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# **Submitting Documents Using Real-World Data and Real-World Evidence to FDA 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)**

**September 2022  
Procedural**

# Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products Guidance for Industry

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## **Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products Guidance for Industry<sup>1</sup>**

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**

To facilitate FDA's internal tracking of submissions to the Agency that include real-world data (RWD) and real-world evidence (RWE), this guidance encourages sponsors and applicants to identify in their submission cover letters certain uses of RWD/RWE. This guidance does not address FDA's substantive review of the RWD/RWE submitted as part of the Agency's standard review process.

This guidance applies to submissions for investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) that contain RWD/RWE intended to support a regulatory decision regarding product 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 include:
  - Electronic health record (EHR) data
  - Medical claims data
  - Product or disease registry data
  - Data obtained from digital health technologies
  - Data gathered from other sources that can inform on health status, such as questionnaires

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<sup>1</sup> 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 and the Oncology Center of Excellence at the Food and Drug Administration.

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- RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated from RWD using many different study designs, including but not limited to, interventional studies<sup>2</sup> (clinical trials) or non-interventional<sup>3</sup> (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 have created interest within the research and medical communities in the use of RWD/RWE to enhance clinical research and support regulatory decision-making.

The 21st Century Cures Act (Cures Act),<sup>4</sup> 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 program (RWE Program) to evaluate the potential use of RWE in regulatory decision-making.<sup>5</sup>

By enhancing FDA's understanding of the scope and use of RWD and RWE submitted to support regulatory decisions, internally tracking these submissions as described in this guidance can inform FDA's RWE program under section 505F of the FD&C Act.<sup>6</sup>

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<sup>2</sup> For the purposes of this guidance, an interventional study or clinical trial is a study in which participants, either healthy volunteers or volunteers with the 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 biomedical or behavioral outcomes.

<sup>3</sup> For the purposes of this guidance, a non-interventional or 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.

<sup>4</sup> Public Law 114-255.

<sup>5</sup> 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.

<sup>6</sup> Information about FDA's RWE Program can be found in the *Framework for FDA's Real-World Evidence Program*, available at <https://www.fda.gov/media/120060/download>.

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### **III. EXAMPLES OF SUBMISSIONS USING RWD/RWE THAT FDA INTENDS TO TRACK**

This guidance focuses on submissions to FDA that rely on RWD/RWE to support a regulatory decision regarding product effectiveness and/or safety. Relevant submission types may include initial IND applications, meeting requests, study protocols, and final study reports submitted to INDs, BLAs, or NDAs. Representative examples of study designs that may be included in regulatory submissions are:

- Randomized clinical trials that use RWD to capture clinical outcomes related to safety or effectiveness
- Single-arm trials that use RWD in an external control arm
- Observational studies, such as observational cohort and case-control studies, that generate RWE intended to help support an efficacy supplement
- Clinical trials or observational studies that use RWD or RWE to fulfill a postmarketing requirement (PMR) or postmarketing commitment (PMC)<sup>7</sup>

This guidance recommends that sponsors and applicants not identify submissions that contain RWD/RWE if those data are not intended to support product labeling. For example, submissions using RWD only to generate hypotheses or to plan a clinical trial (e.g., to identify potential trial participants), studies incorporating RWD only in exploratory modeling or simulations, studies using RWD only to validate an endpoint, or studies using RWD only in the qualification process for Drug Development Tools<sup>8</sup> should not be identified in submissions to FDA for the purposes of this guidance.

### **IV. IDENTIFYING RWD/RWE AS PART OF A REGULATORY SUBMISSION**

We recommend that sponsors include the following specific information in the cover letter of a submission containing RWD/RWE in support of product labeling.<sup>9</sup>

#### **A. Purposes of Using RWD/RWE**

List the proposed purpose or purposes for which RWD/RWE will be used, such as:

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<sup>7</sup> For additional information about postmarketing study requirements and commitments, see the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011). 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>.

<sup>8</sup> Information about FDA's Drug Development Tool (DDT) qualification program is available at <https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs>.

<sup>9</sup> Applicants may use any format to provide the requested information. A sample table containing the requested information is provided in the appendix.

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- Support safety and/or effectiveness for a product not previously approved by FDA
- Support labeling changes for an FDA-approved product, including but not limited to:
  - Adding or modifying an indication
  - Changing the dose, dose regimen, or route of administration
  - Expanding the labeled indication of the product to a new population
  - Adding comparative effectiveness information
  - Adding or modifying safety information
  - Proposing other labeling changes
- Help to support or satisfy a PMR/PMC

### **B. Study Designs Using RWD to Generate RWE**

Identify the clinical study design or designs that involve RWD as part of a submission to support a regulatory decision, including but not limited to:

- Randomized controlled trials that utilize RWD to collect trial endpoints, including the use of RWD to supplement control arm data
- Single-arm trials analyzed with an external (e.g., historical) control arm that relies on RWD
- Observational studies

### **C. RWD Sources Used to Generate RWE**

Indicate the type of RWD sources used to generate RWE, including:

- Electronic health record data<sup>10</sup>
- Medical claims data<sup>11</sup>

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<sup>10</sup> See the draft guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (September 2021). When final, this guidance will represent FDA's current thinking on this topic.

<sup>11</sup> Ibid.

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- Product, disease, or other registry data<sup>12</sup>
- Data collected from digital health technologies in non-research settings
- Other data sources (e.g., questionnaires) that can inform on health status (to be specified)

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<sup>12</sup> See the draft guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (November 2021). When final, this guidance will represent FDA's current thinking on this topic.



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**APPENDIX: SAMPLE PRESENTATION OF INFORMATION TO BE INCLUDED WITH SUBMISSIONS CONTAINING RWD/RWE**

The table below represents an example of how sponsors and applicants can identify a submission containing real-world data (RWD)/real-world evidence (RWE) as part of their cover letter accompanying such submissions to FDA.

<b>General Information</b>
Generic/proprietary name of product: _____
Disease/medical condition: _____
<b>Purposes of Using RWD/RWE as Part of the Submission (select all that apply)</b>
<input type="checkbox"/> To support safety and/or effectiveness for a product not previously approved by FDA
<input type="checkbox"/> To support labeling changes for an approved product, including:
<input type="checkbox"/> Add or modify an indication
<input type="checkbox"/> Change dose, dose regimen, or route of administration
<input type="checkbox"/> Expand the labeled indication of the product to a new population
<input type="checkbox"/> Add comparative effectiveness information
<input type="checkbox"/> Add or modify safety information
<input type="checkbox"/> Other labeling change – specify: _____
<input type="checkbox"/> To support or satisfy a postmarketing requirement (PMR)/postmarketing commitment (PMC)
<b>Study Designs Using RWD to Generate RWE (select all that apply)</b>
<input type="checkbox"/> Randomized controlled trial with pragmatic elements and those using RWD to supplement a control arm
<input type="checkbox"/> Single-arm trial that uses RWD in an external control arm
<input type="checkbox"/> Non-interventional (observational) study
<input type="checkbox"/> Other study design – specify: _____
<b>RWD Sources Used to Generate RWE (select all that apply)</b>
<input type="checkbox"/> Electronic health records data
<input type="checkbox"/> Medical claims data
<input type="checkbox"/> Product, disease, or other registry data
<input type="checkbox"/> Data from digital health technologies in non-research settings
<input type="checkbox"/> Other data sources (e.g., questionnaires) that can inform on health status – specify: _____