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

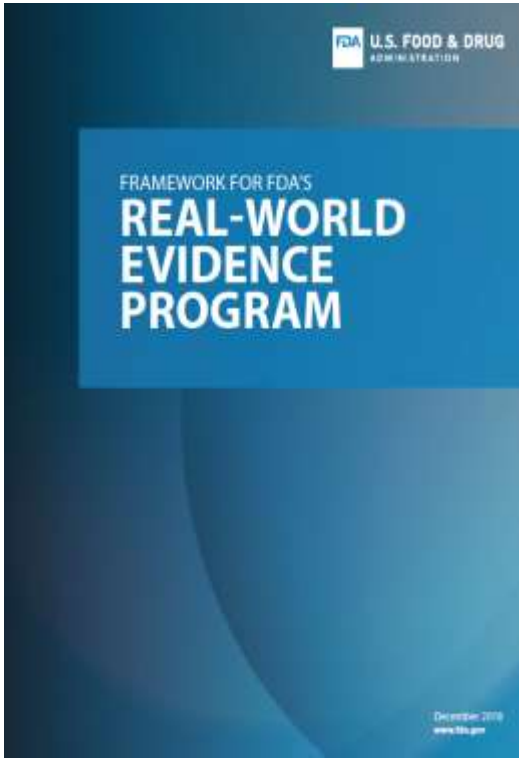
Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (Draft 2019)

“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

https://www.fda.gov/media/120060/download

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

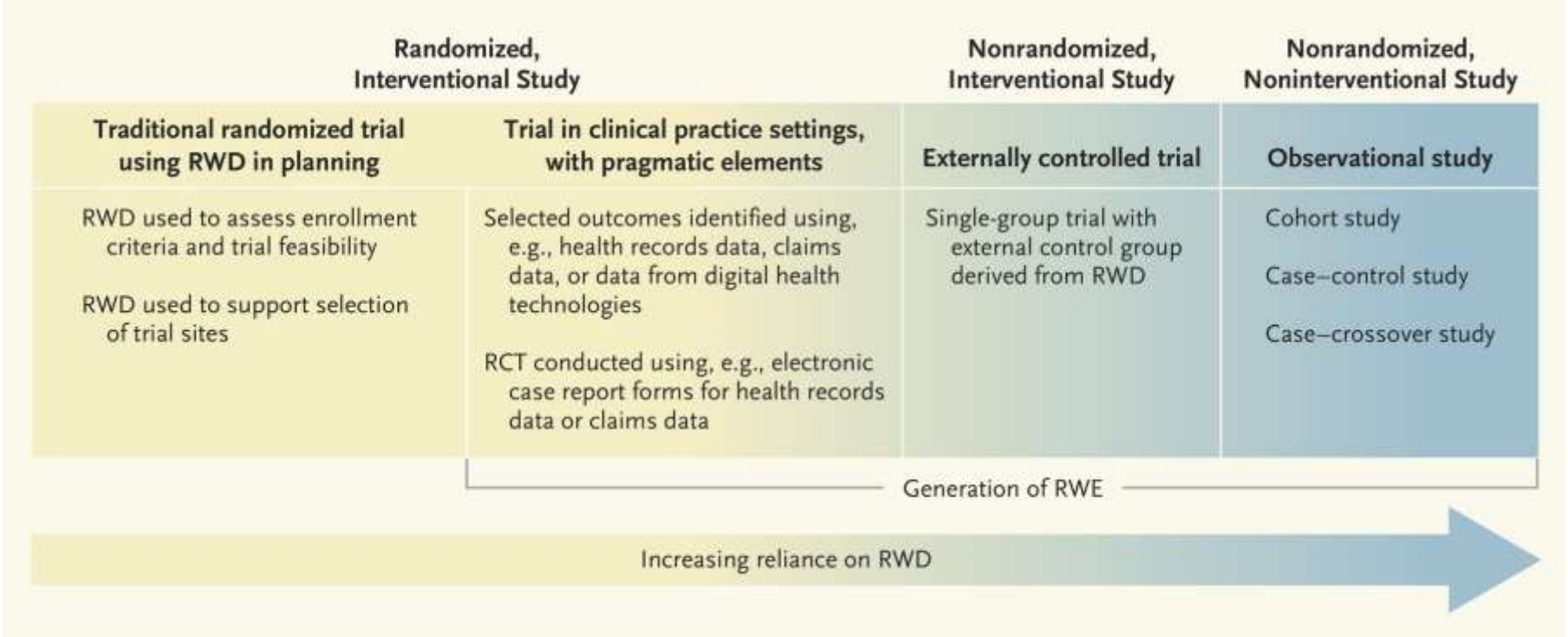
Contemporary Terms for Study Design

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



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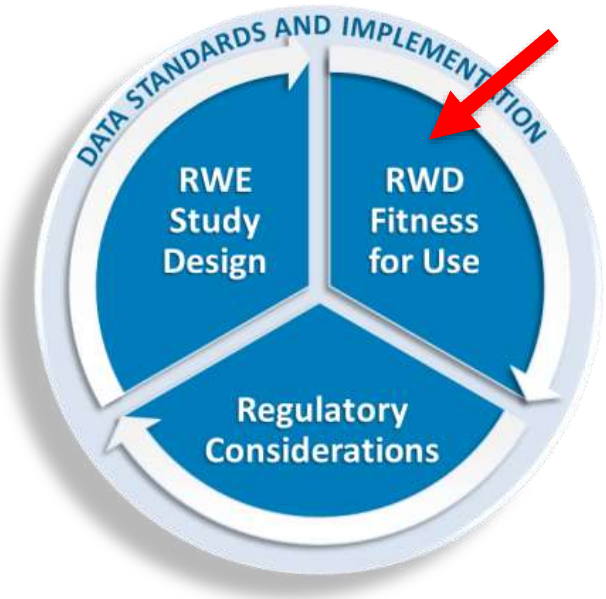
Key Considerations for RWE

Key Considerations: Data



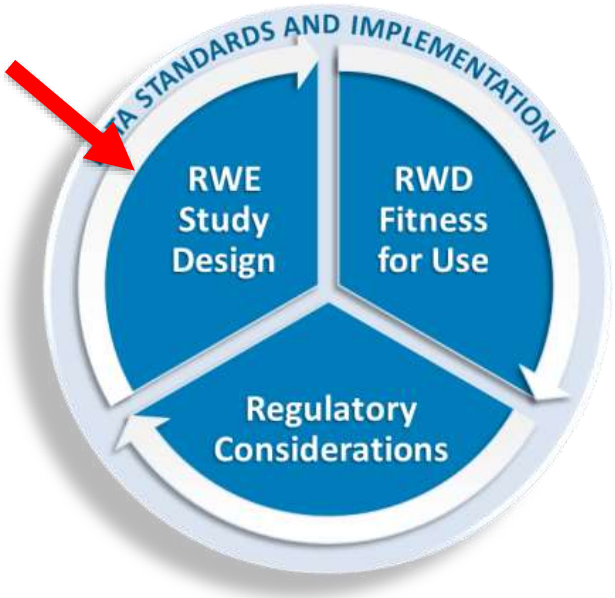
Whether RWD are fit-for-use:

- **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



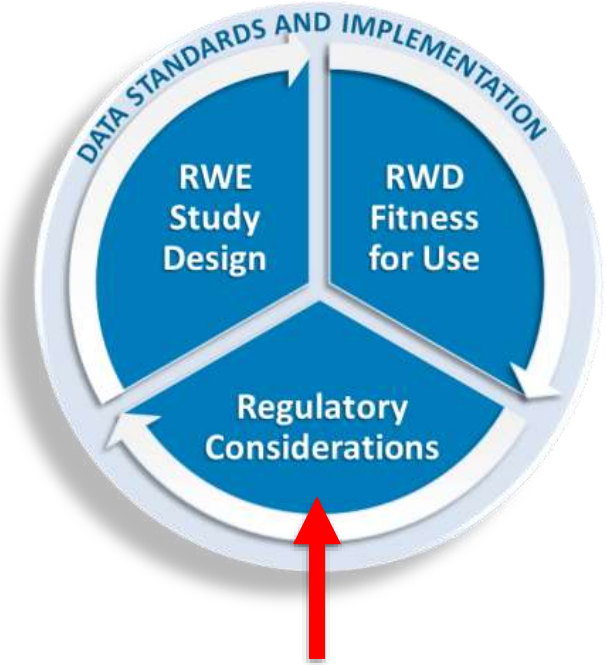
Whether trial or study design can provide adequate scientific evidence to answer or help to answer the regulatory question

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

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

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

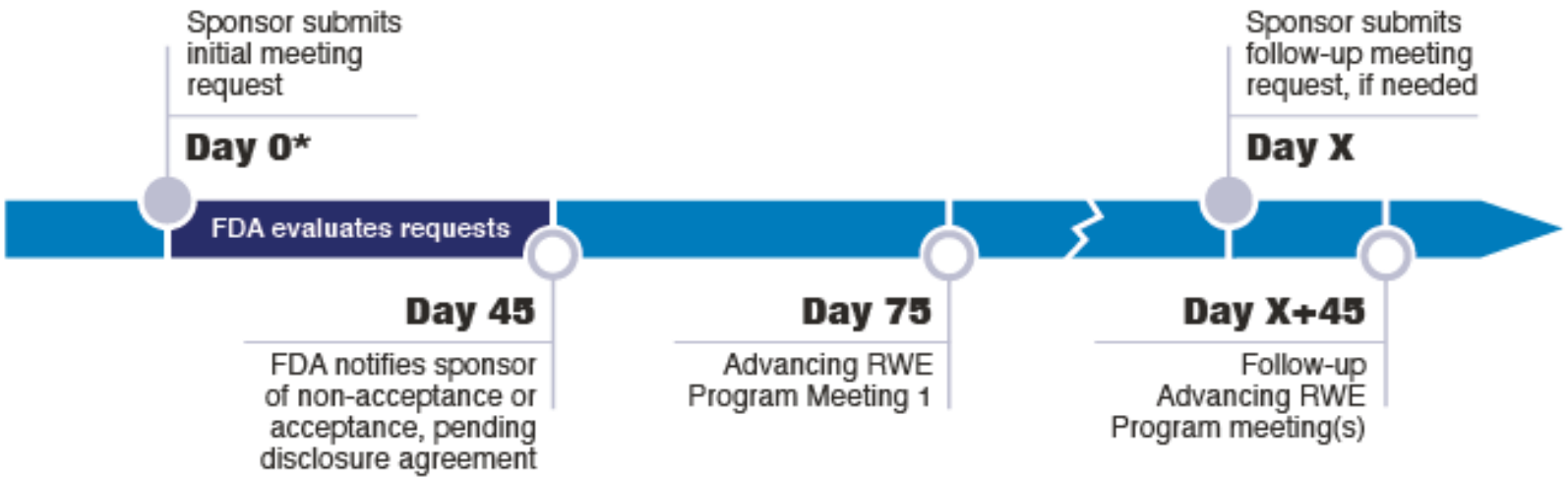
Eligibility Criteria

- 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**

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: _____

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

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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.

U.S. FOOD & DRUG ADMINISTRATION

Questions?

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov


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