
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DRAFT GUIDANCE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
Procedural**

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<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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1 **Submitting Documents Using Real-World Data and Real-World**
2 **Evidence to FDA for Drugs and Biologics**
3 **Guidance for Industry¹**
4

5
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
10 for this guidance as listed on the title page.
11

12
13
14
15 **I. INTRODUCTION**
16

17 This guidance is intended to encourage sponsors and applicants who are using real-world data
18 (RWD) to generate real-world evidence (RWE) as part of a regulatory submission to FDA to
19 provide information on their use of RWE in a simple, uniform format. FDA will use this
20 information for internal tracking purposes only. This guidance applies to submissions for
21 investigational new drug applications (INDs), new drug applications (NDAs), and biologics
22 license application (BLAs) that contain RWE used to support regulatory decisions regarding
23 safety and/or effectiveness.
24

25 For the purposes of this guidance, FDA defines RWD and RWE as follows:
26

- 27 • RWD are data relating to patient health status and/or the delivery of health care that are
28 routinely collected from a variety of sources. Examples of RWD include the following:
29
- 30 – Data derived from electronic health records (EHRs)
 - 31 – Medical claims and billing data
 - 32 – Data from product and disease registries
 - 33 – Patient-generated data, including in-home use and/or other decentralized settings
 - 34 – Data gathered from other sources that can inform on health status, such as mobile
35 devices
 - 36 – Data gathered from other sources that can inform on health status, such as mobile
37 devices
 - 38 – Data gathered from other sources that can inform on health status, such as mobile
39 devices
 - 40 – Data gathered from other sources that can inform on health status, such as mobile
41 devices
 - 42 • 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.

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

45
46 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
47 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
48 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
49 the word *should* in Agency guidances means that something is suggested or recommended, but
50 not required.

51
52

II. BACKGROUND

53
54
55 The availability of RWD and evolving analytic techniques to generate RWE has created interest
56 within the research and medical communities to use RWD/RWE to enhance clinical research and
57 support regulatory decision making.

58
59 Exploring the potential for RWE to inform regulatory decisions is mandated by the 21st Century
60 Cures Act (Cures Act). Section 3022 of the Cures Act requires FDA to establish a program² to
61 evaluate the potential use of RWE to help to support the approval of a new indication for a drug
62 approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and to
63 help to support or satisfy postapproval study requirements.

64
65 To inform FDA’s RWE program under the Cures Act and to help FDA understand the scope and
66 use of RWE submitted to support regulatory decisions regarding safety and/or effectiveness, the
67 Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and
68 Research (CBER) intend to track certain types of submissions using RWE under an IND, NDA,
69 or BLA. To aid in the tracking, CDER and CBER encourage sponsors and applicants to identify
70 submissions that include RWE being used to support a regulatory decision(s) regarding safety
71 and/or effectiveness.

72
73

III. EXAMPLE SUBMISSIONS USING RWD AND/OR RWE

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75
76 Relevant submissions can be in different forms such as a new protocol(s) submitted to an
77 existing IND, a final study report submitted to an NDA or BLA supplement, or a meeting
78 package that discusses the use of RWE. Relevant submissions may include RWE used to
79 support study objectives, such as the following:

- 80
81 • IND submissions for randomized clinical trials that use RWD to capture clinical
82 outcomes or safety data, including pragmatic and large simple trials³

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.”

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- 83
- 84
- New protocols for single arm trials that use RWE as an external control
- 85
- Observational studies⁴ that generate RWE intended to help to support an efficacy supplement
- 86
- 87
- 88
- Clinical trials or observational studies using RWE to fulfill a postmarketing requirement to further evaluate safety or effectiveness and support a regulatory decision
- 89
- 90
- 91

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

- 95
- Natural history studies for development of a clinical outcome assessment or biomarker
- 96
- Feasibility studies using RWE
- 97
- Studies using RWD to perform exploratory analyses and generate hypotheses
- 98
- 99
- 100
- 101

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

104

105

IV. IDENTIFYING RWE SUBMITTED AS PART OF A REGULATORY SUBMISSION

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108

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

113

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

114

115

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

117

- 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)
- 118
- 119
- 120
- 121

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.

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- 122 • To provide evidence in support of labeling changes for an approved product, including:
123
124 – Adding or modifying an indication
125 – Change in dose, dose regimen, or route of administration
126 – Use in a new population
127 – Adding comparative effectiveness information
128 – Adding safety information
129 – Other labeling changes
130
- 131 • To be used as part of a postmarketing requirement to support a regulatory decision
132

B. Study Design Using RWE

133
134
135 The sponsor or applicant should list the clinical study design(s) that includes RWE as part of a
136 submission to support a regulatory decision(s) (e.g., a randomized clinical trial, single-arm trial,
137 or observational study).
138

C. RWD Source(s) Used To Generate RWE

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140
141 The sponsor or applicant should list all the RWD source(s) used to generate the RWE. RWD
142 sources can include the following:
143

- 144 • Data derived from EHRs⁶
145 • Medical claims and/or billing data
146 • Product and/or disease registry data
147 • Other data sources that can inform on health status (e.g., data collected from mobile
148 technologies, patient-generated data)
149

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>.

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

152
153 This table is provided as an example of how sponsors or applicants can identify in the cover
154 letter accompanying the submission that the submission contains real-world data (RWD) or real-
155 world evidence (RWE).
156

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

157