# Using Real-World Data/Real-World Evidence to Support Biosimilar and Interchangeable Product Development and Approval: Challenges and Opportunities

January 10, 2025

**Prepared For:**
Biologics & Biosimilars Collective Intelligence Consortium, LLC
675 N Washington St, Suite 220,
Alexandria, VA, 22314

**Prepared By:**
IQVIA Government Solutions, Inc
3110 Fairview Park Drive, Suite 400
Falls Church, VA, 22042

IQVIA

# TABLE OF CONTENTS

# KEY FINDINGS

## Regulatory pathway(s) for biosimilars

- Section 351(k) was established in 2010 as an abbreviated licensure pathway for biosimilars; this is the primary regulatory pathway for biosimilar approval. Some biosimilar products have also been approved through the 505(b)(2) pathway and 351(a) pathway.

- Biosimilarity determinations are based upon data derived from analytical studies, animal studies, and clinical studies. The analytical studies are the foundation of approval, with subsequent study phases designed to address any “residual uncertainties” from the previous phase.

## RWD/RWE in regulatory submissions for other products

- Real-world data/real-world evidence (RWD/RWE) has been used to meet regulatory requirements for some small-molecule drugs and other drug products, typically drugs used in oncology and rare disease settings.

- Pragmatic trials and single-arm (external comparator) trials which both rely on RWD/RWE have been used to support drug approvals. RWD from registries have also been used in some specific contexts.

- There have been no biosimilar applications in which RWD/RWE has been used to support approval in the US.

## RWD/RWE for expediting biosimilar development and approvals

- RWD/RWE can help to optimize clinical trials (e.g., target patients for study recruitment or identify novel biomarkers), and to expand available clinical data through the further adoption of pragmatic or single-arm studies, or better leveraging existing technologies (e.g., digital health devices) and “big” healthcare databases (e.g., administrative claims or electronic health records).

- There are attributes of the proposed biosimilar and its indication that may make RWD/RWE more acceptable for use in applications like characteristics of reference biologics (e.g., post-market data and marketing history), other biosimilars already being marketed, the severity of condition for which the biosimilar is indicated and limited therapeutic options for patients.

# INTRODUCTION

Biologics have transformed treatment options for patients with complex conditions, but they are costly to develop and bring to market, and therefore costly to patients and the healthcare system more broadly.[1-3] One way to reign in these costs is through competition from greater availability of biosimilar and interchangeable products. Some of the challenges associated with bringing biosimilars to market more quickly were addressed through the 351(k) pathway, but the costs associated with development can still be prohibitive and adoption remains relatively slow among providers.[2,3] RWD/RWE can be leveraged to accelerate the development, approval, and thus availability of biosimilar products by enhancing and expanding the available data necessary to meet regulatory requirements. RWD/RWE may also be able to foster greater physician awareness of biosimilars and acceptance of their therapeutic equivalence.

**This report summarizes the regulatory requirements for biosimilar and interchangeable product approvals, and highlights where RWD/RWE can be used to improve upon clinical development or meet regulatory requirements, using lessons learned from regulatory applications for other drugs.**

## THE REGULATIONS AROUND BIOSIMILARITY AND INTERCHANGEABILITY ALLOW FOR MULTIPLE SUBMISSION PATHWAYS

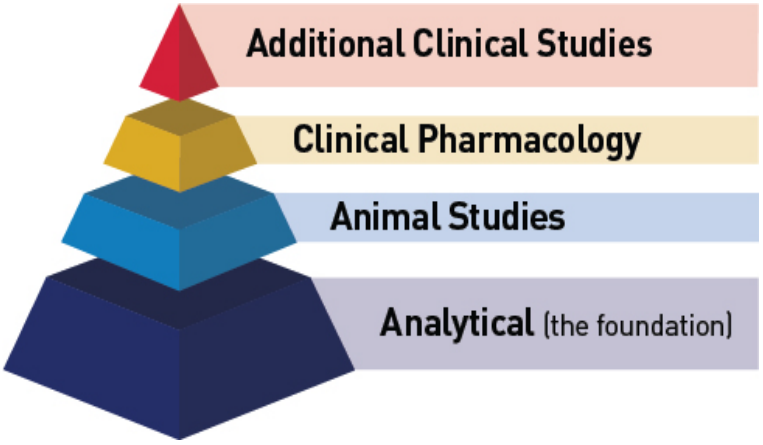
A specified regulatory pathway for biosimilars was established when the Biologics Price Competition and Innovation Act (BPCI) Act was signed into law on March 23, 2010, enacted as part of the Affordable Care Act.[4] The BPCI Act created an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with a Food and Drug Administration (FDA) licensed reference product. Before the BPCI Act, biosimilar applications were submitted through more traditional approval pathways that involved greater evidentiary and cost burdens which slowed the time to biosimilar regulatory approval and market availability.

### Section 351(k): The primary biosimilarity pathway

Added through the BPCI Act, section 351(k) of the Public Health Service (PHS) Act (42 U.S.C. 262(k)) sets forth the requirements for an application for a biosimilar product and an application/supplement for an interchangeable product.[5] Biosimilarity is attained when FDA determines the biological product is highly similar to the reference product (notwithstanding minor differences in inactive components), and that there are no clinically meaningful differences between them with respect to "safety, purity, and potency[i] of the product." The purpose of a biosimilar development program is to support a standardized approach to the demonstration of biosimilarity between a proposed product and a reference product, including an assessment of the effects of any observed differences between the products, but not to independently establish the safety and effectiveness of the proposed product. To obtain licensure,[5-7] the sponsor must demonstrate biosimilarity based upon data derived from:

- Analytical studies (i.e., structural analysis and functional assays) that demonstrate that the biological product is highly similar to the reference product on a molecular level
- Animal studies that assess toxicity and provide additional support for demonstrating biosimilarity
- A clinical study or studies (including comparative pharmacokinetic [PK] and pharmacodynamic [PD] studies, and clinical immunogenicity assessment) that are sufficient to demonstrate "safety, purity, and potency" for conditions for which the reference product is licensed and intended to be used. The types of data and studies that are required vary, depending primarily on the molecule and proposed indication. All extensive structural and functional characterizations of both the proposed product and the reference product serve as the foundation of a biosimilar approval process (**See Figure 1**)[8], and thus

**Figure 1: Hierarchy of evidence for biosimilar approvals**[8]




[i] The standard for licensure of a biological product as "potent" under section 351(a) of the PHS Act has generally been interpreted to include effectiveness.

the development program. Without strong evidence of structural and functional similarity, biosimilarity approval cannot be obtained regardless of the success of any non-clinical or clinical studies.

The FDA recommends that sponsors use a stepwise approach to developing a biosimilarity application.[6,7] At each study phase – analytical, animal, and clinical pharmacology – a sponsor is advised to evaluate the extent to which there is "*residual uncertainty*" about a biosimilar product's "biosimilarity" to the reference biologic and design the next phase of the study program to address that uncertainty. If "*residual uncertainty*" persists, the sponsor must consider what additional comparative clinical data may be needed to address it. While premarket studies may provide adequate clinical data to support biosimilarity, additional post-marketing safety monitoring (i.e., surveillance) and clinical trials may be warranted. The FDA has the discretion to determine that any data element or study phase is unnecessary.

Some of the major challenges associated with the biosimilar approval process were addressed through the abbreviated 351(k) pathway for biosimilars designated by the BCPI act. The time and financial burdens associated with demonstrating biosimilarity (from an industry perspective) and evaluating biosimilarity (from a regulatory perspective) have been significantly reduced since the regulatory review of biosimilars is far more focused on molecular characterization and preclinical studies than from lengthy, and costly, clinical trials.[3] At the same time, leveraging RWD/RWE can inform biosimilarity and help to further reduce the burden associated with bringing biosimilars to market without compromising safety and effectiveness.

## Section 351(k): Interchangeability

To meet the standard for "interchangeability" under section 351(k),[5] a product must first be formally designated biosimilar to the reference product. A sponsor must then demonstrate that the product can be expected to produce the same clinical result as the reference, and that the risks or reduced efficacy associated with switching between the product and its reference is not greater than that of using the reference product without a switch.[9] The data necessary for approval may vary depending on features of the proposed interchangeable product, but typically applications include assessments of critical quality attributes, analytical differences and their potential clinical impact, and differences in mechanisms of action, PK and biodistribution, immunogenicity risks, and toxicities. In addition, a switching study (or studies) is needed to support a demonstration of interchangeability. This study should evaluate whether switching affects clinical responses in relation to safety or reduced efficacy as determined through differences in immunogenicity, PK, and/or PD.[9]

## Other regulatory pathways have been used in more limited instances

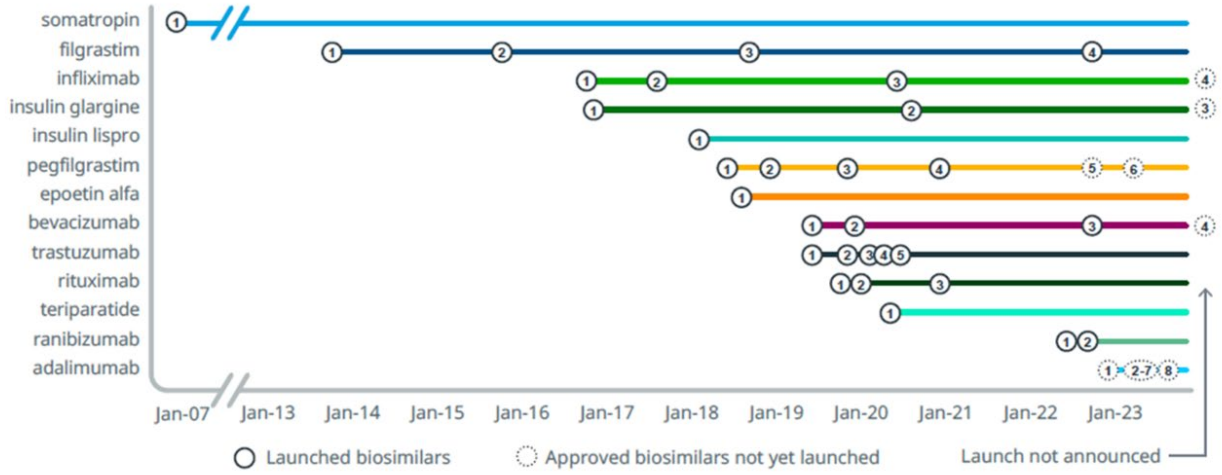
While the 351(k) pathway is the primary regulatory pathway for biosimilars, some biosimilar products have been approved through the 505(b)(2) pathway for abbreviated approvals of nonoriginal products referencing another product in the submission.[10] The 505(b)(2) application contains full reports of safety and effectiveness investigations with information from studies not conducted by or for the submitting sponsor. This application allows greater flexibility in the product's "equivalence" than the traditional abbreviated new drug applications; in other words, the product may not necessarily be bioequivalent, pharmaceutically equivalent, and/or therapeutically equivalent to the listed drug(s) relied upon.

Only one biosimilar, tbo-filgrastim, was approved through a biologics license application (BLA) under the 351(a) pathway because the 351(k) pathway did not yet exist for biosimilar approval.[1] Applications submitted under section 351(a) of the PHS Act are "stand-alone" applications that must contain all information and data necessary to demonstrate that the proposed product is "safe, pure and potent."[11]

## THE BIOSIMILAR MARKET HAS CHANGED SINCE THE FIRST MOLECULE LAUNCHED

The first biosimilar launched in the U.S. in 2007 (Omnitrope), pre-dating the implementation of the BPCI Act. As of January 2023, 30 biosimilars have launched across 12 molecules, with 10 more biosimilars approved and set to launch by the end of 2023; these include biosimilars for the best-selling biologic molecule, adalimumab (**See Figure 2**).[1] Under the 351(k) pathway for biosimilars, 45 products have been approved (25 launched), four with interchangeable status (two launched), including the molecules adalimumab, bevacizumab, epoetin alfa, etanercept, filgrastim, infliximab, insulin glargine, pegfilgrastim, ranibizumab, rituximab, and trastuzumab. Under the 505(b)(2) application pathway, four products have been approved (four launched), including the molecules insulin glargine, insulin lispro, somatropin, and teriparatide. As previously stated, tbo-filgrastim was approved through original BLA under the 351(a) pathway. Many more biosimilars are in clinical development; development is largely being driven by smaller companies, while marketing is done by large companies.[1,2]

**Figure 2: Biosimilars approved and launched in the U.S. as of January 2023**




*Source: IQVIA Institute report[1]*

Biologics are the fastest-growing class of medications in the U.S., and they have revolutionized the care for patients with many complex conditions. However, they account for a substantial and growing proportion of healthcare costs. In the last five years the biologics market has grown, on average, over 12% annually (on an invoice-price basis), and now comprises 46% of drug spending.[1] This could markedly change in the coming years as more biologics come off patent protection and the market has increased competition from biosimilars.[3] While not entirely clear what effect they will ultimately have on healthcare costs, some estimates suggest a reduction on direct spending that could exceed $180 billion over the next five years.[1] At the same time there are many intersecting factors that will impact biosimilar uptake long term, including reimbursement practices and provider training/education and incentives.[2]

## RWD/RWE HAS BEEN USED IN REGULATORY APPLICATIONS, JUST NOT FOR BIOSIMILARITY

The 21st Century Cures Act of 2016 called for the US FDA to develop a plan for increasing the use of RWD for product reviews.[12] While this Act was not specific to biosimilars, it provided an opportunity to increase the efficiency for biosimilar approvals. Subsequently, the FDA has approved applications for small-molecule drugs and other drug products that use RWD/RWE to meet regulatory requirements.[13] This has typically included drugs used in the setting of oncology and rare diseases, and some other limited indications including leukemia, lymphoma, myocardial infarction, and progeria (**See Table 1**). RWD/RWE has been used to supplement applications to extend existing FDA labeled indications, new drug applications (NDAs), market authorization applications (MAAs), and post-marketing analyses (PMAs) for biosimilars.[Pawloski PA, et al under review]

**Table 1: Key examples of where RWD/RWE was used in regulatory applications**

| Examples | Intervention | Clinical Setting | Study Design | RWD/RWE Element(s) | Requirement Met |
|---|---|---|---|---|---|
| **NCT02013167**[13-15] | Blinatumomab | Acute lymphoblastic leukemia | Single-arm trial | Utilized an external, historical control from patient records across multiple clinical study and treatment sites to compare time to remission | Phase 3 study |
| **DAPA-MI study (NCT04564742)**[16] | Dapagliflozin versus placebo | Acute myocardial infarction | Double-blinded, placebo-controlled pragmatic trial | Enrolling patients from two national registries: SWEDEHEART in Sweden and MINAP in the UK. This study will utilize automated capture of routine follow-up data, data queried from mobile devices, and pill bottle caps which record the number of pills dispensed by the patient and allow for real-time adherence tracking | Phase 3 study (ongoing) |
| **L-MIND study (NCT02399085)**[17,18] | Tafasitamab in combination with lenalidomide | Transplant-ineligible patients with relapsed/refractory diffuse large B-cell lymphoma | Single-arm trial | Utilized an external, historical control (cohort from a retrospective observational study) to characterize the safety and efficacy of MOR00208 (tafasitamab) in combination with lenalidomide | Phase 2 study |
| **NCT00425607 & NCT00916747**[19-21] | Lonafarnib | Patients with Hutchinson-Gilford progeria syndrome (HGPS) | Open-label, single-arm trials | Utilized an external, contemporaneous control (cohort of untreated patients with HGPS) to establish survival benefit | Phase 2 studies |

**Note**: This is not an exhaustive list of *all* RWD/RWE use cases in regulatory applications

Pragmatic trials and single-arm (external comparator) trials, which both rely on RWD/RWE, have been used to support drug approvals, yet the RWD/RWE are rarely included in approved drug labels.[Pawloski PA, et al under review] An example where the RWD/RWE was included in the drug label include lutetium Lu 177 (Letathera) for somatostatin-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[22] In addition to clinical trials, RWD/RWE obtained from expanded access programs, electronic health records, patient databases and registries, and existing regulatory data have also been used to support drug approval submissions as shown for alglucosidase alfa (Myozyme) for infantile onset Pompe disease, hepatitis B immune globulin (Human) for the prevention of hepatitis B recurrence following liver transplantation, defibrotide (Defitelio) for hepatic veno-occlusive disease following hematopoietic stem cell transplantation, cerliponase alpha (Brineura) for tripeptidyl peptidase-1 deficiency (CLN2).[22]

RWD/RWE is usually considered acceptable for use in applications when preliminary data suggest effect sizes will be large, and in the context of single-arm trials when using a traditional parallel assignment control arm would be unethical or infeasible in a given clinical setting.[13] In addition to providing support in the setting of large effect sizes for efficacy/effectiveness, RWD/RWE has been used to provide baseline controls, and contextualization.[Pawloski PA, et al under review] Examples

include cholic acid (Orphaco, Cholbam), deferiprone (Ferriprox), eculizumab (Soliris), and metreleptin (Myalept).[22-25] Examples of drugs where RWD/RWE was used to provide contextualization include entrectanib, erdafitinib (Balversa), and polatuzumab.[22,26,27]

***Thus far there have been no biosimilar applications in which RWD/RWE has been used to support approval; however, successful applications of RWD/RWE in other regulatory contexts can provide a suitable roadmap for its potential use in support of biosimilar approvals.***

## HOW CAN RWD ENHANCE RWE OR PROVIDE RWE FOR BIOSIMILAR APPROVALS?

In the context of biosimilar applications, real potential for RWD (e.g., insurance claims, electronic health records [EHRs], registries, etc.) exists to provide supporting data to clinical trials and to generate better evidence from clinical trials to increase efficiencies essential for timely regulatory review. In addition, RWD can supplement clinical data for use in comparative studies and to meet regulatory requirements, notably in rare conditions when traditional trials are unethical or infeasible.

### Where RWD can optimize clinical trials and speed up development, and approval

**Generating hypotheses and study endpoints**

RWD is often used to inform study questions, hypotheses, and endpoints associated with traditional randomized controlled trials (RCTs). By leveraging RWD, a sponsor can adjust prespecified hypotheses and endpoints to better align with regulatory requirements.[13]

**Identifying biomarkers**

RWD can help facilitate improved identification of potential biomarkers or other important clinical data points for use in clinical development. These data may come from labs, available genomic analyses, or even the free text from provider medical records.[13]

**Leveraging clinical pathway analyses**

These types of analyses involve the systematic and comprehensive review of real-world treatment modalities, including the steps involved in diagnosis, treatment selection, and follow-up care. By analyzing clinical pathways sponsors can better design clinical studies (e.g., pragmatic trials and switching studies) by better understanding clinical practice.[28]

**Targeting patients for study recruitment**

Registries or health system EHRs can be used to target potential patients for clinical trials to enhance trial generalizability, identify desired patient sub-groups or prognostic indicators for enriched patient pools, and create efficiencies for stratified studies and/or in evaluating endpoints of interest.[13]

**Assessing trial feasibility**

RWD is critical for understanding how various inclusion/exclusion criteria will impact the available patient pools within a given geographical region or site. To maximize enrollment in studies with strict inclusion/exclusion criteria, RWD can help investigators build distributed research cohorts when finding patients is challenging.[13]

**Informing statistical model development**

RWD can help to provide the empirical basis for prior probability distributions in Bayesian statistical models.[13]

**Leverage disease natural history studies**

Contextual information about disease progression generated from RWD underlies RWE on the benefits and risks of treatment options. Disease natural history studies can be used to inform clinical development, and supplement approval applications.

## Where leveraging RWD can help increase the availability of quality clinical data

**Expand pragmatic trial adoption**

These types of clinical trials can be integrated into the health care system and facilitate data collection at the point of care. Pragmatic RCTs can be open label and can use usual care or alternative therapies as controls.

**Expand single-arm trials with external comparators**

When randomization is not feasible or ethical, single-arm studies are crucial. RWD can be used as the basis for external controls (historical or contemporaneous).

**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. Combining registry data with data collected from pragmatic or other clinical trials can also substantially reduce study-related burdens (e.g., data collection) on both patients and investigators.

**Leverage international data**

Biosimilar designations are sometimes made by other international regulatory bodies like the European Medicines Agency before FDA approval. Although sometimes limited by differences in healthcare systems and medical practice, using patient-level data from other countries on already marketed products can create natural experiments on the safety and effectiveness of products marketed outside the U.S.

**Build on innovative free text data mining**

Natural language processing (NLP) of free text or unstructured data in EHRs to better capture biomarkers, social determinants, or other granular clinical information can expand the available RWD for regulatory use. Implementation of NLP coupled with other advanced analytics like machine learning algorithms can help untap important insights which can inform the development of a clinical study program.

**Build on integration of mobile health technologies**

The expanded use of mobile health technologies can help decrease the burden associated with primary data collection and can expand the available biometric RWD; these data could be combined with patient reported outcomes to allow for a more comprehensive assessment of all relevant patient information.[29]

**Prioritize the use of common data models for network studies**

Standing up large, federated data networks that rely on a common data model (CDM) can further facilitate rapid, reactive, and reproducible studies across many data partners simultaneously. Particularly useful in the context of rare exposures/outcomes where an extensive network data could be leveraged, CDMs allow for efficient querying of multiple data partners EHRs or claims data to support large-scale RWE generation.

## RWE HAS REGULATORY POTENTIAL IN CURRENT LANDSCAPE (IN CERTAIN SCENARIOS)

Biologics constitute some of the most expensive drugs on the market and are a growing share of the overall drug expenditure. Given this backdrop, and the passage of the 21st Century Cures Act, there is a real incentive across industry and federal partners to be innovative in ways to shorten the time from inception and clinical development to approval, as the availability and scaled-up adoption of biosimilars could help moderate the growing costs associated with these therapeutics.[3,12] Fully leveraging RWD/RWE to expedite the approval process is critical, but currently RWD/RWE may be more acceptable for use in some biosimilar applications than others. Some attributes of the proposed biosimilar that may make FDA more amendable to allowing RWD/RWE to meet regulatory requirements include:

- Reference biologic with a long marketing history and known to be safe/effective
- Other biosimilars for the reference biologic are approved and marketed (including those in international settings)
- Indicated for severe or life-threatening conditions
- Limited available therapies for the condition

Additional opportunities for increasing the use of RWD/RWE in regulatory submissions includes the development of existing or novel methodologies for the uptake and analysis of RWD and strategies for implementing RWD/RWE such as enhancing propensity score methodologies, RWD implementation, RWD availability and the use of surrogate markers, validation of synthetic data, meta-analyses of observational studies compared with randomized controlled trials, development of risk identification methods, and the establishment of acceptable RWD endpoints.[30-40]

If precedents are set for leveraging RWD/RWE for specific biosimilar applications, in specific contexts, the framework around RWD use in these types of submissions can be better defined. While not in FDA's purview, it is possible that some market forces (e.g., healthcare costs) may also play a role in the acceptance of RWD in certain biosimilar submissions in addition to FDA considerations like reference biologic marketing history and clinical need. At the same time, sponsors, patient advocacy groups, and other stakeholders should consider when the FDA may be flexible about RWD/RWE, engage with the agency to design RWD/RWE studies that have the potential to fulfil a regulatory requirement, and push for FDA guidance to be expanded to include defined use cases for RWD/RWE in the context of biosimilars.

## WHERE ARE WE NOW AND WHERE DO WE GO FROM HERE?

Biosimilars allow patients access to biologics in a cost-efficient way, creating competitive pressure on reference biologics, but efforts are needed to catalyze further development and expedite approval. One way to accomplish this is to leverage lower costs and readily available RWD/RWE; however, not all RWD/RWE are currently fit-for-purpose or acceptable for meeting regulatory requirements from FDA's perspective. Using RWD/RWE in biosimilar approval applications will require the identification of knowledge gaps associated with regulatory review and a clear understanding of the appropriate RWD/RWE needed in each given regulatory scenario, a targeted approach modeled on its use in applications for oncology drugs or drugs treating rare diseases, leveraging study designs that have been successfully used in those therapeutic settings. FDA has allowed clinical studies incorporating RWD/RWE in approval applications in limited instances, generally in the context of pragmatic and single-arm trials. Thus, FDA may be more amenable to RWD/RWE generated from these types of studies, particularly for proposed biosimilars with an outsized clinical need. There are other areas in which RWD/RWE could be used to build upon existing paradigms for optimizing clinical trials for biosimilars and increasing available clinical data for comparative or contextual use. Some RWD gaps must be addressed for improved regulatory-grade RWE like more claims/EHR data linked to rare disease registries, and enhanced ascertainment of biomedical data.

Under the 21st Century Cures Act of 2016,[12] FDA was tasked with developing an RWE Program to evaluate the potential use of RWD in support of approval for new indications of already approved drugs and biological products, and to support changes to labeling around product comparative effectiveness or safety. Out of the RWE program, the FDA issued a series of draft guidance documents from September through December 2021 covering everything from data sources[41,42] and data standards[43] to considerations for the use of RWD/RWE to support regulatory decision-making.[44] FDA provided recommendations on how to select appropriate claims and EHR data sources, validate study variables, maintain data provenance and quality, design registries, and conform to FDA-supported data standards. The FDA also notes that interventional studies using RWD are subject to investigational new drug application regulations and describes their expectations regarding non-interventional studies that use RWD. Further, the FDA asserts that RWD quality, reliability, and integrity will ultimately affect how they consider the RWE submitted in support of an application. Subsequently, the FDA issued additional specific guidance on designing externally controlled clinical trials[45] and intends to issue another on pragmatic RCTs conducted in routine clinical practice settings.

These guidance documents address what FDA views as reliable and relevant data for use in regulatory settings, but there are considerable areas of uncertainty around how FDA views RWD/RWE in the context of specific types of products or applications where the need for it to support approval may be greater like in biosimilar applications involving rare diseases. While FDA has not offered any formal guidance on the use of RWD/RWE for biosimilar applications, future regulatory decisions and public communications by FDA around biosimilars may provide insights on the context in which RWD/RWE may be acceptable. FDA maintains there is considerable interest in using RWD to generate RWE to support regulatory decisions. In September 2022, the FDA User Fee Reauthorization Act of 2022 was signed into law, which included the second reauthorization of the Biosimilar User Fee Act (BsUFA) for fiscal years 2023-2027.[46] The use of RWD/RWE to advance development of interchangeable products is explicitly noted in the performance and procedural goals of the BsUFA commitment letter. This commitment should facilitate greater investments in RWD/RWE programs for biosimilars to help accelerate their development and approval and meet the needs of patients.

# REFERENCES


1. IQVIA Institute. Biosimilars in the United States 2023-2027: Competition, Savings, and Sustainability; January 2023. 2023. (https://test-www.iqvia.com/-/media/iqvia/pdfs/institute-reports/biosimilars-in-the-united-states-2023-2027/iqvia-institute-biosimilars-in-the-united-states-2023-usl-orb3393.pdf).
2. IQVIA Institute. Unlocking Biosimilar Potential: Learnings from physician across therapy areas; April 2023. 2023. (https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/unlocking-biosimilar-potential/iqi-unlocking-biosimilar-potential-04-23-forweb.pdf).
3. Lyman GH, Zon R, Harvey RD, Schilsky RL. Rationale, Opportunities, and Reality of Biosimilar Medications. N Engl J Med 2018;378(21):2036-2044. DOI: 10.1056/NEJMhle1800125.
4. Public Law No. 111-148: Patient Protection and Affordable Care Act, BCPI: Biologics Price Competition and Innovation Act of 2009.
5. 42 U.S.C. 262 Regulation of Biological Products; 351(k) Biosimilar Applications.
6. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Apr 2015.
7. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Dec 2016.
8. Sue Lim; Director of the Scientific Staff; Therapeutic Biologics and Biosimilars Team. FDA Presentation "Overview of the Regulatory Framework and FDA's Guidance for the Development and Approval of Biosimilar and Interchangeable Products in the US". 2020.
9. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Considerations in Demonstrating Interchangeability with a Reference Product. May 2019.
10. U.S. Food and Drug Administration (FDA). Code of Federal Regulations Title 21; Sec. 314.54 Applications for FDA Approval to Market a New Drug 505(b)(2).
11. U.S. Food and Drug Administration (FDA). Code of Federal Regulations Title 21; Chapter I, Subchapter F, Part 600 Biological Products: General 351(a) Applications.
12. Public Law No. 114-255: 21st Century Cures Act of 2016; Public Law114-255. 2016.
13. Administration USFD. Framework for FDA's Real-World Evidence Program.
14. Przepiorka D, Ko CW, Deisseroth A, et al. FDA Approval: Blinatumomab. Clin Cancer Res 2015;21(18):4035-9. DOI: 10.1158/1078-0432.CCR-15-0612.
15. ClinicalTrials.gov ID: NCT02013167, Blinatumomab Versus Standard of Care Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL). (https://clinicaltrials.gov/study/NCT02013167).
16. ClincalTrials.gov ID NCT04564742, Dapagliflozin Effects on Cardiometabolic Outcomes in Patients With an Acute Heart Attack. (DAPA-MI). (https://clinicaltrials.gov/study/NCT04564742).
17. ClinicalTrials.gov ID NCT02399085, Open Label Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL (L-MIND). (https://clinicaltrials.gov/study/NCT02399085).
18. Zinzani PL, Rodgers T, Marino D, et al. RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma. Clin Cancer Res 2021;27(22):6124-6134. DOI: 10.1158/1078-0432.CCR-21-1471.
19. ClinicalTrials.gov ID NCT00916747, Study of Zoledronic Acid, Pravastatin, and Lonafarnib for Patients With Progeria. (https://clinicaltrials.gov/study/NCT00916747).
20. ClinicalTrials.gov ID NCT00425607, Phase II Trial of Lonafarnib (a Farnesyltransferase Inhibitor) for Progeria. (https://www.clinicaltrials.gov/study/NCT00425607).
21. Suzuki M, Jeng LJB, Chefo S, et al. FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies. Genet Med 2023;25(2):100335. DOI: 10.1016/j.gim.2022.11.003.

22. Izem R, Buenconsejo J, Davi R, Luan JJ, Tracy L, Gamalo M. Real-World Data as External Controls: Practical Experience from Notable Marketing Applications of New Therapies. Ther Innov Regul Sci 2022;56(5):704-716. DOI: 10.1007/s43441-022-00413-0.
23. Bolislis WR, Fay M, Kuhler TC. Use of Real-world Data for New Drug Applications and Line Extensions. Clin Ther 2020;42(5):926-938. DOI: 10.1016/j.clinthera.2020.03.006.
24. Hatswell AJ, Baio G, Berlin JA, Irs A, Freemantle N. Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999-2014. BMJ Open 2016;6(6):e011666. DOI: 10.1136/bmjopen-2016-011666.
25. Jahanshahi M, Gregg K, Davis G, et al. The Use of External Controls in FDA Regulatory Decision Making. Ther Innov Regul Sci 2021;55(5):1019-1035. DOI: 10.1007/s43441-021-00302-y.
26. Feinberg BA, Gajra A, Zettler ME, Phillips TD, Phillips EG, Jr., Kish JK. Use of Real-World Evidence to Support FDA Approval of Oncology Drugs. Value Health 2020;23(10):1358-1365. DOI: 10.1016/j.jval.2020.06.006.
27. Arondekar B, Duh MS, Bhak RH, et al. Real-World Evidence in Support of Oncology Product Registration: A Systematic Review of New Drug Application and Biologics License Application Approvals from 2015-2020. Clin Cancer Res 2022;28(1):27-35. DOI: 10.1158/1078-0432.CCR-21-2639.
28. Aspland E, Gartner D, Harper P. Clinical pathway modelling: a literature review. Health Syst (Basingstoke) 2019;10(1):1-23. DOI: 10.1080/20476965.2019.1652547.
29. Dockendorf MF, Murthy G, Bateman KP, et al. Leveraging Digital Health Technologies and Outpatient Sampling in Clinical Drug Development: A Phase I Exploratory Study. Clin Pharmacol Ther 2019;105(1):168-176. DOI: 10.1002/cpt.1142.
30. Wang C, Lu N, Chen WC, et al. Propensity score-integrated composite likelihood approach for incorporating real-world evidence in single-arm clinical studies. J Biopharm Stat 2020;30(3):495-507. DOI: 10.1080/10543406.2019.1684309.
31. Li H, Chen W-C, Lu N, et al. Novel statistical approaches and applications in leveraging real-world data in regulatory clinical studies. Health Services and Outcomes Research Methodology 2020;20(4):237-246. DOI: 10.1007/s10742-020-00218-4.
32. Weckstein A, Rubinstein E, Patrick A, Jaksa A. Pdg74 Availability of Fda-Approved Surrogate Markers in Real-World Data. Value in Health 2020;23. DOI: 10.1016/j.jval.2020.04.358.
33. Fralick M, Bartsch E, Darrow JJ, Kesselheim AS. Understanding when real world data can be used to replicate a clinical trial: A cross-sectional study of medications approved in 2011. Pharmacoepidemiol Drug Saf 2020;29(10):1273-1278. DOI: 10.1002/pds.5086.
34. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. Cochrane Database Syst Rev 2014;2014(4):MR000034. DOI: 10.1002/14651858.MR000034.pub2.
35. Hong YD, Jansen JP, Guerino J, et al. Comparative effectiveness and safety of pharmaceuticals assessed in observational studies compared with randomized controlled trials. BMC Medicine 2021;19(307). DOI: 10.1186j/s12916-021-02176-1.
36. Ryan PB, Schuemie MJ. Evaluating performance of risk identification methods through a large-scale simulation of observational data. Drug Saf 2013;36 Suppl 1:S171-80. DOI: 10.1007/s40264-013-0110-2.
37. Stewart M, Norden AD, Dreyer N, et al. An Exploratory Analysis of Real-World End Points for Assessing Outcomes Among Immunotherapy-Treated Patients With Advanced Non-Small-Cell Lung Cancer. JCO Clin Cancer Inform 2019;3:1-15. DOI: 10.1200/CCI.18.00155.
38. Griffith SD, Tucker M, Bowser B, et al. Generating Real-World Tumor Burden Endpoints from Electronic Health Record Data: Comparison of RECIST, Radiology-Anchored, and Clinician-Anchored Approaches for Abstracting Real-World Progression in Non-Small Cell Lung Cancer. Adv Ther 2019;36:2122-2136. DOI: 10.1007/s12325-019-00970-1.
39. Shan M, Faries D, Dang A, Zhang X, Cui Z, Sheffield KM. A Simulation-Based Evaluation of Statistical Methods for Hybrid Real-World Control Arms in Clinical Trials. Statistics in Biosciences 2022;14(2):259-284. DOI: 10.1007/s12561-022-09334-w.
40. Sachdeva A, Tiwari RC, Guha S. A novel approach to augment single-arm clinical studies with real-world data. J Biopharm Stat 2022;32(1):141-157. DOI: 10.1080/10543406.2021.2011902.
41. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Real-World Data: Assessing Electronic Health Records and Medical

Claims Data to support REgulatory Decision-Making for Drug and Biological Products. Jul 2024.
42. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products. Dec 2023.
43. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Data Standards for Drug and Biological Product Submissions Containing Real-World Data. Dec 2023.
44. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. Aug 2023.
45. U.S. Department of Health and Human Services Food and Drug Administration (FDA). Guidance for Industry; Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Feb 2023.
46. U.S. Food & Drug Administration (FDA). BsUFA III Commitment Letter. Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027.

**CONTACT US**
**iqvia.com**