

PDUFA VII Real-World Evidence

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Learning Objectives



- Describe the FDA's Real-World Evidence program for drugs and biologics
- Understand FDA's approach to evaluating real-world evidence for effectiveness
- Discuss FDA initiatives related to real-world evidence, including new commitments under PDUFA VII

U.S. Effectiveness Standard

Law

Food, Drug, and Cosmetic Act of 1962: *substantial evidence of effectiveness from adequate and well-controlled investigations*

Food and Drug Administration Modernization Act of 1997: *one adequate and well-controlled investigation and confirmatory evidence*

Regulation

21 CFR 314.126: characteristics of *adequate and well-controlled studies* to support claims of effectiveness for new drugs

Guidance

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft 2019)

“Big Data”



21st Century Cures Act (2016)



- FDA established program to evaluate real-world evidence to:
 - Support new indication for a drug
 - Satisfy post-approval study requirements
- Draft framework issued in 2018 describes sources of real-world evidence, opportunities, and challenges
- Multiple draft guidances issued in 2021-22
- Effectiveness standard unchanged

FDA RWE Framework



- Applies to CDER, CBER, & OCE
- Multifaceted program to implement RWE:
 - internal processes
 - external stakeholder engagement
 - guidance development
 - demonstration projects

Definitions

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Contemporary Terms for Study Design

Interventional study (clinical trial) patients assigned to treatment by study protocol

Non-interventional (observational) study patients receive treatment during routine medical care

A study can have components of **both**, for example, externally controlled trial with interventional treatment arm & non-interventional control arm

Study Design and Real-World Data

Randomized, Interventional Study

Nonrandomized, Interventional Study

Nonrandomized, Noninterventional Study

Traditional randomized trial using RWD in planning

RWD used to assess enrollment
criteria and trial feasibility

RWD used to support selection
of trial sites

Trial in clinical practice settings, with pragmatic elements

Selected outcomes identified using,
e.g., health records data, claims
data, or data from digital health
technologies

RCT conducted using, e.g., electronic
case report forms for health records
data or claims data

Externally controlled trial

Single-group trial with
external control group
derived from RWD

Observational study

Cohort study

Case-control study

Case-crossover study

Generation of RWE

Increasing reliance on RWD

Key Considerations for RWE



Key Considerations: Data



Whether **RWD** are **fit-for-use**:

- **Reliability** - accuracy, completeness, traceability
- **Relevance** – availability of key data elements and sufficient number of representative patients

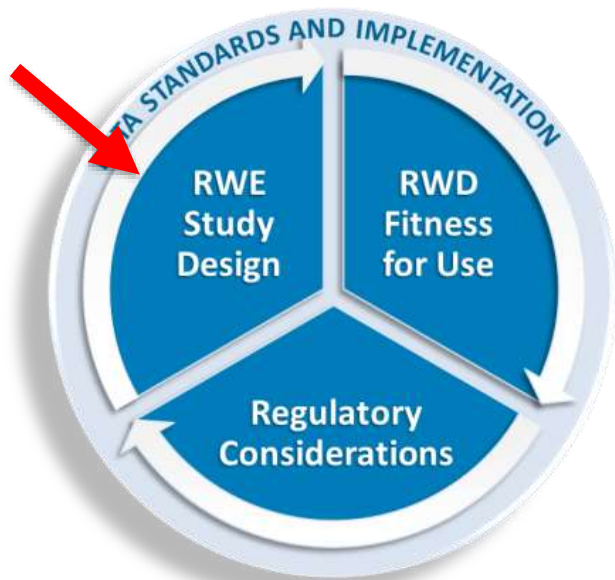


Draft Guidance: Data



- [Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products](#) (Sep 2021)
- [Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products](#) (Nov 2021)
- [Data Standards for Drug and Biological Product Submissions Containing Real-World Data](#) (Oct 2021)

Key Considerations: Study Design



Whether **trial or study design** can provide **adequate scientific evidence** to answer or help to answer the regulatory question

Draft Guidance: Study Design



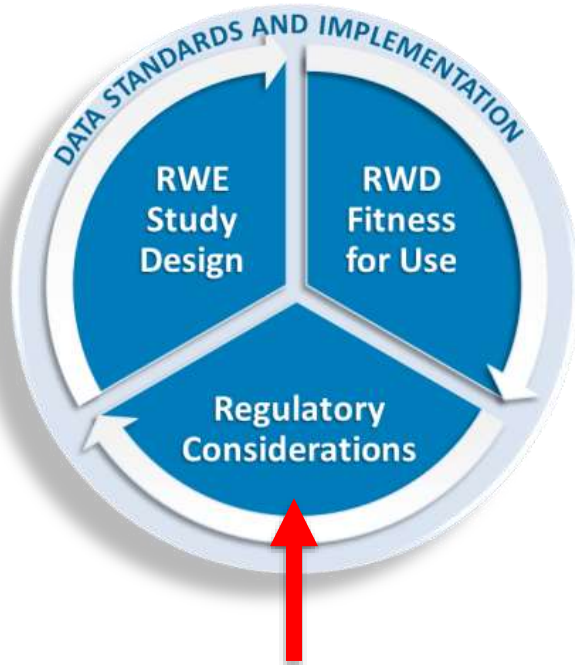
- [Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products](#) (Feb 2023)
- On CDER's 2023 Guidance Agenda:
 - Considerations Regarding Non-Interventional Studies for Drug and Biological Products
 - Using Clinical Practice Data in Randomized Controlled Trials for Regulatory Decision-Making for Drug and Biological Products

Key Considerations: Regulatory



Whether **study conduct** meets FDA **regulatory requirements**

- Protection of human subjects
- Transparency and pre-specification
- Access to data by FDA
- Study monitoring



Draft Guidance: Regulatory Considerations



- [Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making](#)
(Dec 2021)

Key Excerpts: Regulatory Considerations



- 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.
- Sponsors should **engage with FDA in the early stages of designing a non-interventional study** intended to support a marketing application.

RWE in PDUFA VII (FY 2023-2027)

By December 31, 2022:

FDA will **establish an Advancing RWE Program** to identify approaches for RWE that meet regulatory requirements; develop agency processes that promote consistent decision-making; and increase awareness of RWE characteristics that support regulatory decisions

By June 30, 2024:

FDA will **report aggregate data on an annual basis** describing submissions to CDER & CBER, including data sources & study designs used, and types of regulatory requests

By December 31, 2025:

FDA will **convene a public workshop or meeting** to discuss case studies, focusing on how to generate RWE that meets regulatory requirements

By December 31, 2026:

FDA will use lessons learned from the Advancing RWE Program to **update existing, or generate new, RWE-related guidance documents**

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Advancing RWE Program



- Announced October 20, 2022
- Up to four meetings to discuss use of RWE in medical product development
- Optional program; established meeting pathways still available

<https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program>

Advancing RWE Program Goals



- Identify **approaches** for generating RWE that meet regulatory requirements
- Develop agency **processes**
- Promote **awareness** of RWE that can support regulatory decisions

Eligibility Criteria

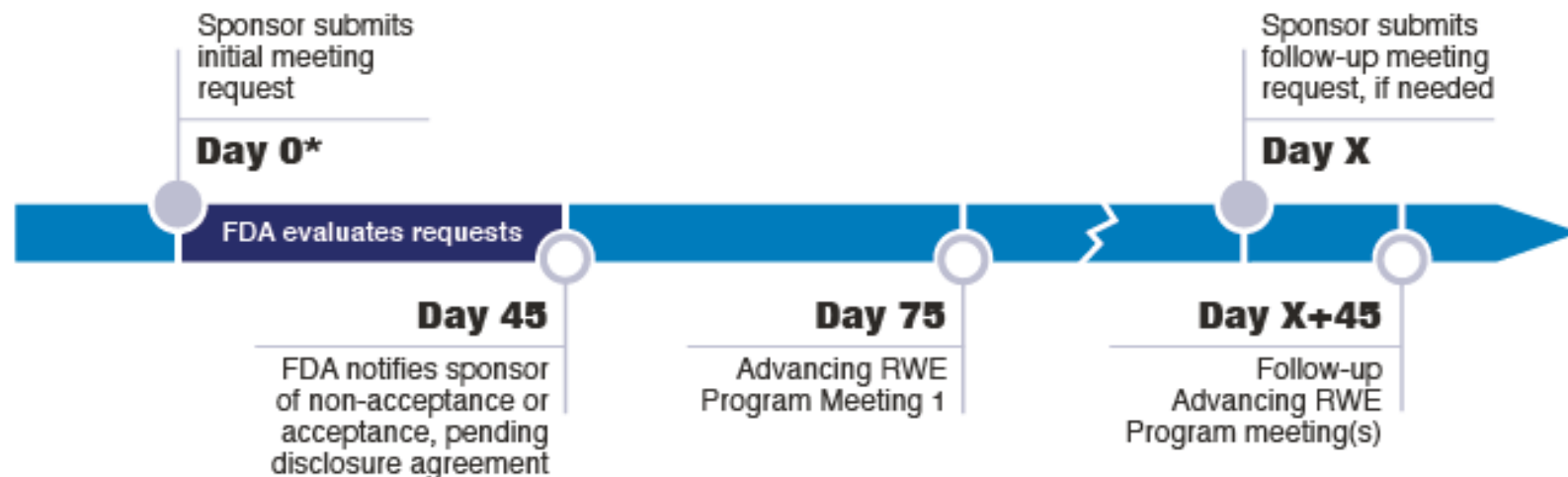
- IND or pre-IND for product
- RWE intended to meet regulatory requirements in support of:
 - labeling for effectiveness (e.g., new indications, populations, dosing information)
 - meeting post-approval study requirements
- Agreement on information to be publicly disclosed

Submission Deadlines and Process



- Semi-annual deadlines: [March 31](#) and [September 30](#) through March 2027
- Initial request contains [12-page summary](#) of proposal
- For each cycle, FDA accepts one to two initial requests in FY 23-24 and one to four in FY25-27 based on:
 - [Scientific merits](#) of proposal
 - [Diversity](#) of data, design, methods, and regulatory indications
- Sponsors notified within 45 days of deadline

Timeline for Each Cycle



*March 31 and September 30

Disclosure Agreement



- Key design elements may be presented by FDA as case studies
- Agency and the sponsor must agree on information that FDA may disclose publicly

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Sept 2022 Final Guidance: Submitting RWD/RWE



- Purpose of Using RWD/RWE
- Study Designs
- Real-World Data Sources

<https://www.fda.gov/media/124795/download>

www.fda.gov

Purposes of Using RWD/RWE as Part of the Submission (select all that apply)

- ☐ To support safety and/or effectiveness for a product not previously approved by FDA
- ☐ To support labeling changes for an approved product, including:
 - ☐ Add or modify an indication
 - ☐ Change dose, dose regimen, or route of administration
 - ☐ Expand the labeled indication of the product to a new population
 - ☐ Add comparative effectiveness information
 - ☐ Add or modify safety information
 - ☐ Other labeling change – specify: _____
- ☐ To support or satisfy a postmarketing requirement (PMR)/postmarketing commitment (PMC)

Study Designs Using RWD to Generate RWE (select all that apply)

- ☐ Randomized controlled trial with pragmatic elements and those using RWD to supplement a control arm
- ☐ Single-arm trial that uses RWD in an external control arm
- ☐ Non-interventional (observational) study
- ☐ Other study design – specify: _____

RWD Sources Used to Generate RWE (select all that apply)

- ☐ Electronic health records data
- ☐ Medical claims data
- ☐ Product, disease, or other registry data
- ☐ Data from digital health technologies in non-research settings
- ☐ Other data sources (e.g., questionnaires) that can inform on health status – specify: _____

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Summary



- FDA RWE Program advancing as described in 2018 Framework
- RWE presents new challenges with data, design, and conduct
- FDA guidances issued to inform use of RWE for regulatory decision-making
- New initiatives aim to help identify and promote awareness of RWE-based approaches that meet regulatory requirements

Challenge Question #1

The 21st Century Cures Act changed the effectiveness standard for new drugs approvals to allow approvals to be based on real-world evidence:

True

False

Challenge Question #2

Which of the following statements is **NOT true?**

- A. Real-world evidence can arise from both interventional and non-interventional studies.
- B. The use of real-world data to understand trial feasibility is considered real-world evidence.
- C. Determining whether data are fit-for-use includes consideration of reliability and relevance.
- D. It is important to engage FDA early when considering use of a non-interventional study to support a marketing application.

Questions?

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