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Welcome to the real world: FDA issues long-awaited framework for evaluating the potential use of real-world evidence to support regulatory decisions for drugs and biologics

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On December 6, the Food and Drug Administration (FDA) published a framework for its Real-World Evidence (RWE) Program to strategically leverage information gathered from real-world data (RWD): data that relates to patient health status and/or the delivery of health care routinely collected from a variety of sources. From RWD, FDA aims to gather RWE – which it defines as "clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD" – in order to inform regulatory decisions for drugs and biologics, such as supplemental approvals and labeling changes, and to satisfy post-marketing study requirements. Examples of RWD include patient-generated data as well as data derived from electronic health records (EHRs), medical claims and billing data, product and disease registries, and other sources that can inform on health status, such as mobile devices.

FDA's RWE Program will evaluate the potential use of RWE to support

- changes to labeling about drug product effectiveness, including adding or modifying an indication, such as a change in dose, dose regimen, or route of administration;
- adding a new population; and
- adding comparative effectiveness or safety information.

In a statement, FDA Commissioner Scott Gottlieb, M.D., called use of RWD a "top strategic priority," citing how designing traditional post-market research studies is an expensive and lengthy process, and predicting greater use of RWD will result in more information on the efficacy of a drug becoming available sooner. In addition, Gottlieb said use of RWD in "active post-market risk identification and analysis (ARIA) is replacing the need for post-marketing studies as a more effective, comprehensive, and achievable tool for post-market evaluation of products."

The framework added that RWD can be useful in

- generating hypotheses for testing in randomized controlled trials;
- identifying drug development tools (including biomarker identification);
- assessing trial feasibility by examining the impact of planned inclusion/exclusion criteria in the relevant population;
- informing prior probability distributions in Bayesian statistical models;
- identifying prognostic indicators or patient baseline characteristics for enrichment or stratification; and
- assembling geographically distributed research cohorts (e.g., in drug development for rare diseases or targeted therapeutics).

The framework aims to comply with the 21st Century Cures Act's requirement that FDA release a comprehensive plan on how drugmakers may make use of these alternative sources of data to support regulatory filings to extend the label for an approved therapy. Among other things, FDA's RWE program will cover clinical trials that generate RWE in some capacity, but that are not traditional clinical trials, and observational studies, which it defines as "non-interventional clinical study designs that are not considered clinical trials."

Three-part approach to assess RWD as evidence of safety and efficacy

Historically, FDA has accepted RWE to support drug product approvals only in a limited number of cases, primarily in the setting of oncology and rare diseases. Additionally, observational studies have been used to support regulatory safety decisions. However, FDA is wary about accepting observational studies in support of effectiveness decisions because those studies lack a control arm, randomization, and blinding. As part of its RWE Program, FDA will evaluate the potential role of observational studies in contributing to evidence of efficacy via a three-part approach, which will include consideration of whether

- the RWD are fit for use for their intended purpose;
- the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question; and
- the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection).

The framework breaks down in greater detail how it will assess data reliability and relevance, and how it will address gaps in RWD sources. The document also covers use of electronic source data, saying FDA will finalize the June 2017 draft guidance "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR part 11 - Questions and Answers" and consider its applicability to different study designs.

FDA expressed concern about the potential lack of transparency in observational studies. Specifically, these studies may not be registered on clinicaltrials.gov and – coupled with the fact that some of these studies can be conducted multiple times and relatively inexpensively with varying study design elements – the use of observational studies may allow drug sponsors to submit only favorable results as if they were the result of a single study with a prespecified protocol. However, FDA said it will consider policies to prevent such practices.

FDA outlines plans for RWE program

FDA said it intends to use the three-part approach outlined in the framework to evaluate individual supplemental applications, and more generally to guide the RWE program, which will involve

- the establishment of demonstration projects;
- engagement with stakeholders;
- the use of internal processes that bring senior leadership input into the evaluation of RWE; and
- the development of guidance documents to assist sponsors interested in using RWE to support their work.

In addition, the program aims to promote data standards, including a common data model (CDM) with common representation, including terminologies, vocabularies, and coding schemes.

According to Dr. Gottlieb, FDA hopes the RWE Program will "make better use of the information from patients and providers during the lifecycle of a marketed medical product." He also stated that FDA plans to issue guidance "about how to interpret [the] evidentiary standard in the context of today's modern informatics and advanced analytics, which provide new openings for the collection of data and the generation of evidence." Similarly, the commissioner has high hopes for RWE stating that "we have more tools to leverage this information to inform patient care. As we look toward the future, finding ways to collect and apply that evidence will bring us closer to providing better overall health care." We recommend companies start thinking about how to use RWE in their submissions to the agency, and to stay tuned for more from FDA.

This framework does not apply to medical devices, which are covered under the FDA guidance "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," finalized in August 2017.

Framework promises no specific action

While the framework provides useful analysis and a window into FDA thinking on the use of RWE, it merely constitutes a work plan for these issues. The key for industry going forward will be whether and how the agency takes the specific steps identified in the framework and implements any policy changes regarding RWE in the immediate future. The framework should be read cautiously on these points, as it does not promise specific action beyond stakeholder meetings.

Finally, we note that the 21st Century Cures Act requires FDA to issue a draft guidance on RWE by December 2021. With this in mind, we believe that there will be a continued – and significant – opportunity for the regulated industry to help shape FDA policy regarding RWD and RWE in the near term.

If you have any questions on FDA's Real-World Evidence Program, or how you may be able to benefit from the use of real-world data, please contact any of the authors listed below or the Hogan Lovells lawyer with whom you regularly work.

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