WHITE PAPER

# The FDA Expands the Types of Confirmatory Evidence Sources to Support Drug Effectiveness Studies

## Incorporate Evidence from Natural History Studies and Other Sources of Real-world Data into Your Strategic Plan

UBC

# The 2023 Draft Guidance

There is considerable interest in using real-world data (RWD) to generate real-world evidence (RWE) to support regulatory decisions about the efficacy and effectiveness of drug products. Historically, the use of RWD by pharmaceutical sponsors has primarily been in demonstrating product safety.[1] Several years ago, the U.S. Food and Drug Administration's (FDA) RWE Program began to evaluate the potential use of RWE to support regulatory decisions about product effectiveness. As part of this effort, a new draft guidance was published in September 2023, titled *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence Guidance for Industry* (the 2023 draft guidance).[2] In this guidance, the FDA expanded on the types of confirmatory evidence it will accept from sponsors submitting one adequate and well-controlled clinical study to demonstrate drug effectiveness.

The 2023 draft guidance, which expands upon the discussion in the 2019 draft guidance of meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation, emphasizes that the quality and quantity of confirmatory evidence are important considerations.[3] Confirmatory evidence should be "evidence generated from quality data derived from an appropriate source." Additionally, the number of confirmatory sources (i.e., quantity) will be influenced by "the features and results of the single adequate and well-controlled clinical investigation the confirmatory evidence is intended to substantiate."

In this guidance, the FDA lists seven examples of types of confirmatory evidence that can be used to substantiate one adequate and well-controlled investigation (listed below). This white paper reviews considerations for evidence from two sources in the list: natural history and RWD/RWE.

- Clinical evidence from a related indication
- Mechanistic or pharmacodynamics evidence
- Evidence from other members of the same pharmacologic class
- Evidence from a relevant animal model
- Evidence from expanded use of an investigational drug
- ***Evidence from natural history***
- ***Real world data/evidence (RWD/RWE)***

## Related Guidance

The 2023 draft guidance discussed here expands upon the 2019 version, titled *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, which identifies four types of confirmatory evidence that are considered appropriate to support a single adequate and well-controlled study. The 2023 version describes additional types of evidence that may be considered acceptable: evidence from a relevant animal model, real-world data/evidence, and evidence from expanded use of an investigational drug.

The 2019 guidance complements and expands upon the 1998 guidance, titled, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*[3], which was issued in response to the Food and Drug Administration Modernization Act of 1997 (FDAMA).[3] FDAMA introduced flexibility in the evidence needed to support effectiveness, specifically clarifying that a single adequate and well-controlled clinical trial and confirmatory evidence can be used to support approval.

Since the 21st Century Cures Act (2016), where the FDA developed a program to evaluate the potential use of RWE to support approval for a new indication or to satisfy post-approval study requirements, the FDA has created the RWE Framework (2018) and released multiple guidance documents concerning the use of RWD/RWE.[4]

## Confirmatory Evidence from Natural History

A natural history study is an observational, longitudinal epidemiologic cohort study designed to describe risk factors, concurrent conditions, current standards of care, and outcomes of patients who have been diagnosed with a specific condition or disease. Natural history studies do not follow cohorts based on exposure to a specific product(s), but rather cohorts of patients with a specific disease or condition regardless of their available treatments. UBC previously published a white paper focused on the strategic role of natural history studies during drug development and beyond.[5] During the development process, natural history studies are commonly used by pharmaceutical sponsors to inform indication prioritization, clinical development portfolio design, and patient eligibility criteria for clinical studies and to understand background safety events and current methods of treatment. Natural history studies also allow sponsors to establish generalizability of drug efficacy and safety assessments and anticipate drug-drug interactions. A natural history cohort can be used to determine whether the experience of the randomized comparator cohort is similar to that seen in the natural history cohort, adding to the confidence in the single pivotal study. After the investigational product has been approved for marketing, patients being treated with the new product will be included in the natural history cohort providing an opportunity to identify patterns of post-authorization drug utilization and to understand effectiveness and safety in real-world practice.

At the recent NORD Summit in October 2023, Sandra Retzky, the FDA's Director of the Office of Orphan Products Development moderated a session on how natural history data may be useful in the approval process for rare disease drugs in particular, noting the difficulty in running a second trial in most rare disease populations, and citing natural history studies as a potential source of confirmatory evidence.[6] In 2023, the FDA approved two drugs where natural history studies were used to support the application: Skyclarys® (omaveloxolone) for Friedreich's ataxia and Daybue™ (trofinetide) for Rett syndrome.[6]

The concept of a natural history study providing confirmatory evidence is not new. In 2019, the FDA released a draft guidance on the use of natural history studies for drug development for rare diseases.[7] In recent years, the FDA has approved regulatory submissions that have included natural history studies, as well as other sources of RWE, with 80% of approvals relying on external controls derived from natural history cohorts for rare diseases where populations are small, or the unmet need is high.[8] RWD, including data from natural history studies, have also been submitted to the European Medicine Agency (EMA) to support efficacy claims and/or to provide information on disease epidemiology to contextualize efficacy claims on medicinal products for both initial marketing authorization applications (MAA) and extension of indication (EoI).[9]

## Confirmatory Evidence from Real-World Data Sources

In the U.S. and Europe, early discussions with regulatory bodies and the use of fit-for-purpose data are important tactics when incorporating RWD into the development program. Sponsors planning to use confirmatory evidence from RWD to support a marketing application for drug effectiveness need to address the appropriateness of the proposed RWD sources for their drug development program. In the 2023 draft guidance, the FDA recommends that sponsors discuss with the relevant review divisions any plans to use RWD/RWE as confirmatory evidence in a regulatory submission. This discussion should take place early in the submission planning process, to ensure that the FDA can provide feedback in a timely manner regarding whether the proposed RWD and RWE are appropriate to substantiate the trial results.

Whether a RWD source may be appropriate to develop RWE that serves as confirmatory evidence depends on several factors, including but not limited to (1) *reliability* of evidence generated and (2) *clinical relevance* to the specific drug development program. Table 1 provides an overview of important real-world data characteristics that may impact reliability and relevance of a RWD source to support a submission for effectiveness of a therapy for a particular indication. These criteria are particularly important when RWD/RWE are being considered for use as a comparator population, such as an external control arm or reference population, that will be used to provide context to the results seen in a single arm trial.

| TABLE 1. OVERVIEW OF ASSESSMENT CRITERIA FOR EVALUATING THE APPROPRIATENESS OF RWD/RWE TO SUPPORT AN FDA SUBMISSION, I.E., FIT-FOR-PURPOSE | |
|---|---|
| **Sample Size** | A sufficient number of patients with the disease of interest to enable meaningful and reliable evidence to be generated. Adequate size for hypothesis-testing needs to be evaluated. |
| **Comparability between the RWD and the clinical trial populations** | • Demographics (age, gender, geographic location)<br>• Trial Inclusion/exclusion criteria<br>• Insurance type (may be relevant if it impacts patient adherence to treatment regimens due to high out-of- pocket cost)<br>• Other factors potentially related to drug effectiveness (e.g., dosing, exposure duration) |
| **Continuity of Coverage *Prior to* Drug Initiation** | Should have sufficient continuous enrollment in the data source *before* drug initiation to reliably evaluate evidence of contraindicated diagnoses or treatment history (e.g., baseline treatments). |
| **Continuity of Coverage *Post* Drug Initiation** | Should have sufficient continuous enrollment in the data source *after* drug initiation to reliably evaluate:<br>• Effectiveness endpoints<br>• Impact of repeated exposure over time (e.g., duration) on effectiveness<br>• Evidence of concomitant treatments for same indication (e.g., type of treatment and duration) |
| **Exposure Details of Standard of Care (SOC) Medications** | Variables to define treatment effectiveness of Standard of Care (SOC)<br>• Drug identifier (NDC, ATC, and HCPCS procedure codes)<br>• Prescription/dispensing dates<br>• Strength/dose<br>• Days supplied<br>• Refill dates |
| **Clinical Details to Evaluate Effectiveness Endpoints** | Diagnoses, laboratory results, etc., for reliable assessment of endpoints. |
| **Data Quality and Transparency** | • Clear and transparent strategy for data quality assessment.<br>• Acceptable approaches for handling missing data.<br>• Data source well documented. |
| **Established History of Use in Drug Effectiveness Studies** | Ideally, proposed data sources would have current, relevant journal publications as an indicator of the acceptance of the data source for studies that evaluate drug effectiveness. Also, credibility could be provided by data sources that already have acceptance by regulators. |

Abbreviations: RWD=real-world data; RWE=real-world evidence; FDA=US Food and Drug Administration; SOC= standard of care; NDC = National Drug Code; ATC= Anatomical Therapeutic Chemical; HCPCS = Healthcare Common Procedure Coding System

Mahendraratnam et. al. conducted a retrospective landscape analysis to identify and characterize instances where RWE was included in the evidence package submitted to support effectiveness.[10] Evaluators identified 34 instances where RWE was submitted between 1954 and 2020, with 26% of applications for oncology, 18% for hematology, and 12% for neurology. Over 50% of the medical products were indicated for use in rare disease or pediatric populations, and 82% of products where RWE was submitted received an orphan designation, and RWE was included in the product label in 59% of instances. Importantly, feedback from the FDA regarding why submitted RWE on occasion did *not* significantly contribute to regulatory decision-making despite being included in the sponsor's evidence package included: lack of pre-specification of study design and analysis, as well as data reliability and relevancy concerns. Overall, based on their review of the 34 articles, the authors concluded that: "While there is historical use of RWE to support medical product effectiveness for oncology and rare diseases, potential exists to leverage the strengths of RWE to support other therapeutic areas and capture outcomes that are most relevant to patients."

A larger and more systematic review of publicly available FDA approval documents was conducted by researchers at Aetion.[11] The comprehensive review was intended to quantify how many approvals incorporated RWE in any form, and the intended use of RWE in those applications (i.e., to support therapeutic context, safety, and/or effectiveness). A total of 116 approvals from January 2019 to June 2021 were identified that incorporated RWE for any purpose. Of these, 15% used RWE to support only effectiveness, and 30% used RWE to support safety and effectiveness. Most approvals where RWE studies impacted decision-making were in oncology, infectious disease, and neuroscience. Among the studies where the RWE supported the demonstration of product effectiveness, RWE study appeared in one or more of parts of the submission, including:

- Conclusion on the substantial evidence of effectiveness
- Integrated overview of efficacy
- Statistical clinical evaluation
- Product label

An important finding of the Aetion research, similar to the Mahendraratnam study, was that the FDA occasionally rejected the sponsor's proposed use of RWE to substantiate their clinical trial findings. Specifically, the FDA either did not consider the RWE at all or did not find the evidence adequate to support an approval. The authors describe a consistent theme that emerged when RWE was rejected: "methodologically-sound RWE rooted in principled study design and analysis supported FDA's decisions, whereas studies that FDA found not to meet this bar bore far less impact."

As part of the FDA's efforts to broaden the understanding on the potential use of RWD and RWE to support the approval of new drug indications or to satisfy post-approval study requirements for approved drugs, the agency announced four U01 grant awards in 2023, in addition to four grants initially awarded in 2020, to examine the use of RWD to generate RWE in regulatory decision-making.[12] Through this program, the agency seeks to 'encourage innovative approaches to further support the use of RWE while ensuring that scientific evidence supporting marketing approvals meet FDA's evidentiary standards." The selected 2023 projects include:

- Methods to Improve Efficiency and Robustness of Clinical Trials Using Information from Real-World Data with Hidden Bias
- Generating Reproducible Real-World Evidence with Multi-Source Data to Capture Unstructured Clinical Endpoints for Chronic Diseases
- Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making
- Development of Novel Methods to Enable Robust Comparison of Real-World Progression Free Survival (rwPFS) and Clinical Trial PFS in Multiple Myeloma

## Case Study

The Blincyto® (blinatumomab) study is an example of RWE supporting the registration of a product by enabling comparative analyses of effectiveness to be conducted in a single-arm clinical trial.[13] Blinatumomab, indicated to treat adults with B-precursor Ph-negative relapsed/ refractory acute lymphoblastic leukemia, was initially approved by the FDA under accelerated approval with a control arm from an historical dataset. The dataset was pooled from European national study groups and large individual sites from Europe and the United States.

The historical cohort included 694 patients with complete remission (CR) data and 1112 patients with overall survival (OS) data, extracted from over 2000 patient records, compared with 189 patients with CR and survival data in the blinatumomab trial. The weighted analysis revealed a CR rate of 24% (95% CI: 20–27%) and a median OS of 3.3 months (95% CI: 2.8–3.6) in the historical cohort compared with a CR/CRh rate of 43% (95% CI: 36–50%) and a median OS of 6.1 months (95% CI: 4.2–7.5) in the blinatumomab trial. Propensity score analysis estimated increased odds of CR/CRh (OR=2.68, 95% CI: 1.67–4.31) and improved OS (HR=0.536, 95% CI: 0.394–0.730) with blinatumomab. The authors advise that statistical analyses involving data from historical controls must address potential biases when comparing historical data with those from clinical trials.

## A Note from Aaron Berger, UBC's Senior Vice President, Head of Evidence Development

As we look to the future of drug development, the September 2023 guidance from FDA represents an important evolution in drug development and life cycle management. This guidance paves the way for a tremendous opportunity to capitalize on recent technological advancements in real world data acquisition and curation that accelerate the important work of life science stakeholders to bring effective and safe treatments to patients.

## Bringing it All Together Under an Integrated Evidence Development Program to Support the Evaluation of Drug Effectiveness

Inclusion of RWD/RWE in regulatory submissions that involve drug effectiveness, from natural history studies and other sources of RWD, should be considered as part of an overall evidence generation strategy that can expedite the regulatory approval process and help fulfill unmet medical needs.

## About UBC

United BioSource LLC (UBC) is the leading provider of evidence development solutions with an expertise in uniting evidence and access. UBC helps biopharma mitigate risk, address product hurdles, and demonstrate safety, efficacy, and value under real-world conditions. Bringing over 30 years of experience, UBC is uniquely positioned to develop end-to-end integrated evidence generation strategies, identify fit-for-purpose data sources, operationalize planned studies, and ensure regulatory-grade, publishable outputs.

To learn more about how UBC can help you develop an integrated, real-world evidence strategy reach out to us at contact@ubc.com.

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