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# FDA Embraces Real-World Evidence in New Final Guidance

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On August 31, 2017, the U.S. Food and Drug Administration (FDA) finalized its guidance document entitled, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices." The final guidance reiterates the principles outlined in the July 27, 2016, draft document. Both the draft and final guidance's are part of FDA's efforts to take creative approaches to the evidence required to support regulatory decision-making.[1] As described in our earlier alert regarding the draft guidance, the document is intended to clarify when real-world evidence (RWE) can be used in FDA decision-making and reaffirms that RWE retains a place in the medical device regulatory landscape.

FDA's willingness to consider the utility of real-world data in regulatory decision-making aligns with a general shift in the way these data are viewed by the larger scientific community, as well as a new congressional mandate to evaluate their utility. The FDA Reauthorization Act of 2017 (FDARA),[2] which became law on August 18, 2017, includes a requirement for FDA to establish one or more voluntary postmarket pilot programs to provide timely and reliable information on the safety and effectiveness of marketed devices, and to evaluate innovative new methods for compliance with Sections 519 [3]and 522[4] of the Federal Food, Drug, and Cosmetic Act (FDCA). The pilot programs are intended to collect RWE and to prioritize devices for which the collection and analysis of such evidence is likely to advance the public health. FDARA also requires FDA to commission an independent third party to evaluate the "strengths, limitations, and appropriate use of evidence collected" pursuant to the pilot programs for informing regulatory decision-making, as well as the pilot programs efficiently generate "reliable and timely evidence about the effectiveness or safety surveillance of devices." The final RWE guidance serves as one part of FDA's commitment to optimizing use of these types of data. It dovetails, for example, with the Agency's ongoing work to develop the National Evaluation System for health Technology (NEST) as a resource for obtaining access to real-world data (RWD).

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1 Additional recent FDA guidance that fits into this category includes collection of patient preference information and adaptive clinical trial designs.
2 Pub.L. 115-52, see https://www.govtrack.us/congress/bills/115/hr2430/text.
3 Section 519 concerns Records and Reports on Devices, including medical device reports (MDRs), device tracking, unique device identification (UDI) system, reports of removals and corrections, and postmarket risk identification and analysis.
4 Section 522 concerns Postmarket Surveillance.

As explained in the Agency's guidance, RWD are "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" such as electronic health records, claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, among other sources. Meanwhile, RWE is the "clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD."

Though success in use of real-world data has been mixed in practice, the messages emphasized in the Agency's final guidance will undoubtedly be well-received by industry. While the final guidance is generally consistent with the draft guidance and with our experience using RWE to support marketing applications for medical devices in the last year, it includes some important expansions and clarifications.

First, the final guidance provides greater clarity regarding the expected scope of use for RWE. While the draft guidance noted that RWE may be used to address a number of pre- and post-market regulatory requirements, the final guidance clarifies that RWE may be used as evidence to support Humanitarian Device Exemptions (HDE), Premarket Approval Applications (PMA), De Novo petitions, as well as to identify, demonstrate, or support the clinical validity of a biomarker, to support device reclassification petitions, and to preclude the need for 522 post-market surveillance studies, among others. The final guidance also places additional emphasis on the need for prospectively-defined protocols to eliminate bias in the collection of RWD, provides additional examples of how RWE may be used and additional guidance on the applicability of investigational device exemption (IDE) regulations to collections of RWD, and stresses a "quality system approach," consistent with FDA's recent structural alignment and Total Product Life Cycle (TPLC) initiative.

Although the draft guidance touched on the importance of a prospective study protocol and analysis plan for the collection of RWD, the final guidance suggests that such plans and protocols are expected to be followed to address concerns of bias, regardless of whether the RWD were previously collected (retrospective), or whether these data will be collected in the future (prospective). According to the final guidance, such protocols and analysis plans should address the same elements that would be addressed in a traditional clinical trial protocol and statistical analysis plan. Appropriate study design, protocols, and analysis plans may be key factors for FDA in assessing the relevance of RWD to the regulatory questions at issue. The final guidance indicates that in making these determinations, FDA will evaluate whether the RWD contains sufficient detail to assess for confounding factors that may impact the exposure or outcomes of interest, and whether the RWD study design, study protocol, and/or analysis plan are appropriate to address the regulatory questions in a timely manner. Companies are encouraged to submit their study protocol and analysis plan to FDA for review and comment via pre-submission prior to either analyzing retrospective RWD or collecting prospective RWD.

Like the draft guidance, the final guidance stresses that determinations of whether an IDE is required for the collection of RWD depends on the particular facts of the situation and require case-by-case analysis. The final guidance stresses that FDA does not regulate the practice of medicine. RWD collected from administration of a cleared or approved device for an unapproved indication usually would not require an IDE, if within the normal course of medical practice in the context of a legitimate practitioner-patient relationship. However, if RWD are being gathered to determine the safety and effectiveness of the device for the unapproved use, or if the collection

protocol or analysis plan impacts patient care, such as by requiring certain follow-up activities, it likely would not be considered within the normal course of medical practice, and an IDE likely would be required. Companies and IRBs are encouraged to contact FDA if they have questions about whether an IDE is required.

The final guidance was also modified to summarize sources with recommendations for how to improve RWD quality and to stress the importance of using a "quality system approach" with a risk-based quality assurance and monitoring plan. These recommendations are consistent with FDA's TLPC initiative, which integrates pre- and post-market specialties within CDRH into product-based teams to increase consistency, FDA knowledge of products, and streamline regulatory decision making.

Overall, we see the final guidance and all of FDA's efforts regarding RWD as a positive development for the medical device industry. Although there has been some resistance to the use of RWE to support regulatory decision making, with FDA having a tendency to revert to its historical preference for prospective, controlled clinical studies, we have seen some review branches suggesting the use of RWE to support marketing submissions. We expect that industry can still expect a rocky road ahead, but issuance of the final guidance signals the agency's commitment, at least at a policy level, to use reliable data from other sources to support regulatory determinations.

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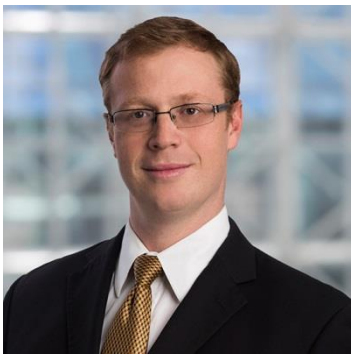

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