REAL-WORLD EVIDENCE ALLIANCE

info@rwealliance.org
rwealliance.org

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

Re: Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence; Draft Guidance for Industry; Availability (Docket No. FDA-2023-D-2318)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the draft guidance titled "Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence" ("Draft Guidance").[1] We are a coalition of real-world data ("RWD") and analytics organizations with a common interest in harnessing the power of real-world evidence ("RWE") to inform regulatory decision-making to improve the lives of patients. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies.[2]

The RWE Alliance envisions a future in which data from electronic health records, administrative claims and billing records, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence to support regulatory decision making related to medical product safety and effectiveness. To achieve these goals, the RWE Alliance advocates for policies that will (1) advance FDA's RWE Framework, (2) encourage the use of RWE to better understand treatment effects in underrepresented populations, (3) enhance opportunities for RWE

[1] 88 Fed. Reg. 64445 (September 19, 2023).

[2] For information about our members, please see our website, https://rwealliance.org/who-we-are/.

organizations to consult with FDA, (4) increase communication on the generation and use of RWE, and (5) recognize the unique aspects of and opportunities for RWD/E.[3]

The Draft Guidance addresses an important issue—how different sources of evidence, both clinical and other types such as mechanistic, may be brought together to evaluate a drug's effectiveness as confirmatory evidence. We appreciate that the Draft Guidance lists real-world data as a potential source to generate this confirmatory evidence when substantiating the result of one adequate and well-controlled clinical investigation.

In general, we note that the content of Section III, in particular subsections E (Natural History Evidence), F (Real-World Data/Evidence), and G (Evidence from Expanded Access Use of an Investigational Drug), overlaps to some degree, as real-world data may be used as a data source for both natural history studies[4] and expanded access programs.[5] The Draft Guidance may lead a reader to misconstrue that these are distinct sources or types of confirmatory evidence, when in fact there are areas where these types of evidence overlap. We recommend that FDA (the "Agency") better distinguish how the Draft Guidance describes approaches to developing confirmatory evidence (i.e., natural history studies and expanded access) versus how RWD—a data source—can be used within these approaches. By delineating what can be accomplished with various data sources across different approaches to developing confirmatory evidence, FDA can highlight the many circumstances where RWD is already recognized by the Agency as a potential source of confirmatory evidence for the effectiveness of treatments, including when leveraged in certain subpopulations.

We also offer four comments for FDA's consideration regarding specific sections as they are currently organized in the Draft Guidance.

- In Section III.E., we suggest that FDA acknowledge that RWD is an important source for natural history data.

- In Section III.E., lines 367–68 state that natural history data used as confirmatory evidence should be "distinct from any data used as a control for the single adequate and well-controlled clinical investigation." We suggest that FDA clarify whether patients in a natural history study could be included as a control arm for confirmatory evidence if there are two different time periods in the disease progression/journey used. For example, a sponsor can use patients from a natural history study who have progressed in their disease as an external control

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[3] Additional information about what we believe is available on our website, https://rwealliance.org/what-we-believe/.

[4] FDA, Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry (2021).

[5] Reagan-Udall Foundation for the FDA, Leveraging Real-World Treatment Experience from Expanded Access Protocols (2018).

arm for a single arm trial; these patients are the same, but data points would differ over time.

- In Section III.F., FDA should provide specific examples of when RWD may be appropriate for use as confirmatory evidence, as FDA does in other subsections for other types of data (e.g., clinical trial data from a related indication, mechanistic data, animal data, natural history data, and patient outcome information collected under expanded access). We suggest that FDA include, among others, the following examples of when RWE may be appropriate for use as confirmatory evidence:
    - When documenting and providing data on natural history (e.g., in rare diseases);
    - When providing data relating to off-label use of an approved drug, including to assess effectiveness in a broader, clinically relevant population than the population included in the pivotal randomized controlled trial in order to support a label expansion;
    - When documenting and confirming diversity data for those historically underrepresented in clinical trials or to support a sponsor's diversity plan;
    - When documenting the real-world effectiveness of a commercially available agent(s) within the same class of drugs as the item being evaluated in the sponsor's application for a new approval or label expansion (subject to any applicable legal protections for the other product); and
    - When providing data for the control arm in an externally controlled clinical investigation, including cases where a randomized controlled trial is possible but may not be feasible due to ethical or practical considerations.

- In Section III.F., footnote 19, we suggest that FDA cross reference to FDA's draft guidance titled "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products."

The RWE Alliance appreciates the Agency's commitment to the use of RWD/E in regulatory decision making. Thank you for considering these comments, and please let us know if you have any questions. We welcome the opportunity to discuss further.

Best regards,

The RWE Alliance