REAL-WORLD EVIDENCE ALLIANCE

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

Re: Reauthorization of the Prescription Drug User Fee Act; Public Meeting; Request for Comments (Docket No. FDA-2021-N-0891)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the proposed commitment letter for the reauthorization of the Prescription Drug User Fee Act ("PDUFA") for fiscal years 2023 through 2027 (the "Commitment Letter").[1] We are a recently formed 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 patients' lives. 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.

The RWE Alliance envisions a future in which data generated in everyday clinical practice and everyday life through electronic health records, administrative claims and billing data, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence that complements clinical trial data to inform regulatory decisions. To achieve this goal, the RWE Alliance advocates for policies that will advance FDA's RWE Framework, encourage the use of RWE to better understand treatment effects in underrepresented populations, enhance opportunities for RWE organizations to consult with FDA, and increase communication on the generation and use of RWE.[2]

The RWE Alliance strongly supports FDA's RWE initiatives, including those outlined in the Commitment Letter. RWD and RWE can benefit patients by playing a key role in drug development efforts as well as regulatory decision making across therapeutic areas. The Commitment Letter outlines important steps FDA will take toward realizing the potential that RWD and RWE offer. These commitments focus on interactions

[1] 86 Fed. Reg. 47316 (Aug. 24, 2021).
[2] Additional information about what we believe is available on our website, https://rwealliance.org/what-we-believe/.

between product sponsors and FDA, which are of course essential. We believe that opportunities for data and analytics organizations to engage with FDA are important to help advance the collection and use of RWD/E in line with Agency standards, which can in turn help advance key PDUFA initiatives described in the Commitment Letter. For example, RWD/E can help evaluate the feasibility of new surrogate endpoints[3] and identify endpoints for evaluating the effectiveness of a rare disease therapy;[4] fulfill post-marketing commitments and safety monitoring for cell and gene therapy products;[5] and contribute to the use of modeling to inform drug development efforts,[6] such as by identifying alternative dosing regimens that can improve patient access to and compliance with a prescribed therapy. The RWE Alliance strongly believes RWD/E can also make valuable contributions in a variety of areas beyond these examples, and additional opportunities for direct interactions between FDA and data and analytics companies would greatly facilitate that progress by allowing these organizations to share their expertise with FDA on general topics.

Looking beyond the Commitment Letter, the RWE Alliance hopes to work with FDA to identify channels for communication between RWD/E organizations and the Agency to discuss RWE methodology and study designs outside the context of an individual sponsor's drug development program. For all of the reasons noted above, we believe that FDA engagement will help advance RWD/E and ultimately benefit patients.

We offer further comments on specific sections of the Commitment Letter below.

I. Advancing Real-World Evidence for Use in Regulatory Decision Making

The RWE Alliance applauds FDA's commitment to furthering the use of RWE in regulatory decision making by establishing the Advancing RWE Program. The objectives of this pilot program—providing a dedicated pathway for participating sponsors to receive early feedback on potential uses of RWE, developing Agency processes to ensure consistent decision making and internal alignment regarding RWE, and providing insights to the public regarding RWE that can support regulatory decisions—have the potential to meaningfully advance the use of RWE for regulatory purposes.

The importance of timely and early Agency feedback on a planned use of RWE cannot be overstated. Sponsors participating in the pilot program will receive valuable input from Agency experts at an important juncture in the development process, before

[3] *See* Commitment Letter § I.K.3.
[4] *See id.* § I.K.4.
[5] *See id.* § I.O.
[6] *See id.* § I.L.3.

protocol development and study initiation. Although there are well-established methods and statistical approaches for generating valid, reliable, and transparent RWE, consulting with FDA experts will help program participants better understand the Agency's expectations and address particular questions that can arise in a specific use case.

With this in mind, we are encouraged by the Commitment Letter's express assurance that other channels for interacting with FDA and receiving Agency feedback—such as through formal PDUFA meetings with the review division—will continue to be available to sponsors.[7] The RWE Alliance views these meetings as critical to obtaining the Agency's views on the use of RWE for regulatory purposes and, to this end, we strongly support the use of FDA resources—including appropriated funds from budget authority—to ensure adequate bandwidth and appropriate expertise are available for these efforts.

We are similarly pleased to see that learnings from the Advancing RWE Program will be used to support FDA's efforts to develop, finalize, and expand on RWE guidance documents. The RWE Alliance strongly supports FDA's ongoing efforts—under section 505F of the Federal Food, Drug, and Cosmetic Act ("FDCA")[8] and otherwise—to provide additional guidance on appropriate methods and uses for RWE in regulatory submissions. These efforts are already well underway, as reflected by the multiple RWE-related guidance documents on CDER's 2021 guidance agenda[9] and the Agency's recent publication of draft guidances entitled "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products" and "Data Standards for Drug and Biological Product Submissions Containing Real-World Data." We encourage FDA to continue prioritizing its efforts to issue guidance in the near term while it also establishes new programs, such as the Advancing RWE Program, that may lead to additional recommendations in the future. Similarly, we greatly appreciate FDA's efforts to pursue other RWE programs and demonstration projects that will yield other learnings informing future guidance. We encourage FDA to continue and expand on these efforts.

II. Enhancement and Modernization of the FDA Drug Safety System

The RWE Alliance applauds FDA's commitments to better leverage RWE to improve the power and efficiency of post-market surveillance with respect to both safety and

[7] *See id.* §§ I.K.6.b.vi and xiii.
[8] FDCA § 505F(e) (describing guidance to be issued by December 2021 regarding FDA's use of RWE and appropriate standards and methodologies for collection and analysis of RWE).
[9] CDER Guidance Agenda, New & Revised Draft Guidance Documents Planned for Publication in Calendar Year 2021 (July 2021), https://www.fda.gov/media/134778/download.

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effectiveness. In particular, we support FDA's commitments to enhance the use of RWE for surveillance as part of the Sentinel Initiative[10] and to better capture post-approval information for novel biologics and other products.[11]

FDA has a long and successful history of leveraging RWD and RWE for active drug surveillance through the Sentinel Initiative. The Commitment Letter builds on this history by using RWD to study post-market medical product use and pregnancy outcomes in women exposed to these products, an important population that is underrepresented in clinical trials. Furthermore, the development projects to expand the capabilities of existing Sentinel Initiative surveillance systems (Sentinel and BEST) will facilitate greater understanding of how RWE can be used to evaluate effectiveness and, by extension, expand the information that can be drawn from real-world utilization of approved and licensed products. Providing greater transparency in the methodologies used to evaluate effectiveness across data sources would advance the FDA goal to use RWE for regulatory purposes by sponsors and would encourage RWD/E organizations to dedicate resources to develop these methodologies. The Alliance welcomes the public workshop planned to address the proposed Sentinel Initiative projects and looks forward to learning more about the Agency's implementation of this commitment.

In particular, we are encouraged by the planned FDA investment in methodologies to increase the robustness and certainty of valid causal inference made using RWE. Unmeasured or unobserved confounders, and design flaws more generally, can prevent making such valid inference in non-randomized studies, and advancing methodologies such as negative controls will help to build confidence in RWE study designs and methodologies when appropriately applied to fit-for-purpose data. We encourage FDA to share detailed learnings from these development projects in a public forum and support the commitment to publish a report on the results.[12] We also suggest that the Agency collaborate with sponsors and RWD/E organizations during this process so all stakeholders can better understand how structured and unstructured data can be better aligned across the industry and academia to complement the Sentinel data. We recommend that FDA be transparent about the Agency's methodology and data quality standards for these development projects, which could be instructive for RWD/E

[10] *See* Commitment Letter § I.M.2.
[11] *See id.* §§ I.O.2.d and I.O.3.
[12] To the extent that publicly disclosed information implicates data submitted by sponsors, this information should be presented only at an aggregated level and consistent with protections for confidential commercial information and trade secrets, unless a sponsor first agrees to the sharing of its data in this context.

submitted to the Agency for regulatory purposes and for broader discussions regarding the use of RWE in regulatory decision making.

RWD/E can add significant value as a tool for satisfying post-marketing commitments and requirements. Congress recognized this potential when adding section 505F(a) to the FDCA, and the use of RWE can extend to satisfying requirements under section 505(o) and generating other information to inform appropriate warnings, precautions, and other labeling information. In addition, we strongly agree that RWE can and should be used to confirm the clinical benefit of products approved under the accelerated approval pathway, as the Commitment Letter suggests for regenerative medicine therapies.[13] In appropriate cases, RWD/E may be able to reveal information faster and more efficiently than might be possible through a traditional clinical trial. They can also help to address some of the challenges associated with conducting a randomized clinical study of a marketed product. For example, in some cases it may be impractical or even unethical to study an approved product in a randomized trial with controls, such as when there is no longer equipoise to conduct a placebo treatment regimen due to a change in the standard of care.

For these reasons, we encourage FDA to consider additional ways it can facilitate greater use of RWE in post-marketing studies. We believe such efforts could include, for example:

- Measures to ensure that post-market commitments and requirements—including 505(o) requirements and confirmatory studies under the accelerated approval pathway—are drafted to maximally leverage RWD/E, including by identifying circumstances upfront where an RWE study may be able to satisfy the commitment or requirement; and/or

- Additional guidance for industry on using RWD/E in evaluating the safety and effectiveness of products for their approved uses, including on topics such as using information on clinical practice patterns; using RWD/E to add, remove, or update warnings, precautions, or other safety information; adding RWE studies to the labeling of approved products; and using RWE to characterize subpopulations.

III. Information Technology and Bioinformatics Goals

The RWE Alliance strongly supports FDA's ongoing efforts to modernize its information technology and data management infrastructure, including through the newly

[13] *See* Commitment Letter § I.O.3.

established Office of Digital Transformation.[14] The Commitment Letter outlines promising steps that FDA will take to improve the Agency's capabilities in the coming years.

The Commitment Letter states that "[c]loud and cloud-based technology offer significant advantages over traditional on-premise data repositories and analytics."[15] The RWE Alliance agrees and, in particular, supports FDA's plans to consider how cloud-based technologies may be used effectively to streamline the sharing of regulatory information in interactions between sponsors and FDA.[16] It will be just as important to begin considering how cloud-based technologies could be used to acquire information that may be useful to a regulatory filing (e.g., data from wearable devices, results from imaging studies, source patient level RWD in multiple formats, and results from diagnostic tests). The Commitment Letter appears to contemplate exploring this issue in the context of data derived from digital health technology ("DHT"),[17] and the RWE Alliance supports these plans.

More generally with respect to DHT, the RWE Alliance is broadly supportive of the Commitment Letter's substantial focus on using these technologies to support drug development and review. Because multiple data sources and technology platforms may be combined to generate evidence to support medical product approvals and innovative trial designs, we believe a comprehensive approach to policy development in this area is warranted, with input from across the health and technology sectors and a particular focus on engagement with data and analytics experts.

The RWE Alliance would especially welcome the opportunity to provide input on several aspects of the planned DHT Framework document, such as content on improving the Agency's capacity to receive and analyze increasing amounts of complex data from multiple sources; data standards; and the capture, quality, and curation of these data. Because this area is quickly evolving, we believe data standards should be flexible enough to accommodate future changes in DHT and the types of data that may be collected and included in regulatory submissions. RWD/E organizations play an active role in the collection and use of healthcare data, and we believe routine Agency engagement with these organizations (in addition to sponsors and other stakeholders) will enhance FDA's insights into the feasibility of potential arrangements for data submission, management, and analysis in the near term as well as help the Agency

[14] FDA News Release, *FDA Advances Data, IT Modernization Efforts with New Office of Digital Transformation* (Sept. 15, 2021), https://www.fda.gov/news-events/press-announcements/fda-advances-data-it-modernization-efforts-new-office-digital-transformation.
[15] Commitment Letter § IV.A.6.
[16] *See id.*
[17] *See id.* § IV.A.6.c.i.

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respond to technological changes over time. With broad stakeholder engagement and Agency transparency during this process, RWD/E organizations and sponsors can better focus their development efforts and implement compatible standards and processes to help ensure the success of FDA's modernization efforts.

IV. Conclusion

Thank you for considering these comments and for FDA's continued work to advance the use of RWE in regulatory decision making. Please let us know if you have any questions regarding these comments, and we would welcome the opportunity to discuss further.

Best regards,

The RWE Alliance