The Potential of Real-World Data (RWD) for Informing FDA Biosimilar and Interchangeable Biosimilar Regulatory Decisions: Recommendations from a Multi-Stakeholder Expert Panel

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RWD162

BACKGROUND

The U.S. Food and Drug Administration (FDA) and other regulatory agencies are interested in applications for real-world data (RWD) to inform pre-market regulatory decisions. Enacted through the Biologics Price Competition and Innovation Act (BPCI) Act of 2010, section 351(k) of the Public Health Service Act created an abbreviated licensure pathway for biosimilars and interchangeable biosimilars.

Biosimilarity is based largely on the comparative analytical assessment, molecular characterization, and preclinical studies rather than on lengthy and costly clinical trials. If there is any residual uncertainty about biosimilarity, the FDA has the discretion to require additional clinical trials.

While Section 351(k) created an abbreviated licensure pathway for biosimilars and interchangeable biosimilars, the use of RWD to generate some of the evidence could further expedite development, review, and approval. RWD have been used in regulatory applications for other kinds of drugs (e.g., products for rare diseases); however, to date, no applications to FDA for approved biosimilars or interchangeable biosimilars have included RWD/RWE.

OBJECTIVE

To elicit expert recommendations on how and when RWD could be used in regulatory decisions, using the test cases of biosimilars and interchangeable biosimilars.

METHODS

We engaged a multi-stakeholder panel of nine individuals with expertise in biosimilar development, regulatory science and policy, and RWD. The panel completed a pre-meeting questionnaire, and then met for two, two-hour, moderated virtual meetings to examine the nuances for where and how to integrate RWD into the biosimilar regulatory process in the US. Transcripts of the discussions were summarized into a set of themes and recommendations for adopting RWD in the regulatory process.

RESULTS

Panelists reported general optimism for using RWD in regulatory approvals, but also concern for the quality and relevance for meeting FDA evidentiary needs, emphasizing the lingering uncertainty in operationalizing regulatory-grade RWD.

In the first discussion, panelists reacted to a series of applications where RWD could be used (**Table 1**).

In the second discussion, panelists refined their recommendations and posed a series of considerations to promote success for RWD in regulatory assessments (**Table 2**).

PANEL RECOMMENDATIONS

1. Advocate for continued **education** on **appropriate uses** of RWD can be to facilitate approvals without compromising assessment of safety and effectiveness;
2. Sponsors should **engage early with FDA** to proactively discuss proposed uses of RWD to inform study protocols;
3. Focus on **promising use cases** and emphasize **data quality** and fitness for use;
4. Continue efforts and investment in **enriching existing data sources** through linkage between disparate data sources;
5. Incentivize consistency and completeness of **data collection** through **provider incentives** (e.g., quality measures);
6. Be innovative in **leveraging foreign (non-US) RWD** through partnerships where biosimilars achieved early adoption and broad utilization, especially in Europe.

DEFINITIONS

Biosimilar – A biological product that is highly similar to, and has no clinically meaningful differences from, an existing FDA-approved reference product.

Interchangeable biosimilar – A biosimilar that meets additional requirements that allow it to be substituted for the original product at the pharmacy without the need to consult the prescriber, subject to state law.

Real-World Data (RWD) – data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.

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

Table 1. Panel Discussion and Consensus

RWD proposed use	Key take-aways from Panel discussion
Generate hypotheses and study endpoints	• Hypothesis generation would have occurred with the originator biologic, but RWD may be useful to identify alternative endpoints (measure of clinical effect vs pharmacokinetics). • We don't really need RWD to refine comparative clinical efficacy studies--we need them to replace them
Identify biomarkers or other clinical datapoints for use in clinical development	• PK and biomarker endpoints are not usually present in RWD. • RWD plays a very different role in demonstrating substantial evidence of effectiveness, vs supportive information for "no clinically meaningful differences"
Review clinical pathway analyses to inform the design of pragmatic clinical trials	• Unlike an innovator medicine, we're not looking for an unmet need to address for clinical development. The goal is to demonstrate similarity, not independently establish safety/efficacy
Target patients for study recruitment	• This is a big area where RWD could be useful but concerns about structural racism making it non-representative; The goal is to obviate the need for a comparative efficacy study
Assess trial feasibility	• Feasibility assessments for trials seem more appropriate for new drugs • If a clinical trial is needed, RWD should be used to explore how different inclusion and exclusion criteria would impact the feasibility of a protocol, to avoid problems with recruitment
Inform statistical model development	• Hypothetically, RWD can be used to create hybrid control arms so that they contain both prospectively enrolled and patients. Outcomes of interest need to be routinely measured
Leverage disease natural history studies	• This RWD use does not apply to biosimilars as they would have already been done in the development of the originator biologic
Expand pragmatic trial adoption	• Pragmatic trials may not result in an adequately sensitive endpoint to detect a difference (if there is one); Devil is in the details of what data can be collected
Expand single-arm trials with external comparators	• A single arm study for a biosimilar is challenging to consider when the intent [of] the study is to evaluate similarity between the reference product and the biosimilar
Increase linkage across registries and databases	• RWE will benefit from better linkage between clinically rich registry data, often used in oncology or rare disease settings, and expansive electronic healthcare data like administrative claims or EHRs; linkages can be costly, so careful assessment of feasibility and appropriateness are necessary
Leverage international data on products already approved/ marketed outside the U.S.	• International data makes sense for biosimilars, even if populations are different, as long at there is appropriate population cohort matching; this may make switching and other biosimilar studies easier
Integrate mobile health technologies	• Everyone lives on their phones, and patients love telehealth. The data available are very informative and can lead to insights not captured in a single health care visit as long as absolute true linkage among data sources is possible
Use of common data models for network studies	• Elements of data models are relevant to study question and data missingness is minimized, this could yield much more interpretable RWD

Table 2. Considerations For RWD for Regulatory Assessment

There is a "golden opportunity" to use RWD to abbreviate comparative clinical studies
RWD could address residual uncertainty about impacts from biosimilar switching or safety, and address concerns about immunogenic response
Label expansion is a very promising use of RWD in general, though does not apply to biosimilars
RWD quality, standardization, privacy issues, and potential biases and confounding must be carefully considered in all cases
A structured framework for confidently applying RWD would be helpful
In addition to claims and electronic health records, registries are potentially rich sources of data, including clinical outcomes, that should be utilized more
Consistency of measurement and availability of endpoints or variables of interest are essential in assessing data quality
There is a need for broader linkage of disparate data sources to provide more robust information
As not all people in the U.S. are included in healthcare databases, there may be a problem understanding what results are representative
Finding a matched group and a relevant set of outcomes for clinical effectiveness is not always straightforward
External/synthetic control arms are an opportunity for including reference product users
Detecting a rare event – as is the case when a biosimilar is expected to behave the same as the reference product – benefits from large data sets suggesting that typical clinical trials are underpowered to be meaningful
Non-US RWD should be explored more thoroughly – this would be potentially very valuable for supporting biosimilarity and potentially interchangeability

CONCLUSION

While there are still challenges in using RWD in the US regulatory context, there are opportunities where RWD would be successful in meeting evidentiary needs, and areas for further methods development and data enrichment.

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