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GUIDANCE DOCUMENT

CONSIDERATIONS FOR THE USE OF REAL-WORLD DATA AND REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR DRUG AND BIOLOGICAL PRODUCTS

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
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Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The 21st Century Cures Act (Cures Act),[2] signed into law on December 13, 2016, is intended to accelerate medical product development and bring innovations faster and more efficiently to the patients who need them. Among other provisions, the Cures Act added section 505F to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355g). Pursuant to this section, FDA created a framework for a Real-World Evidence (RWE) Program[3] to evaluate the potential use of RWE in regulatory decision-making for drugs.[4]

FDA is issuing this guidance as part of its RWE Program to satisfy, in part, the mandate under section 505F of the FD&C Act to issue guidance about the use of RWE to help support approval of a new indication for a drug already approved under section 505(c) of the FD&C Act (21 U.S.C. 355(c)) or to help support postapproval study requirements.[5]

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Oncology Center of Excellence at the Food and Drug Administration.

[2] Public Law 114-255.

[3] See the *Framework for FDA's Real-World Evidence Program*, available at https://www.fda.gov/media/120060/download. The framework and RWE Program also cover biological products licensed under the Public Health Service Act.

[4] For the purposes of this guidance, all references to *drug* or *drugs* include both human drugs and biological products.

[5] See section 505F(e) of the FD&C Act.

For the purposes of this guidance, FDA defines real-world data (RWD) and RWE as follows:

- RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

This guidance discusses the applicability of FDA's investigational new drug application (IND) regulations under part 312 (21 CFR part 312) to various clinical study[6] designs that utilize RWD. The guidance also clarifies the Agency's expectations concerning clinical studies using RWD submitted to FDA in support of a regulatory decision regarding the effectiveness and safety of a drug (e.g., as part of a new drug application (NDA) or biologics license application (BLA)) when such studies are not subject to part 312. This guidance focuses primarily on clinical study designs that are non-interventional.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

For the purposes of this guidance, the term *interventional study* (also referred to as a clinical trial) is a study in which participants, either healthy volunteers or volunteers with the condition or disease being studied, are assigned to one or more interventions, according to a study protocol, to evaluate the effects of those interventions on subsequent health-related outcomes. One example of an interventional study is a traditional randomized controlled trial in which some participants are randomly assigned to receive a drug of interest (test article), whereas others receive an active comparator drug or placebo. Other examples of interventional study designs include randomized clinical trials with pragmatic elements (e.g., broad eligibility criteria, recruitment of participants in routine care settings) and single-arm trials.

For the purposes of this guidance, a *non-interventional study* (also referred to as an observational study) is a type of study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol. Examples of non-interventional study designs include, but are not limited to, (1) observational cohort studies, in which patients are identified as belonging to a study group according to the drug or drugs

[6] For the purposes of this guidance, the term *clinical study* means research that evaluates human health outcomes associated with taking a drug of interest. Clinical studies include interventional (clinical trial) designs and non-interventional (observational) designs (see section II in this guidance). The fact that this guidance refers to clinical trials as a type of clinical study should not be read to suggest that FDA considers clinical trials to be studies under section 505(o) of the FD&C Act (21 U.S.C. 355(o)), which authorizes FDA under specific conditions to require postapproval clinical trials and studies.

received or not received during routine medical practice, and subsequent biomedical or health outcomes are identified and (2) case-control studies, in which patients are identified as belonging to a study group based on having or not having a health-related biomedical or behavioral outcome, and antecedent treatments received are identified.

III. REGULATORY CONSIDERATIONS ADDRESSED

A. Applicability of 21 CFR Part 312

This section discusses the applicability of part 312 (Investigational New Drug Application) to studies involving the use of RWD.

- FDA regulations under part 312 outline procedures and requirements governing the use of investigational new drugs, including the requirements for an IND submission to and review by FDA. Under § 312.3, a clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice."

- Interventional studies involving drugs generally meet the definition of a clinical investigation under § 312.3 and are subject to FDA regulations under part 312 as described in § 312.2. FDA recognizes the potential utility of using RWD in interventional studies; for example, to identify potential participants for a randomized controlled trial, to ascertain endpoints or outcomes (e.g., occurrence of stroke or other discrete events, hospitalization, survival) in a randomized controlled trial, or to serve as a comparator arm in an externally controlled trial,[7] including historically controlled trials.[8]

- Non-interventional studies 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, rather than assignment of a participant to a study arm according to a research protocol. As such, non-interventional studies are not clinical investigations as defined under § 312.3 and do not require an IND.

[7] An externally controlled trial is an interventional study, which will generally be subject to part 312 regardless of the source of the data for the external control. Additional considerations for external controls are addressed in the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] FDA regulations under 21 CFR 314.126 outlining the characteristics of adequate and well-controlled studies discuss the use of historical controls as comparators in clinical studies. Additional considerations for historical controls are addressed in the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019) (when final, this guidance will represent FDA's current thinking on this topic) and in the guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001).

B. Regulatory Considerations for Non-Interventional Studies

This section discusses regulatory considerations for non-interventional studies involving the use of RWD.

1. Overview

- Regardless of a study's interventional or non-interventional design, the evidence submitted by a sponsor in a marketing application to support the safety and/or effectiveness of a drug must satisfy the applicable legal standards for the application to be approved or licensed.[9]

- Although many non-interventional studies involve only the analysis of data reflecting the use of a marketed drug in routine medical practice, certain non-interventional studies include protocol-specified activities or procedures (e.g., questionnaires, laboratory tests, imaging studies) that collect additional data to help address questions of interest in these studies. FDA does not consider these types of studies to be clinical investigations under part 312, and an IND is not required.[10] Nonetheless, the protection of human subjects under these circumstances is critical, and sponsors must ensure that applicable requirements per FDA regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards) are met.

- Various sources of RWD can be analyzed in non-interventional studies, including registries, electronic health records (EHRs), and medical claims. The topics discussed in this guidance apply to any type of RWD, including data on products used in clinical practice under an emergency use authorization (EUA).[11]

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[9] See section 505 of the FD&C Act (21 U.S.C. 355), section 351 of the Public Health Service Act (42 U.S.C. 262), and 21 CFR parts 314 and 601. Similarly, non-interventional studies may be required by FDA as a postmarketing requirement under section 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)) (or other authorities) or agreed upon between FDA and an applicant as a postmarketing commitment. Such studies carry specific obligations not addressed in this guidance. See, e.g., the discussion of postmarketing requirements and postmarketing commitments in the revised draft guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). When final, this guidance will represent FDA's current thinking on this topic.

[10] If the protocol-specified activities or procedures alter the patients' treatment regimens or plans, the study becomes interventional and requires an IND, unless exempt, because the drug is no longer being used "in the course of medical practice." See 21 CFR 312.3(b).

[11] Under section 564 of the FD&C Act (21 U.S.C. 360bbb-3), during the effective period of a declaration of emergency or threat justifying EUA, FDA may authorize for use during an actual or potential emergency unapproved products or unapproved uses of approved products to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, or nuclear threats when certain criteria are met. When products are used in clinical practice under EUA, outcomes and other variables of interest may be captured in relevant RWD sources, such as a patient's EHR. When fit for use, RWD reflecting the use of a product under EUA can be used to generate RWE about the safety and/or effectiveness of that product. Thus, considerations for the inclusion, in an application or submission to FDA, of data 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.

- When appropriate, sponsors should consult with experts who consider data privacy issues to provide input on the protocol as part of the study design process for a non-interventional study, as these experts may help identify and address data privacy and security concerns raised when accessing health care data.

2. Transparency Regarding Data Collection and Analysis

- Sponsors planning to use a non-interventional study to support a marketing application should engage with FDA early in the drug development process using an appropriate regulatory pathway (e.g., requesting a Type C meeting through an existing IND for the product).[12] Early engagement will help address the appropriateness of using a non-interventional study design and the proposed data sources to address the research question of interest. Additionally, early engagement will allow for timely identification of challenges in the design and planning of a non-interventional study and for discussion of how such challenges might be addressed. When submitting a meeting request, sponsors should include adequate information—as outlined in FDA guidance for formal meetings—for FDA to both assess the potential utility of a meeting and to identify relevant FDA subject matter experts who should address the proposed agenda items.

- Sponsors should provide draft versions of their proposed protocol and statistical analysis plan (SAP) for Agency review and comment, prior to finalizing these documents and before conducting the study analyses.

- To adequately assess the results of a non-interventional study supporting a marketing application, FDA must be confident (based on corresponding documentation) that particular data sources or databases were not selected, or that specific analyses were not conducted, to favor a certain conclusion. The protocol and SAP should be finalized and shared with FDA prior to conducting the prespecified analyses described in the protocol and SAP. In addition, any revisions to the protocol should be date-stamped, and the rationale for each change should be provided.

- FDA recognizes that evaluation of relevant data sources or databases is an important step in the design of a study and in evaluating a study's feasibility. Such evaluations of data sources or databases for feasibility purposes serve as a way for the sponsor and FDA to (1) assess if the data source or database is fit for use to address the research question being posed and (2) estimate the statistical precision of a potential study without evaluating outcomes for treatment arms.

- Sponsors should describe in the study protocol, or as an appendix to the protocol, the data sources evaluated when designing the study, including results from feasibility evaluations or exploratory analyses of those data sources. Sponsors should provide a justification for selecting or excluding relevant data sources from the study. Sponsors should also

[12] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent FDA's current thinking on this topic.

describe how the choice of the final data sources, study design elements, and analytic approaches aligns with the research question of interest and that the data sources, study design elements, and analytic approaches were not selected to favor particular study findings.

- To ensure transparency regarding their study design, sponsors should post their study protocols on a publicly available website, such as ClinicalTrials.gov[13] or the web page for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for post-authorization studies.[14]

- In their final report, sponsors should describe the patient characteristics of the source population (i.e., the population from which the study population is drawn) and the study population (i.e., the population for which analyses are conducted) and should note any differences that may impact the final study findings.

- In their final report, sponsors should document the analyses performed on the final dataset or datasets according to the SAP; any additional analyses should be described as exploratory.

- Sponsors should enable and maintain audit trails of data, starting from extracting RWD sources through maintenance and retention of dataset(s). This process should include the tracking of user access, data changes, changes to the protocol, and analyses performed.

3. Access to RWD

- In the early stages of designing a non-interventional study intended for use in a marketing application, sponsors should discuss with the relevant review division the expectations regarding access to RWD used in their development program. Sponsors must ensure that they are able to submit patient-level data for any RWD that have been analyzed as part of the clinical study included in a marketing application when required under 21 CFR 314.50 and 601.2.

- If certain RWD are owned and controlled by other entities, sponsors should have agreements in place with those entities to ensure that relevant patient-level data can be provided to FDA and that source data[15] necessary to verify the RWD are made available for inspection as applicable.

[13] See https://www.clinicaltrials.gov. For an interventional study that meets the definition of an *applicable clinical trial*, legal requirements exist for submission of certain information relating to the study. See 42 CFR part 11.

[14] See https://www.ema.europa.eu/en.

[15] For the purposes of this guidance, *source data* include all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.

- If an appropriate justification exists for why a sponsor cannot submit patient-level data to FDA through traditional channels, regulatory pathways exist for third parties to provide patient-level data to FDA to support a sponsor's marketing application. Specifically, the third-party provider can choose to open either a pre-investigational new drug application (pre-IND) or a Type V drug master file (DMF). The sponsor should provide a letter of authorization from the third party for FDA to reference the data in a third party's pre-IND or DMF. FDA does not currently accept links to external databases for such data.

- Sponsors should ensure that RWD and associated programming codes and algorithms submitted to FDA are documented, well-annotated, and complete, which would allow FDA to replicate the study analysis using the same dataset and analytic approach.[16]

4. Study Monitoring

- Study monitoring is one of the principal quality control activities critical to ensuring that (1) the study is conducted according to the protocol, (2) data submitted to FDA are reliable, and (3) data are appropriately protected. For non-interventional studies, monitoring should begin at the data extraction from RWD sources and focus on the protection of human subjects, as applicable, and on maintaining data integrity.[17]

- As part of study monitoring of a non-interventional study, sponsors should, at a minimum:

  - Ensure that the RWD required by the protocol are accurate and consistent with the source records

  - Ensure that prespecified plans (e.g., SAP), protocol, and study procedures (e.g., for curation and transformation and reporting of results) were followed

  - Ensure that deviations from the prespecified plans and protocol and study procedures are identified and documented, and when necessary, promptly evaluated and remediated according to the significance of the deviations that have been identified

- FDA encourages sponsors to use a risk-based quality management approach to study oversight.[18] This approach focuses sponsor oversight activities on (1) processes critical

[16] For further information, see the draft guidances for industry (1) *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products* (September 2021) and (2) *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* (October 2021). When final, these guidances will represent FDA's current thinking on these topics.

[17] For the purposes of this guidance, *data integrity* refers to the completeness, consistency, and accuracy of data; the data should also be attributable, legible, contemporaneously recorded, and an original or a certified copy.

[18] Additional considerations for risk-based monitoring practices that may be relevant for non-interventional study oversight can be found in (1) the guidance for industry *Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring* (August 2013), (2) the guidance for industry *A Risk-Based Approach to Monitoring of*

to human subject protection that are relevant when additional protocol-specified activities or procedures are included in a non-interventional study[19] and (2) preventing or mitigating important and likely risks to study quality.

5. Safety Reporting

- Applicants of NDAs and BLAs and other responsible parties are subject to regulatory requirements regarding postmarketing safety reporting. Non-interventional studies examine the use of a drug in routine medical practice, and the Agency requires that applicants comply with postmarketing safety reporting regulations regarding the occurrence of relevant adverse events.[20]

- For non-interventional studies, FDA recognizes that sponsors will often use only a subset (often called an analytic dataset) of a larger real-world dataset to conduct their analyses to support labeling changes. For example, a larger dataset may contain information regarding a product's approved and unapproved uses in clinical practice. If the sponsor is conducting a study to support a specific labeling change (e.g., a new indication), FDA does not expect the sponsor to search the entire database regarding all uses of the product for adverse events that would meet the reporting requirements under FDA's postmarketing reporting regulations. Nonetheless, if a sponsor identifies adverse events that are subject to postmarketing reporting requirements during the course of conducting a non-interventional study, such events must be reported in accordance with applicable postmarketing reporting requirements.[21]

6. Other Sponsor Responsibilities

- For a marketing application containing data from a non-interventional study submitted to support regulatory decisions regarding the safety or effectiveness of a product, the

Clinical Investigations: Questions and Answers (April 2023), and (3) the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

[19] When a non-interventional study includes additional protocol-specified activities and procedures, study monitoring should also ensure that applicable human subject protection requirements are met and data integrity is maintained. See, e.g., 21 CFR 56.111, which includes as a criterion for IRB approval of research that the research plan, where appropriate, makes adequate provision for monitoring data collected to ensure the safety of subjects.

[20] See 21 CFR 314.80, 314.81, and 600.80.

[21] FDA recommends that applicants, at a minimum, have knowledge of the following four elements before considering any clinical incident for submission to FDA in an individual case safety report: (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect drug or biological product, and (4) an adverse experience or fatal outcome suspected to be due to the drug or biological product. See the draft guidance for industry *Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines* (March 2001). When final, this guidance will represent FDA's current thinking on this topic. Also see the guidance for industry *Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application* (July 2009) and the guidance for industry and FDA staff *Postmarketing Safety Reporting for Combination Products* (July 2019).

electronic systems used by the sponsor to manage the data and produce required records should comply with 21 CFR part 11.[22]

- Sponsors who submit non-interventional studies for regulatory review should take responsibility for all activities related to the design, conduct (including data analysis), and oversight of the studies. These activities should include, but not be limited to:

  - Selecting researchers qualified by training and experience to perform study-related activities and confirming that researchers have the skills and information needed to perform their roles in the study

  - Ensuring that the study is conducted in accordance with the final protocol and SAP and documenting any deviations

  - Maintaining and retaining adequate study records

  - Ensuring that FDA can access and verify relevant records (see section III.B.3 of this guidance for data access considerations)

  - Ensuring appropriate oversight of the study, including (when applicable) selecting a monitor qualified by training and experience

- FDA expects that the sponsor will retain and make available to the Agency upon request a log of any researcher or researchers who have significant involvement in the design or conduct of the study. The log should contain information on researchers, including:

  - Researcher's name and affiliations

  - Description of roles or activities performed

  - Qualifications regarding education, training, and experience to perform the proposed study role

- If sponsors engage third parties (e.g., data service providers or contract research organizations) to perform certain study-related tasks, sponsors should document the roles and responsibilities of the organization or organizations performing the tasks. These documents should be made available to FDA upon request. Sponsors should remain responsible for all study-related activities unless a sponsor has transferred its responsibility to a contract research organization.

[22] For further information, see (1) the guidance for industry *Part 11, Electronic Records; Electronic Signatures – Scope and Application* (August 2003), (2) the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* (March 2023) (when final, this guidance will represent FDA's current thinking on this topic), and (3) the guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018).