Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

May 2019
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Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to encourage sponsors and applicants who are using real-world data (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format. FDA will use this information for internal tracking purposes only. This guidance applies to submissions for investigational new drug applications (INDs), new drug applications (NDAs), and biologics license application (BLAs) that contain RWE used to support regulatory decisions regarding safety and/or effectiveness.

For the purposes of this guidance, FDA defines RWD and RWE as follows:

- RWD are data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources. Examples of RWD include the following:
  - Data derived from electronic health records (EHRs)
  - Medical claims and billing data
  - Data from product and disease registries
  - Patient-generated data, including in-home use and/or other decentralized settings
  - Data gathered from other sources that can inform on health status, such as mobile devices
- RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated, for example, by

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

collecting information about effectiveness or safety outcomes from an RWD source in randomized clinical trials or in observational studies.

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

The availability of RWD and evolving analytic techniques to generate RWE has created interest within the research and medical communities to use RWD/RWE to enhance clinical research and support regulatory decision making.

Exploring the potential for RWE to inform regulatory decisions is mandated by the 21st Century Cures Act (Cures Act). Section 3022 of the Cures Act requires FDA to establish a program[2] to evaluate the potential use of RWE to help to support the approval of a new indication for a drug approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and to help to support or satisfy postapproval study requirements.

To inform FDA's RWE program under the Cures Act and to help FDA understand the scope and use of RWE submitted to support regulatory decisions regarding safety and/or effectiveness, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) intend to track certain types of submissions using RWE under an IND, NDA, or BLA. To aid in the tracking, CDER and CBER encourage sponsors and applicants to identify submissions that include RWE being used to support a regulatory decision(s) regarding safety and/or effectiveness.

III. EXAMPLE SUBMISSIONS USING RWD AND/OR RWE

Relevant submissions can be in different forms such as a new protocol(s) submitted to an existing IND, a final study report submitted to an NDA or BLA supplement, or a meeting package that discusses the use of RWE. Relevant submissions may include RWE used to support study objectives, such as the following:

- IND submissions for randomized clinical trials that use RWD to capture clinical outcomes or safety data, including pragmatic and large simple trials[3]

[2] Information about this program can be found in the "Framework for FDA's Real-World Evidence Program," available at https://www.fda.gov/scienceresearch/specialtopics/realworldevidence/default.htm.

[3] Additional information about clinical trials and observational studies using RWE can be found in the "Framework for FDA's Real-World Evidence Program."

- New protocols for single arm trials that use RWE as an external control

- Observational studies[4] that generate RWE intended to help to support an efficacy supplement

- Clinical trials or observational studies using RWE to fulfill a postmarketing requirement to further evaluate safety or effectiveness and support a regulatory decision

FDA does not intend to track RWE submissions that are not tied to a specific product or are not being used to support a regulatory decision regarding safety and/or effectiveness. Submissions that sponsors and applicants need *not* identify as containing RWE include, for example:

- Natural history studies for development of a clinical outcome assessment or biomarker

- Feasibility studies using RWE

- Studies using RWD to perform exploratory analyses and generate hypotheses

FDA encourages sponsors and applicants to consult the appropriate review division with questions about whether a specific submission should be identified as containing RWE.

IV. IDENTIFYING RWE SUBMITTED AS PART OF A REGULATORY SUBMISSION

In the cover letter accompanying a submission, the sponsor or applicant should identify the submission as containing RWE by including the following information. To facilitate FDA tracking, a sponsor or applicant can include this information in a table or highlight this information in the cover letter:[5]

A. Purpose of Using RWE as Part of the Regulatory Submission

The sponsor or applicant should list the purpose(s) for using RWE in the submission:

- To provide evidence in support of the effectiveness or safety for a new product approval (e.g., collecting information about effectiveness or safety outcomes from an RWD source in a randomized clinical trial)

[4] Ibid.

[5] Applicants may use any format that provides the requested information. A sample table containing the requested information is provided in the Appendix.

- To provide evidence in support of labeling changes for an approved product, including:
  - Adding or modifying an indication
  - Change in dose, dose regimen, or route of administration
  - Use in a new population
  - Adding comparative effectiveness information
  - Adding safety information
  - Other labeling changes
- To be used as part of a postmarketing requirement to support a regulatory decision

B. Study Design Using RWE

The sponsor or applicant should list the clinical study design(s) that includes RWE as part of a submission to support a regulatory decision(s) (e.g., a randomized clinical trial, single-arm trial, or observational study).

C. RWD Source(s) Used To Generate RWE

The sponsor or applicant should list all the RWD source(s) used to generate the RWE. RWD sources can include the following:

- Data derived from EHRs[6]
- Medical claims and/or billing data
- Product and/or disease registry data
- Other data sources that can inform on health status (e.g., data collected from mobile technologies, patient-generated data)

[6] Recommendations regarding the collection and utilization of EHR data in clinical investigations can be found in the guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

APPENDIX: SAMPLE PRESENTATION TO INCLUDE IN COVER LETTER FOR SUBMISSIONS INCLUDING REAL-WORLD EVIDENCE

This table is provided as an example of how sponsors or applicants can identify in the cover letter accompanying the submission that the submission contains real-world data (RWD) or real-world evidence (RWE).

Purpose(s) of Using RWE as Part of the Submission (Select all that apply)
☐ To provide evidence in support of effectiveness or safety for a new product approval
☐ To provide evidence in of support labeling changes for an approved drug, including:
☐ Add or modify an indication
☐ Change in dose, dose regimen, or route of administration
☐ Use in a new population
☐ Add comparative effectiveness information
☐ Add safety information
☐ Other labeling change. Specify:
☐ To be used as part of a postmarketing requirement to support a regulatory decision
Study Design(s) Using RWE (Select all that apply)
☐ Randomized clinical trial
☐ Single arm trial
☐ Observational study
☐ Other study design. Specify:
RWD Source(s) Used To Generate RWE (Select all that apply)
☐ Data derived from electronic health records
☐ Medical claims and/or billing data
☐ Product and/or disease registry data
☐ Other data source that can inform on health status. Specify: