

# An Analysis of the Framework for the FDA's Real-World Evidence Program





#### Introduction

The 21st Century Cures Act mandated the US Food and Drug Administration (FDA) to develop guidance for use of real-world data (RWD) / realworld evidence (RWE) in regulatory decisions.

In December 2018, the FDA released a framework outlining how the agency will evaluate RWE intended to support approval of a new indication for an approved drug or biologic, or to help support or satisfy drug post-approval study requirements.

\* NOTE: This framework does not apply to medical devices.

### Framework Overview

The new framework will serve as a roadmap for the inclusion of RWD and RWE in regulatory decisions, including standards on how RWD is defined, collected, and analyzed. The FDA will also be providing guidance on RWE study methodologies and designs that meet regulatory requirements in generating evidence of effectiveness, among other topics.

NOTE: The use of RWD to improve the efficiency of traditional clinical trials is not covered in this guidance

# The new framework addresses the following



Definition and fitness of RWD for regulatory decision-making



Study designs with potential to generate scientifically adequate RWE to support product *effectiveness* 



Study conduct considerations to ensure regulatory requirements are met





### What is RWD?

RWD is data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources.

Examples include data generated from:

- Electronic health records (EHRs)
- Medical claims and billing records
- Product and disease registries
- Patients (including in-home-use settings)
- Other sources that can inform on health status, such as mobile devices



#### What is RWE?

RWE is clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

There are a variety of study designs that could possibly be used for RWE generation, depending on the study question and need.

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FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval.

Janet Woodcock, MD, Director, CDER

### Can These Study Designs Generate RWE?



By definition, a traditional RCT cannot generate RWE because the FDA has defined RWE as evidence derived from sources other than traditional clinical trials.





## Example of Pragmatic Clinical Trial Generating RWE

ADAPTABLE\* (NCT02697916), a randomized pragmatic trial using RWD, was conducted to assess the effects of aspirin dosing on ASCVD\*\* patients with high risk for ischemic events. These patients were randomly assigned in a 1:1 ratio to receive an aspirin dose of 81 mg/day vs. 325 mg/day within routine clinical care. The primary endpoint was a composite of allcause death, hospitalization for non-fatal MI\*\*\*, or hospitalization for stroke identified from EHR and claims data.

\* ADAPTABLE = Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term \*\*ASCVD = Atherosclerotic cardiovascular disease

ASCVD – Atheroscierotic cardiovascular disea

\*\*\*MI = myocardial infarction



### Current Use of RWE by the FDA

The FDA already uses RWE to:

- Improve efficiencies of drug development programs (e.g., informing randomized controlled trial (RCT) hypotheses, developing drug development tools including biomarker qualification)
- Assess safety of products after approval (e.g., <u>Sentinel System</u>)
- Support product effectiveness in very specific and limited cases, such as vaccines, oncology, and rare diseases



#### **RWE Program Key Considerations**



The RWE Program will evaluate the potential use of RWE to support changes to labeling about product effectiveness. Changes include:

- Adding or modifying an indication (e.g. change in dose, dose regimen, or route of administration)
- Adding a new population
- Adding comparative effectiveness or safety information



Simpler, low risk challenges are likely the best and safest situations for considering use of RWE without further guidance in place. Scenarios with substantial safety concerns, such as expanding to pediatric populations, would not be recommended.



A big question will be "what are the regulatory requirements for RWE?"

- Will they differ if using a database vs another data collection approach?
- What about retrospective vs prospective studies?

Again, early discussions with RWE experts and the FDA RWE Program are recommended to inform study development.



#### FDA's Three-Part Approach to Evaluate Individual Supplemental Applications

Whether the RWD are fit for use

Whether the RWE study design can provide adequate scientific evidence to answer/help answer the regulatory question

Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

10





Select RWD based on suitability to address specific regulatory questions.

Data should be collected and maintained in a way that provides an appropriate level of reliability.



## Is One Type of RWD Preferred Over Another?

The FDA does not endorse one type of RWD versus another but expects study sponsors to justify the choice of data source.

Different RWD sources will have different strengths and limitations.



### Is One Type of RWD Preferred Over Another?

FDA plans to issue guidance on how to:

- Assess the reliability and relevance of RWD from medical claims and electronic health records (EHR)
- Assess the reliability and relevance of registry data

The FDA is working with various organizations across multiple stakeholders to discuss issues pertaining to data standards, requirements for registering observational studies, etc.

- Standards regarding the structure, format, definitions, and exchange of data will make regulatory submissions consistent and predictable
- ClinicalTrials.gov is designed for RCTs and not currently ideal to accommodate RWD needs

Pilot efforts are underway to gain insights to aid in the development of the guidance documents.

#### Examples include:

- Replication of RCTs using RWD to derive better rules for the conduct of observational RWD studies
- Pragmatic and adaptable trial designs
- Safety studies
- MyStudies App; open source app for prospective, patientcentered data collection
- Clinical Trial Transformation Initiative (CTTI) to evaluate the use of RWD in randomized trials to generate RWE about medical products



#### **Challenges with RWD Sources**

Some challenges may arise when considering RWD sources. For instance, important data elements may not be captured (e.g., disease severity, worsening disease status, patient-reported outcomes [PROs]), events that do not result in medical care are not captured, changes in healthcare or insurance providers can create data gaps, formats across EHR platforms and datasets differ, and fragmentation of the US healthcare system exists.

The FDA also expressed additional concerns when considering international (non-US) data. The fitness of data from other geographical regions could be limited; with datasets, there are differences in the standard of care, populations are not generalizable, and there are limitations and unfamiliarity with datasets. The FDA RWE Program will explore these considerations, but the framework document is currently focused on US sources of RWD.

### **Guidance Development**

The RWE program will develop guidance to address:

- Using pragmatic trial elements at every stage of the clinical trial for the development of RWE
- RWD to provide external/historical control arms
- Using observational studies for the generation of RWE

The RWE program will also address regulatory considerations to:

- Evaluate guidance cited for their continued appropriateness to address study designs using RWD to generate RWE
- Finalize guidance on informed consent and collection of data through electronic means under 21 CFR Part 11
- Issue additional guidance as applicable

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#### **Next Steps**

The FDA RWE program will be developing several guidance documents based on this framework, although timing has not been made available yet. Our understanding is that this framework opens the door to early discussions with the FDA through its RWE Program. Companies interested in using RWE should also plan to engage internal and/or external experts in RWE.

#### Early discussions will:

- ✓ Help inform the FDA on potential RWE uses to aid in development of the guidance documents
- Help ensure alignment of early RWE use cases with regulators and reduce the risk of using RWE during study development while the FDA guidance documents are being developed





#### Some Questions Still Remain

While the release of this framework document is an important step forward, the FDA acknowledges that some questions have not yet been fully addressed. The FDA has been developing data standards for regulatory submissions and will consider this topic for the RWE program.

The FDA will also explore strategies for filling data gaps using mobile technologies, electronic PRO tools, wearable devices, and biosensors.



### FAQs of Interest to Biopharmaceutical Companies

## Q: Can natural history studies serve as a source of RWE for drug development?

A: Yes, natural history studies (conducted prospectively or retrospectively) can supplement data from clinical trials, particularly for rare diseases. At least 13 product approvals have used RWE to demonstrate efficacy.<sup>1</sup> The framework document indicates that RWE can support approvals "when using a parallel control arm is unethical or not feasible and usually when the effect size is expected to be large, based on preliminary data."

#### Q: Can database studies serve as a source of RWE?

A: Yes, the FDA framework outlines that they would consider a study based on secondary use of existing data when the evidence generated from such a study would meet their criteria for regulatory quality evidence. Such studies must adhere to good pharmacoepidemiology practices and there are ongoing discussions regarding issues such as transparency (e.g., posting of protocols), etc.

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<sup>1</sup> Source: https://pink.pharmaintelligence.informa.com/PS123648/A-Bakers-Dozen-Of-US-FDA-Efficacy-Approvals-Using-Real-World-Evidence. Subscription required.

# FAQs of Interest to Biopharmaceutical Companies

#### **Q:** Are pragmatic trials considered RWE?

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A: It depends. As there is a continuum between traditional RCTs and pragmatic trials, and there are several elements that can make a trial more versus less pragmatic, there are some pragmatic trials that would be considered to generate RWE (e.g., if chart reviews or medical records are used for endpoint determination). Randomization and masking considerations will be crucial at the design phase of such studies and could help overcome some of the limitations of observational RWE studies.

#### Q: Can RWE be used in other settings with the FDA?

A: Yes, there is a separate guidance for medical devices, and other uses of RWE during Phase II/III development are addressed by the FDA in other guidance. This framework should be referenced specifically for the post-marketing setting.

#### FAQs of Interest to Biopharmaceutical Companies

**Q: Will Commissioner Scott Gottlieb's departure from the FDA or any other staff changes derail progress on this initiative?** A: No, we don't expect so. The requirement to consider RWE is mandated by Congress.

## Q: Why doesn't the framework cover regulatory decisions for medical devices?

A: A guidance for medical devices called "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" was already released by the FDA on August 31, 2017.



### Helpful References

Please visit the references listed below to further educate yourself on related FDA frameworks and guidances:

- Framework for FDA's Real-World Evidence
  Program
- <u>FDA Guidance: Best Practices for</u> <u>Conducting and Reporting</u> <u>Pharmacoepidemiologic Studies using</u> <u>EHR Data</u>
- FDA Guidance: E10 Choice of Control Group and Related Issues in Clinical Trials
- FDA's webpage on Real-World Evidence
- <u>Real-World Evidence What is It and What</u> <u>Can It Tell Us?</u>

For more information or to discuss your RWE strategy in light of the new framework, contact info@evidera.com

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