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Client Alert Commentary

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FDA Releases Final Guidance on Considerations for the Use of Real-World Data and Real-World Evidence

The Guidance amends the 2021 draft guidance regarding products used under an Emergency Use Authorization and use of patient-level data from third parties.

On August 31, 2023, the US Food and Drug Administration (FDA or the Agency) released final guidance on "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" (the RWD/RWE Guidance).[1] This RWD/RWE Guidance finalizes the draft guidance of the same name issued on December 9, 2021, and discusses the applicability of FDA's investigational new drug application (IND) regulations under 21 C.F.R. Part 312 to various clinical study designs that utilize real-world data (RWD).[2] The RWD/RWE Guidance also clarifies the Agency's expectations concerning both real-word evidence (RWE) and clinical studies using RWD that are submitted to FDA to support regulatory decisions regarding the effectiveness and safety of drugs when such studies are not subject to Part 312.[3]

FDA notes that the RWD/RWE Guidance changes the draft guidance in several ways, including (1) additional language about data generated in clinical practice for products used under an Emergency Use Authorization (EUA), consistent with a mandate under the Food and Drug Omnibus Reform Act of 2022 (FDORA),[4] and (2) clarifying information about the use of existing regulatory pathways for third parties to provide patient-level data to FDA when sponsors cannot submit such data through traditional channels.[5]

This Client Alert analyzes the new RWD/RWE Guidance and provides examples of how such RWD/RWE Guidance fits into FDA's larger plan to broaden access to RWD and RWE and give sponsors more options when conducting clinical trials.

Background

Section 3022 of the 21st Century Cures Act (Cures Act)[6] of 2016 amended the Federal Food, Drug, and Cosmetic Act (FDCA) by adding § 505F, entitled "Utilizing Real World Evidence."[7] Under FDCA § 505F, FDA is required to issue guidance about using RWE in regulatory decision-making and to establish a program evaluating the potential use of RWE to help support the approval of a new indication for a drug already approved under FDCA § 505(c) and to help support or satisfy drug post-approval study requirements. In December 2021, FDA issued a draft guidance outlining considerations for the use of RWD and RWE in regulatory decision-making to satisfy the Cures Act's mandate.[8] The final RWD/RWE Guidance was released ahead of FDA Commissioner Robert Califf's comments on September 19, 2023

that he expects the use of electronic health records to collect RWE to become more commonly used as a tool to expand a product's indication.[9]

Content of the RWD/RWE Guidance

At a high level, the RWD/RWE Guidance discusses two major topics: (1) applicability of 21 C.F.R. Part 312 to studies using RWD and (2) regulatory considerations for non-interventional (observational) studies involving the use of RWD. Regulatory considerations addressed by the RWD/RWE Guidance include: (1) transparency for data collection and analysis, (2) access to RWD, (3) study monitoring, (4) safety reporting, and (5) other sponsor responsibilities.

Definitions

The RWD/RWE Guidance defines RWD as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources," while RWE is defined as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[10]

Applicability of Existing Regulations to Studies Using RWD

Interventional studies involving drugs typically meet the definition of a clinical investigation under 21 C.F.R. § 312.3 (i.e., "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects") and are therefore subject to FDA regulations under Part 312. FDA's RWD/RWE Guidance recognizes the potential utility of using RWD in interventional studies. For example, RWD may be used to (1) identify potential participants for a randomized controlled trial, (2) ascertain endpoints or outcomes in a randomized controlled trial, or (3) serve as a comparator arm in an externally controlled trial.[11]

Regulatory Considerations for Interventional Studies

Although the RWD/RWE Guidance does not specifically discuss considerations to support regulatory review of interventional studies utilizing RWD/RWE, FDA expressed a plan in its 2018 "Framework for FDA's Real-World Evidence Program" to issue additional guidance on regulatory considerations raised by different study designs using RWD to generate RWE that is submitted to support drug product effectiveness. Consequently, FDA issued a guidance document in February 2023[12] that includes two primary regulatory considerations for externally controlled trials, a specific type of interventional study in which outcomes in participants receiving the test treatment are compared to outcomes in a group of people external to the trial who did not receive the same treatment.

- **Communication with FDA.** FDA encourages sponsors to consult with the relevant FDA review division early in a drug development program about the potential use of an externally controlled trial rather than a randomized control trial.[13] In connection with these discussions, FDA suggests that sponsors provide a detailed description of the (1) reasons why the proposed study design is appropriate, (2) proposed data sources for the external control arm and an explanation of why they are fit for use, (3) planned statistical analyses, and (4) plans to address FDA expectations for the submission of data.[14]

- **Access to Data and Documents.** FDA recommends that sponsors include in their marketing applications relevant patient-level data (i.e., data on each participant in the externally controlled trial) for both the treatment and external control arms, and ensure that FDA has access to source documents and data for the external control arm as part of an FDA inspection or request.[15] If sponsors do not own the data used for the external control arm, sponsors could structure their

agreements with the data owners in a manner that ensures patient-level data can be provided to FDA in support of the marketing application.[16]

On the other hand, non-interventional studies, which analyze data reflecting the use of a marketed drug administered in routine medical practice according to a medical provider's clinical judgment and based on patient characteristics, are not clinical investigations as defined under 21 C.F.R. § 312.3 and do not require an IND. Thus, additional regulatory considerations affect the use of RWD and RWE in non-interventional studies.

Regulatory Considerations for Non-Interventional Studies

- **Transparency for data collection and analysis.** To ensure transparency regarding data collection, FDA encourages sponsors to post their protocols on a publicly available website (e.g., ClinicalTrials.gov), describe in the protocol (or an appendix to the protocol) the data sources evaluated when designing the study, and include a justification for selecting or excluding relevant data sources from the study.[17] The draft protocol and statistical analysis plan may also be shared with FDA for review and comment so that FDA can "be confident" that the sponsor did not choose the data source or analytical plan to "favor a certain conclusion."[18] With respect to data analysis, FDA suggests that sponsors maintain data audit trails, and describe the patient characteristics of the source and study populations and document the analyses (including any exploratory analyses) performed on the datasets in the final report.[19] Such transparency may be helpful in relation to Califf's recent warning that researchers using RWD should be aware of the "time-zero problem" in prospective studies, i.e., the problem of determining when to start tracking data in follow-up studies so that they are meaningful and do not lead to biased conclusions.[20]

- **Access to RWD.** If RWD are owned and controlled by third parties, FDA provides the same guidance as noted above for interventional studies, i.e., that sponsors enter into agreements with those entities to ensure that relevant patient-level data can be provided to FDA and that source data necessary to verify the RWD are made available for inspection as applicable.[21] FDA also recommends that RWD and associated programming codes and algorithms submitted to the Agency are "documented, well-annotated, and complete" so that FDA can replicate the study analysis.[22]

- **Study monitoring.** For non-interventional studies, FDA suggests that study monitoring begin at the data extraction from RWD sources and focus on the protection of human subjects, as applicable, and on maintaining data integrity.[23] As part of study monitoring, FDA encourages sponsors to ensure that (1) the RWD required by the protocol are accurate and consistent with source records; (2) prespecified plans, protocols, and study procedures were followed; and (3) deviations from these items are identified and documented and, when necessary, evaluated and remediated promptly.[24] The RWD/RWE Guidance encourages sponsors to use a risk-based quality management approach to study monitoring.[25]

- **Safety Reporting.** For non-interventional studies, FDA recognizes that sponsors often use only a subset of a larger real-world dataset to conduct their analyses to support labeling changes.[26] If a sponsor is conducting a study to support a specific labeling change, FDA does not expect the sponsor to search the entire database regarding all uses of the product for adverse events that would meet the safety reporting requirements under FDA's post-marketing reporting regulations.[27] However, if the sponsor identifies adverse events that are subject to post-marketing reporting requirements during the course of conducting a non-interventional study, FDA encourages sponsors to report such events in accordance with applicable post-marketing reporting requirements.[28]

- **Other sponsor responsibilities.** FDA also lists other responsibilities for sponsors conducting non-interventional studies in the RWD/RWE Guidance,[29] such as (1) documenting the roles and responsibilities of any third parties performing certain study-related tasks, and (2) retaining a log of any researcher or researchers who have significant involvement in the design or conduct of the study.[30]

Differences Between the Draft Guidance and the Final RWD/RWE Guidance

The RWD/RWE Guidance includes updates to the draft guidance by, for example, (1) adding language about data generated in clinical practice for products used under an EUA, consistent with a mandate under FDORA, and (2) including clarifying information about the use of existing regulatory pathways for third parties to provide patient-level data to FDA when sponsors cannot submit such data through traditional channels.

- **Data related to EUA products.** For context, under FDCA § 564 (21 U.S.C. § 360bbb-3), during the effective period of a declaration of emergency or threat justifying EUA, FDA may authorize for use unapproved products or unapproved uses of approved products to diagnose, treat, or prevent serious or life-threatening diseases or conditions when certain criteria are met. The RWD/RWE Guidance states that when products are used in clinical practice under EUA, outcomes and other variables of interest may be captured in relevant RWD sources (e.g., a patient's electronic health records), and RWD reflecting the use of a product under EUA could potentially be used to generate RWE about the safety and/or effectiveness of that product.[31] Thus, FDA explains that the considerations for the inclusion, in an application or submission to FDA, of RWD obtained regarding the use of medical products under EUA are the same for the inclusion of RWD obtained regarding the use of other medical products in clinical practice.[32]

- **FDA access to third-party RWD.** The RWD/RWE Guidance clarifies that if an appropriate justification exists for why a sponsor cannot submit third-party patient-level data to FDA through traditional channels, the third party can choose to open either a pre-IND or a Type V drug master file (DMF).[33] In that situation, FDA suggests that the sponsor provide a letter of authorization from the third party for FDA to reference the data in the third party's pre-IND or DMF.[34]

Examples of Other FDA Actions Related to RWD and RWE

In addition to the release of the RWD/RWE Guidance, FDA has issued other guidance related to use of RWD/RWE in connection and has initiated an "Advancing RWE Program" to facilitate meetings with sponsors interested in utilizing RWE. FDA also released a broad RWE framework in 2018, outlining FDA's plan to implement the Cures Act mandate discussed above.

- **RWE framework.** In 2018, FDA created a "Framework for FDA's Real-World Evidence Program" for evaluating the potential use of RWE to help support the approval of a new indication for a drug already approved under FDCA § 505(c) or to help support or satisfy drug post-approval study requirements.[35] In addition to drug and biological products approved under FDCA § 505(c), this framework is also intended to apply to biological products licensed under the Public Health Service Act.[36] As relevant here, the framework lays out FDA's plans to issue a variety of RWD/RWE guidance documents, including "guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision-making."[37] As noted above, FDA issued such guidance in December 2021 and finalized the

RWD/RWE Guidance in August 2023 as part of the plan expressed in the framework to issue RWE/RWD guidance about observational study designs using RWD.

- **Advancing RWE Program.** In October 2022, FDA established the Advancing RWE Program, which seeks to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims.[38] The Advancing RWE Program fulfills an FDA commitment under PDUFA VII, incorporated as part of the FDA User Fee Reauthorization Act of 2022.[39] The Advancing RWE Program provides sponsors who are selected the opportunity to meet with Agency staff — before protocol development or study initiation — to discuss the use of RWE in drug development.[40] The Advancing RWE Program has three goals: (1) identify approaches for generating RWE that meet regulatory requirements in support of labeling for effectiveness or for meeting post-approval study requirements; (2) develop agency processes that promote consistent decision-making and shared learning regarding RWE; and (3) promote awareness of characteristics of RWE that can support regulatory decisions by allowing FDA to discuss study designs considered in the Advancing RWE Program in a public forum.[41] Sponsors planning to utilize RWD, particularly in connection with observational studies, may be able to utilize the RWD/RWE Guidance as a resource to understand the types of regulatory considerations at play when planning for meetings with FDA through the Advancing RWE Program.

- **Other guidance documents.** FDA has also issued several other guidance documents on specific uses of RWD and RWE, and recent comments from Califf suggest that stakeholders should expect additional RWD and RWE guidance documents in the future.[42] The RWD/RWE Guidance and its predecessor, for example, were adapted and built from a previous guidance from May 2013 concerning best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data.[43] FDA has also been very focused on increasing diversity in clinical trials, and has issued two guidance documents on how to promote this effort. The documents include recommendations on using RWD to promote more efficient recruitment of a diverse population (e.g., by using claims data and electronic health records to identify potential sites and participants) for clinical trials, and a separate guidance document on how to collect data on diverse populations (using means such as RWD) in the postmarket setting as a potential alternative if the sponsor's strategies to recruit a representative population in the premarket setting are unsuccessful, "despite their best efforts."[44]

Conclusion

The recently issued RWD/RWE Guidance contains minor changes from the draft guidance issued in 2021, but generally reflects the same regulatory considerations for use of RWD in connection with observational studies and provides the same guidance on the applicability of FDA's IND regulations to clinical trials utilizing RWD. Interested parties may submit written or electronic comments on the RWD/RWE Guidance at any time. The RWD/RWE Guidance expands on and complements previously issued guidance documents and FDA's framework for RWE and may be a useful resource for sponsors to consult prior to meeting with FDA to discuss the use of RWD in a study, whether such meetings occur through the Advancing RWE Program.

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Endnotes

[1] *See* FDA, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (Aug. 2023), https://www.fda.gov/media/171667/download.

[2] *Id.* at 2.

[3] *Id.*

[4] *See* Latham & Watkins, *Client Alert: FDA Omnibus Reform Act: Examining the Policy Changes* (Jan. 9, 2023), https://www.lw.com/en/people/admin/upload/SiteAttachments/Alert%203050.pdf.

[5] *See* 88 Fed. Reg. 60215, 60216 (Aug. 31, 2023), https://www.federalregister.gov/documents/2023/08/31/2023-18841/considerations-for-the-use-of-real-world-data-and-real-world-evidence-to-support-regulatory.

[6] *See* Latham & Watkins, *Client Alert: President Obama Signs the 21st Century Cures Act Into Law* (Dec. 13, 2016), https://www.jdsupra.com/post/fileServer.aspx?fName=f6723986-6402-4e53-8e96-7f765f25f4ce.pdf.

[7] 21 U.S.C. § 355g.

[8] *See* FDA, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (Dec. 2021), https://downloads.regulations.gov/FDA-2021-D-1214-0002/attachment_1.pdf.

[9] *See* Ferdous Al-Faruque, *FDA's Califf: Expect to See More RWE-Based Regulatory Decisions*, RAPS (Sept. 22, 2023), https://www.raps.org/News-and-Articles/News-Articles/2023/9/FDA%E2%80%99s-Califf-Expect-to-see-more-RWE-based-regulato.

[10] *See* FDA, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (Aug. 2023), at 2, https://www.fda.gov/media/171667/download.

[11] *Id.* at 3.

[12] *See* FDA, *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (Feb. 2023), https://www.fda.gov/media/164960/download.

[13] *Id.* at 16.

[14] *Id.*

[15] *Id.*

[16] *Id.*

[17] *See* FDA, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (Aug. 2023), at 5-6, https://www.fda.gov/media/171667/download.

[18] *Id.* at 5.

[19] *Id.* at 6.

[20] *See* Ferdous Al-Faruque, *FDA's Califf: Expect to See More RWE-Based Regulatory Decisions*, RAPS (Sept. 22, 2023), https://www.raps.org/News-and-Articles/News-Articles/2023/9/FDA%E2%80%99s-Califf-Expect-to-see-more-RWE-based-regulato.

[21] *See* FDA, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (Aug. 2023), at 6, https://www.fda.gov/media/171667/download.

[22] *Id.*

[23] *Id.* at 7.

[24] *Id.*

[25] *Id.*

[26] *Id.* at 8.

[27] *Id.*

[28] *Id.*

[29] *See id.* at 9.

[30] *Id.*

[31] *Id.* at 4 n.11.

[32] *Id.*

[33] *Id.* at 7.

[34] *Id.*

[35] *See* FDA, *Framework for FDA's Real-World Evidence Program* (Dec. 2018), https://www.fda.gov/media/120060/download.

[36] *See id.*

[37] *Id.* at 22.

[38] *See* FDA, *Advancing Real-World Evidence Program*, https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program (last updated July 25, 2023).

[39] *See* Latham & Watkins, *Continuing Appropriations Act Includes FDA Reauthorization of User Fees* (Oct. 4, 2022), https://www.lw.com/en/people/admin/upload/SiteAttachments/Alert-3016.pdf.

[40] *Id.*

[41] *Id.*

[42] *See* Ferdous Al-Faruque, *FDA's Califf: Expect to See More RWE-Based Regulatory Decisions*, RAPS (Sept. 22, 2023), https://www.raps.org/News-and-Articles/News-Articles/2023/9/FDA%E2%80%99s-Califf-Expect-to-see-more-RWE-based-regulato.

[43] *See* FDA, *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013), https://www.fda.gov/media/79922/download.

[44] *See* FDA, *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (Nov. 2020), https://www.fda.gov/media/127712/download; FDA, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials* (Apr. 2022), https://www.fda.gov/media/157635/download; FDA, *Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products* (Aug. 2023), https://www.fda.gov/media/170899/download.