarket settings regarding medical product safety and efficacy.

We also believe FDA could provide more specific guidance on the use and appropriateness of RWD in postmarket settings to obtain RWE on treatment outcomes in populations underrepresented in clinical trials, regardless of the reasons or basis for the underrepresentation. As FDA guidance on and authority to require diversity action plans becomes implemented, the expectation is that premarket clinical trials will become appropriately representative. However, if despite meaningful efforts from sponsors to implement diversity action plans certain populations remain underrepresented in premarket trials, then postmarket data collection is indeed warranted. However, should sponsors struggle or fail to enroll representative populations in premarket trials, it is reasonable to assume that this struggle or failure is also likely at the postmarket phase. We believe one way to address this issue is by collecting and leveraging RWD in usual care settings, especially in traditionally underserved communities. This could be possible through point-of-care trials implemented to observe the comparative effectiveness of newly approved therapies/labels against standard of care treatment(s).

As noted in the present draft guidance and other related FDA draft guidance on RWD/E, several RWD sources could be useful to generate evidence on treatment efficacy and safety in underrepresented populations at the postmarket phase (e.g., registries, claims data, electronic health record data). We recommend the final guidance discuss possible strategies for sponsors to leverage or support the development and use of registries intentionally designed to capture longitudinal, fit-for-purpose RWD on treatment outcomes in underrepresented populations. Additionally, FDA notes that information from postmarketing studies "can potentially be added to drug labeling, when appropriate." We encourage the agency to provide some guidance here or elsewhere to describe how information collected from real-world settings might be best incorporated into drug labels. Is Section 14 of the drug label the appropriate place to add such information? If so, how should evidence generated from RWD-based approaches be described? When would it be appropriate to include such evidence?

Overall, we believe FDA could provide more specific guidance on postmarket study mechanisms it might support to more closely observe medical product safety and efficacy among underrepresented

populations in real-world treatment settings. Populations underrepresented in pre-market clinical trials might encounter or experience barriers in access to new therapies via trials conducted in the postmarket phase. Therefore, we also encourage the FDA to collaborate with sponsors and underrepresented communities to contemplate and devise appropriate RWE study designs that address and eliminate such barriers.

Lastly, high quality RWD may be particularly useful in postmarket settings to supplement common subgroup analysis constraints that may stem from a lack of diverse real-world subpopulations in clinical trials. Also, and importantly, RWD has the potential to fill knowledge gaps related to the long-term safety and efficacy of treatments among and across patient subgroups that may be at a relatively higher risk of poor treatment outcomes in the real world due to comorbidities and/or distinct biological, environmental, discriminatory, or demographic factors. Therefore, we recommend that FDA acknowledge this and extend practical guidance on strategies to evaluate high-risk subgroups for treatment indications/contraindications and other outcomes that may not be observable in controlled clinical trial settings.

As the FDA continues to release and update RWE guidance, Duke-Margolis looks forward to continuing the advancement of RWD and 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 at rachele.hendricks.sturrup@duke.edu.

Sincerely,

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Appendix

Real-World Evidence Collaborative Advisory Group (as of April 5, 2023)

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