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*Additional information:*

*The preceding article is based the a workshop, "Horizon Scanning—Identifying and Estimating Future Impact of Emerging Innovations on US Health Care," given at the ISPOR 20th Annual International Meeting, May 16-20, 2015, Philadelphia, PA, USA.*

To view the panel's presentation, go to: http://www.ispor.org/Event/ReleasedPresentations/2015Philadelphia#workshoppresentations

This topic will be presented at the ISPOR 21st Annual International Meeting in Washington, DC, USA, during Workshop 9: "Five Years Of Health Care Horizon Scanning For AHRQ – Results And Lessons Learned." See pages 30-31 for further meeting details.

# A Real-World Research Perspective for Biosimilars

**Jaclyn L. F. Bosco, PhD, MPH**, Director, Epidemiology and Outcomes Research, Real-World & Late Phase Research, Quintiles, Cambridge, MA, USA

KEY POINTS . . .

Real-world evidence is needed to support claims of safety, effectiveness, and value of biosimilars.

Methodological considerations will be affected by the evolving regulatory and policy landscape on issues such as non-harmonized naming conventions, interchangeability and automatic substitution, as well as decisions regarding reimbursement and physician adoption of biosimilars.

Accurate identification of the biosimilar from its originator is critically important to attribute safety and effectiveness outcomes to the correct product.

## Introduction

Biologics are effective and life-altering therapies used to treat cancer, rheumatologic diseases, diabetes, and other conditions. However, biologics may cost from $15,000 to $150,000 per year [1], far exceeding the cost of most small-molecule drugs. Biologics represented 27% (€36 billion) of drug spending in Europe (EU) in 2011 [2] and 28% ($92 billion) in the US in 2013 [3], yet they accounted for less than 1% of all prescriptions dispensed in the US in that year. While biosimilars are intended to be more affordable to patients than the originator, the cost savings are not as great as for small-molecule generics because of the complexity of synthesizing biosimilars using living organisms. In the EU, biosimilar prices are discounted by an average of at least 25% compared with the originator biologic [4]. The first US biosimilar is being marketed at a wholesale price 15% lower than its originator [5].

Biosimilars are similar or highly similar versions of an approved biologic (or originator) and hold the promise of reducing health care costs, increasing patient access, and promoting innovation [4]. The European Medicines Agency (EMA) has approved 21 biosimilars since the introduction of their *similar biological medicinal product* guidance in 2006, and currently 20 are marketed [6]. The US Food and Drug Administration (FDA) approved its first biosimilar under the 351(k) regulatory pathway [7] on 06 March 2015 and the first biosimilar hit the US market on 03 September 2015 [5]. An estimated 12 biologic patents will have expired by 2020; thus, the availability of biosimilars is expected to increase across the globe.

## Biosimilars Considerations

Careful design and implementation of real-world studies are needed for high-quality evidence generation to fully understand biosimilars. However, the lack of harmonization in naming conventions for biosimilars, the variability in regulations on interchangeability of biosimilars for originators and for automatic substitution, reimbursement decisions, and physician awareness and prescribing adoption must

be taken into consideration when designing a real-world biosimilar study as these factors may vary by country or even at the local state or regional level.

Regulators require both comparative analytical, nonclinical studies, and clinical studies for biosimilars marketing approval. Clinical studies include a pivotal phase III trial with a head-to-head comparison between the biosimilar and originator to demonstrate bioequivalence. This pivotal phase III trial is conducted in patients who are being treated for an indication that is determined, through discussions with regulators (e.g., FDA, EMA), to be the "most sensitive" indication. After demonstrating bioequivalence, it is highly likely that the biosimilar manufacturer may be granted extrapolations to all other approved indications for the originator without conducting clinical studies in these indications. Approval of extrapolation is based on scientific justifications for the mechanism of action of each condition in which licensure is sought (e.g., target receptors for each relevant activity; the binding, or dose/concentration response for extrapolations which is provided by the manufacturer, etc. [8,9].

Regulations relating to interchangeability and automatic substitution differ by the governing body. For example, interchangeability is the responsibility of the national competent authorities within the EU, and does not fall under the remit of the EMA Committee for Medicinal Products for Human Use (CHMP) [10]. In contrast, the FDA can approve a biosimilar as 'interchangeable' or 'not interchangeable,' [11] with state laws regulating the ability of a pharmacist to substitute a biosimilar for a branded biologic or not.

Careful design and implementation of real-world studies are needed for high-quality evidence generation to fully understand biosimilars.

With the goal of harmonizing biosimilar naming, the World Health Organization proposed including a four-letter suffix assigned at random as a biologic qualifier (BQ) for naming purposes [12]. However, naming conventions for biosimilars still vary by jurisdiction. For example, South Korea uses only the proprietary name [13], while the EMA licenses biosimilars under the same International Nonproprietary Name (INN) as the originator. The FDA approved its first US biosimilar as 'filgrastim-sndz' [14]. The FDA proposed naming includes a temporary INN with a company-specific four-letter suffix, and it is expected that future US approvals will follow the same naming guidance [15]. The FDA, however, has yet to decide whether products granted interchangeability will have a unique suffix or the same suffix as the originator.

## Stakeholder Needs

Once marketing approval has been granted, regulators tend mainly to focus on safety issues. There is potential for differences from the originator, for example, due to minor modifications to manufacturing processes that could cause immunogenicity or other safety events in real-world populations [16]. As with any new therapeutic, there is almost always a requirement for a risk-management or pharmacovigilance plan that may mimic pharmacovigilance measures for the originator and may include additional data collection for the biosimilar. Post-marketing studies may also be mandated, which may reflect uncertainties around biosimilar purity and real-world safety and effectiveness. The variability in naming conventions and policies relating to interchangeability and automatic substitution have important implications for pharmacovigilance reporting, impacting researchers' ability to track precisely which medication has been used in routine clinical practice.

The abbreviated approval pathway and the absence of extensive clinical data for all approved indications make some physicians cautious about prescribing a biosimilar over the originator, particularly for indications that were granted approval through extrapolation. Clinicians and patients are interested in both effectiveness and safety, in addition to the comparative risks and benefits of the various treatment options, particularly in indications where extrapolation was granted.

Payers have generally comparable interests to those of providers and patients, and include factors of economic benefit-risk as well as information providing insights into medical care, especially in high-cost populations such as the elderly. The local health care system will, in part, determine the time frame of economic considerations. Any delayed risks or benefits are a key element for systems such as the UK National Health Service that provide universal lifetime coverage. Many US private health insurance companies cover adult members for only short periods, which makes evaluations of delayed risks or benefits of much less of an interest. Economic factors are also extremely important to patients and health care providers, since in some countries—such as China and India—patients may pay for these life-altering therapies directly out-of-pocket.

Real-world evidence (RWE) can help fill the knowledge gap for biosimilars for various health care stakeholders and can address questions about their safety and effectiveness in broader populations than those typically included in clinical trials. Real-world studies can often be used to provide more substance to regulatory submission packages, and to provide content for subsequent marketing efforts through presentations and publications. These studies have the additional benefit of providing an added value of engaging physicians and payers in a constructive manner.

## Methodological Considerations

***Study Design***

The research needs and the uptake of biosimilars in the target market will determine the appropriate study design for RWE generation. RWE can help demonstrate safety and effectiveness, evaluate treatment heterogeneity, and identify delayed risks and benefits related to biosimilars. The appropriate study design will depend on the research question, as well as an understanding of the local regulations and clinical practice. Study design options may include prospective non-interventional studies with *de novo* data collection, chart review studies, database studies taking advantage of existing data sources, or pragmatic clinical trials.

Database availabilities will vary by geography, and it is highly unlikely that any one database will include all data needed to distinguish whether substitution occurred, full details on clinical characteristics, and whether the prescribed drug was the one administered. Prospective follow-up can be achieved through >

*de novo* data collection, recording the brand of biologic/biosimilar administered, and allowing for collection of patient- and physician-reported outcome data. Pharmacy and other data may be used to supplement prospectively collected data, depending on data availability and locality. The availability and affordability of biosimilars may also be a consideration if some are reimbursed and others are not, or if some hospitals/pharmacies supply certain brands, but not others. A pragmatic clinical trial may be the only feasible option if, for example, a biosimilar receives reimbursement over the branded biologic, especially in countries with national health care coverage.

***Exposure Classification***

Knowing how the biosimilar is administered (e.g., self-administered injection or intravenous infusion) will help determine where to find the relevant data on treatment exposure, and in the US, whether the drug is covered under the medical or pharmacy benefit. Chronic use of a biologic and/or biosimilar is also an important aspect to consider when defining exposure to treatment, in terms of being able to record start and stop dates, dose escalations or reductions, and to distinguish treatment holidays from discontinuation for the biosimilar versus the originator. Drug switching must also be taken into consideration because depending on reimbursement decisions and local substitution laws, switching between the biosimilar, originator, or other biosimilars for the same originator may occur multiple times throughout the duration of a study without physician awareness. Being able to distinguish the biosimilar from its originator is imperative to accurately attribute the benefits and risks to the correct product.

In the case of comparative studies, naming conventions and interchangeability/substitution practices may affect the feasibility of identifying and selecting appropriate comparators, and this will depend on the target market. The choice of comparator will depend on routine local clinical practice and product availability, and may be the originator, other biosimilars of the same originator, or other therapeutic options. Since patients, physicians, and payers are interested in current treatment choices, the collection of contemporaneous comparators can be useful for addressing the complex issue of having sufficiently detailed, clinically relevant, or timely data. Historical comparators are susceptible to bias due to changes over time in confounding risk factors that may contribute to potentially erroneous observed differences between the biosimilar and safety and effectiveness outcomes. Different patients may be treated now, with different regimens and dosing, making it nearly impossible to address these issues using historical comparators. Thus, the validity of the comparison may be in question if other comparator choices are available. External comparators are useful for understanding the observed effects and to assess the generalizability of study findings. External comparator data are often generated from different methods and some data elements that are commonly used in randomized clinical trials may be unavailable when real-world methods are used. Practical considerations, as well as minimizing the potential for confounding and bias, are critical aspects for selecting the appropriate comparator group in a non-randomized setting.

## Confounding and Channeling Bias

Confounding is a concern in all non-interventional studies, and particularly so in real-world studies, where patients have chronic and severe conditions and may receive other concurrent medications. As an example, cancer patients receiving pegfilgrastim will also receive chemotherapy, making it challenging to tease apart the effects of the two treatments. Since biosimilars will be approved for the same indications and at the same doses as the originator, little to no confounding would be expected by patient-level factors or prognostic characteristics. However, there is a potential confounding by physician and patient preference, product supply, and insurance coverage, posing challenges to separate actual treatment effects from these extraneous factors. Channeling bias, which occurs when therapies for similar indications are administered to subpopulations of patients with prognostic differences, can also be a concern. Physicians may prescribe new treatments more often to patients who have already failed an existing or first-line treatment. In France, for example, the biosimilar law does not allow biosimilars to be substituted for an originator if a patient has already started treatment [17]. Physician preference for prescribing a biosimilar or not will be a challenge to consider when designing, implementing, and interpreting results of real-world biosimilar studies, as it could obscure any differences between the biosimilar compared with the originator on long-term safety and effectiveness outcomes.

## Policy Considerations

If the marketplace agrees to accept biosimilars on the basis of regulatory approval, subsequent decisions to buy and use these products would likely be based largely on pricing and availability. Assuming biosimilars are indeed highly similar to their originators, the availability of these more affordable treatments represent important opportunities for cost-conscious payers. However, the benefits of lower-cost options will need to be tempered by systematic evaluations of evidence to assure practical clinical comparability of effectiveness, as well as careful monitoring of safety—particularly immunogenicity. As described here, biosimilar considerations will likely have an impact on the design of real-world studies. Collectively, biosimilar-specific and methodological considerations will be important factors to take into account in order to perform any meaningful analyses for high-quality evidence generation.

## Conclusion

The future of biosimilars will rest on many factors that differ from those impacting generic versions of small-molecule therapeutics. These factors will vary between markets based on variations relating to issues such as interchangeability and automatic substitution, naming conventions, reimbursement, clinical guidelines, and physician awareness and uptake of biosimilars. Real-world studies have the potential to generate clinical evidence to supplement the findings from pivotal clinical comparative studies, helping to build physician confidence in biosimilar safety and effectiveness, assure payers of value, and educate patients on appropriate treatment options. Of critical importance in real-world evidence generation will be the ability to accurately identify and attribute safety and effectiveness outcomes to the biosimilar from the originator.

### Acknowledgements

*We are grateful to the other speakers, Dr. Nancy Dreyer, Dr. Robert DuBois, and Dr. Jeff White. Their participation greatly enhanced the discussion.*

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*Additional information:*

*The preceding article is based on the issues panel, "Distinguishing Biosimilarity – How Can We Generate Real-World Evidence To Support Decision-Making?" given at the ISPOR 20th Annual International Meeting, May 16-20, 2015, Philadelphia, PA, USA.*

To view Dr. Bosco's presentation, go to: http://www.ispor.org/Event/ReleasedPresentations/2015Philadelphia#workshoppresentations

This topic will be presented at the ISPOR 21st Annual International Meeting in Washington, DC, USA, during Workshop 3: "Biosimilars: Current Developments And Real-World Evidence Generation" See pages 30-31 for further meeting details.