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PERSPECTIVE

US Food and Drug Administration's Advancing Real-World Evidence Program: Initial Experience

Kimberly A. Smith[1,*], Yin Huang[2], Theresa Kehoe[1], Stefanie Kraus[1], Mark Levenson[1], Jie Li[1], Kristen Miller[1], Ann Punnoose[1], Donna R. Rivera[3], Yueqin Zhao[1], Richard Forshee[2] and John Concato[4]

Advances in the availability and analysis of real-world data (RWD) have enabled the generation of robust real-world evidence (RWE) to support regulatory decision making by the US Food and Drug Administration. Realizing the full potential of RWE in a regulatory environment requires cross-discipline expertise and collaboration to increase confidence in RWE-based approaches. The FDA's Advancing RWE Program was established to address this need by providing a new option for regulatory interactions on RWE-based approaches.

RATIONALE FOR THE PROGRAM

The FDA regularly engages with sponsors to discuss their development plans, including potential approaches to establish safety and effectiveness that involve the use of RWD.[1] The use of RWD to generate RWE for regulatory decision making can often benefit from additional, early interactions with FDA to address key challenges. This includes, for example, assessing the relevance and reliability of RWD sources; ensuring study designs are appropriate to answer the regulatory question of interest and analytic plans are adequate to mitigate biases; and adhering to regulatory requirements, such as human subject protections, submission of patient-level data to FDA, and the ability of FDA inspectors to access source records.[2,3]

During Prescription Drug User Fee Amendments negotiations for fiscal years 2023 through 2027 (PDUFA VII), FDA and industry sought a mechanism to identify and promote awareness of approaches for generating RWE that could meet regulatory requirements in support of labeling for effectiveness or for meeting post-approval study requirements. In addition, there was a need to develop Agency processes to promote consistent decision making and shared learning regarding RWE. As a result, FDA developed the Advancing RWE Program, which was announced in the Federal Register on October 20, 2022.[4]

PROGRAM OVERVIEW

The Advancing RWE Program is a pathway for sponsors selected into the program to meet with staff from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Oncology Center of Excellence (OCE) to discuss the use of RWE in medical product development. Sponsors can submit an initial meeting request to the program on a rolling basis through March 31, 2027, and FDA reviews all requests received in the preceding 6-month submission cycle after each submission deadline. FDA may grant up to two initial meeting requests per semi-annual submission cycle during the first two program years (fiscal years 2023 and 2024) and up to four initial meeting requests per cycle in subsequent years (fiscal years 2025–2027). After an initial program meeting, sponsors can request up to three follow-up meetings to continue discussions of their proposed studies.

The Advancing RWE Program is administered by CDER's Office of Medical Policy under the leadership of a team comprised of representatives from CDER's Offices of Medical Policy, New Drugs, Biostatistics, Surveillance and Epidemiology, and Regulatory Policy as well as representatives from CBER's Office of Biostatistics and Pharmacovigilance and the OCE. Meetings with sponsors include relevant review staff and leadership from these groups as well as from primary review divisions with

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [2]Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [3]Oncology Center of Excellence, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [4]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA. *Correspondence: Kimberly A. Smith (kimberly.smith@fda.hhs.gov)

Received January 14, 2025; accepted April 17, 2025. doi:10.1002/cpt.3700

Table 1 Reasons for denial of initial Advancing RWE Program meeting requests

Reason for denial[a]	Number
Concerns regarding interpretability of non-randomized studies given characteristics of disease and approaches to treatment	6
Supportive role of proposed study in development program	5
Need for additional safety data	4
Insufficient scientific rationale to support proposed new indication	2
Unlikely to be able to identify population and/or outcomes of interest using RWD	2
Better served through established procedures	2
Not RWD/RWE (randomized controlled trial without use of RWD)	2

[a]Submissions may have more than one reason for denial.

jurisdiction over the product and indication. Details regarding program design and requirements are available at: https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program.

INITIAL EXPERIENCE

Since the Advancing RWE Program's launch and through the first four submission cycles, FDA received 21 initial meeting requests and accepted four, with one sponsor completing participation.

The sponsor that completed participation in the program was pursuing a new indication for the treatment of a type of cardiomyopathy for a drug already approved by the FDA for a different indication. The drug is often used off-label for this purpose, a setting in which it is believed to reduce heart failure symptoms. The sponsor proposed a retrospective cohort study using commercially available claims databases to assess cardiac-related hospitalizations and all-cause mortality over a 3-year follow-up period in patients receiving the drug of interest compared with patients receiving an active comparator.

FDA focused primarily on two areas. The first was that there were likely to be substantial differences between the treatment arms in the characteristics of patients, providers, concomitant treatments, and facilities given clinical prescribing patterns. In clinical practice, patients with more advanced disease are more likely to receive the drug of interest than the comparator and to undergo interventions, such as surgical myectomy, septal ablation, or dual chamber pacing—and facilities that routinely prescribe the drug of interest are generally specialty centers that are also capable of performing such interventions. The ability of design elements and statistical methods to adjust for potential biases depends, in part, on the availability of relevant data for important predictors of patient outcomes; however, key markers of disease severity for the condition of interest are not well captured in claims data. The second area of FDA focus was the impact of selecting endpoints several steps removed from the more immediate effects of the drug based on its mechanism of action, thereby making it more challenging to conclude that any observed between-group differences in these more distal outcomes were a result of the drug rather than the influences of other factors. These key design features were likely to limit the interpretability of the proposed study.

Three sponsors accepted into the program are still engaging with FDA through the program as of December 2024. One sponsor is developing a vaccine for use in women of child-bearing potential and is exploring the use of a non-interventional case–control study using electronic health record (EHR) data to extend the indication to include the prevention of disease in the neonates of vaccinated mothers. Another sponsor is pursuing the potential use of a non-interventional cohort study using claims and EHR data to fulfill a post-marketing requirement to assess cardiovascular safety. A third sponsor is exploring the use of a non-interventional cohort study using EHR data to fulfill a post-marketing commitment to evaluate clinical outcomes in children in subsequent viral seasons following administration of an agent to prevent viral illness in the preceding viral season.

Seventeen initial meeting requests have been denied, with sponsors either receiving a separate advice letter from the primary review division with comments on their proposed study or a recommendation to request a meeting with the primary review division if the sponsor remains interested in pursuing the proposed study. As shown in **Table 1**, the most common reason contributing to denial has been concerns regarding the interpretability of a non-randomized study given characteristics of the disease and approaches to treatment ($n = 6$). This category includes studies in diseases or conditions with heterogeneous patient populations and variable clinical courses, treatment regimens that evolve based on clinical response or for which significant channeling bias is expected, and/or symptom-based endpoints known to have large placebo treatment effects.

The second most common reason contributing to a denial has been the role of the proposed study in the development program ($n = 5$). This category includes studies intended to provide "supportive" information, such as context for interpreting or generalizing the findings of randomized trials; to develop analytic methods; or to validate endpoints for use in clinical trials. Although such studies represent an important use of RWD/RWE, they do not directly meet regulatory requirements in support of labeling for effectiveness or for meeting post-approval study requirements, the primary goal of the Advancing RWE Program.

Additional reasons for denial have included the need for additional safety data (preclinical and/or clinical) to support the proposed indication ($n = 4$), including studies to support an indication for chronic use of a product currently approved only for short-term use or use in a new population for which risks may differ from those of the currently indicated population; insufficient scientific rationale to support the proposed new indication ($n = 2$), including studies of products for which the mechanism of action lacks biological plausibility to support the proposed indication; and challenges using RWD sources to identify the population and/or outcomes of interest ($n = 2$). Two other proposals were for studies better served through established procedures to engage with the Agency. The primary review division had already provided feedback on one study, including

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reviews of versions of the study protocol and analytic plan, and another was a descriptive, single-arm safety study that did not present novel data, design, or regulatory considerations. Finally, two proposals were for traditional randomized trials, which the sponsors indicated were designed to mimic how the product would be used in the "real world." Neither trial proposed to incorporate RWD to generate RWE, and the trials therefore did not fall within the scope of the Advancing RWE Program.

Despite the denial of several initial meeting requests, the program has contributed to shared learning regarding the characteristics of RWE that can support regulatory decision making, both through internal discussions leading up to the denial and feedback provided via the primary review division to sponsors afterwards. Of note, over this same time, the product centers have also maintained a robust pipeline of meeting requests and submissions through established pathways that include proposals for RWE for regulatory decision making, often in situations where sponsors would like to focus more broadly on their development program during the meeting to include non-RWE topics. Such discussions can move the field forward, regardless of the forum for interactions.

CONCLUSION

The first four semi-annual cycles of the Advancing RWE Program have provided opportunities to bring varied perspectives from across the Agency, including CDER, CBER, OCE, and Center leadership, together to discuss and align on an approach to a diverse group of study proposals. Such interactions have allowed for enhanced communication and application of the principles put forth in FDA guidance related to RWD and RWE.[3] We anticipate that such program-specific interactions and shared problem-solving will continue to improve the quality and acceptability of RWE-based approaches that can meet regulatory requirements in support of labeling for effectiveness or for meeting post-approval study requirements.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work. This article reflects the views of the authors and should not be construed to represent FDA's view or policies. Dr. Concato was with FDA when this work was conducted.

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