Enhancing Biosimilar Adoption With Real-World Evidence

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KEY POINTS

Biosimilars have the potential to improve access to effective therapies by lowering costs, but their demand is regulated by physicians.

Physicians express reservations regarding biosimilar safety, efficacy, and immunogenicity, and may require additional evidence to prescribe biosimilars.

Real-world evidence studies can address evidence gaps and convince all stakeholders, including physicians, about long-term biosimilar use in specific populations.

INTRODUCTION

Biologics comprise nucleic acids, proteins, and/or sugars within complex molecular structures and are derived from living organisms, as opposed to traditional small-molecular medicines.[1] Biosimilars are highly similar to existing biologics in biological, safety, efficacy, and purity characteristics.[1] Because of savings in research and discovery, clinical trials, and production, biosimilars can be offered at lower prices than originator biologics, creating the potential for cost savings while enabling consistent therapeutic access for patients.[2] Future biosimilar development and possible cost savings depend on the extent of biosimilar adoption.[3]

Biosimilar adoption is influenced by regulatory frameworks, economic incentives, clinical evidence, and patient preferences; these factors vary widely across markets.[4] Physician confidence in biosimilars has been recognized as an important factor in adoption across global markets.[4] The objective of this review is to summarize attitudes towards biosimilars among physicians and provide recommendations for enhancing biosimilar adoption using real-world evidence (RWE).

ATTITUDES TOWARDS BIOSIMILARS AMONG PHYSICIANS

While the approval of a biologic is based mainly on clinical studies demonstrating efficacy and safety, biosimilar approval is focused mostly on analytical studies that demonstrate high molecular similarity and equally low levels of impurities to the originator biologic.[2] A biosimilar may be approved for the same indications as the originator biologic without being tested directly in all indicated populations (referred to as extrapolation), provided that the biosimilar is equivalent to the originator biologic in at least 1 indication.[2] Studies demonstrating the safety of switching from the originator biologic to the biosimilar are not required for approval. Consequently, key concerns for physicians and patients about biosimilars include safety, efficacy (particularly in extrapolated indications), immunogenicity, and effects of switching to a new biosimilar, possibly due to perceptions of insufficient study follow-up time or clinical data collection.[5] Globally, some physicians believe the abbreviated approval process for biosimilars suggests reduced product safety, and many physicians are hesitant to switch patients from originator products to biosimilars without evidence from switching studies.[1,6]

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In addition to efficacy and safety concerns, biosimilar familiarity and acceptance vary across individual markets due to market maturity, prescribing policies, and other factors. Europe has the most mature biosimilar market, having developed the first regulatory framework for approving biosimilars in 2005.[5] Likewise, a higher proportion of European physicians report biosimilar familiarity and acceptance as compared to counterparts in the United States, Japan, and Latin America.[6-9] When examined closely, these survey results suggest incomplete acceptance among physicians globally and fundamental differences in acceptance across markets. Some differences may be related to different regulatory and economic incentives for providers across markets. European countries may enforce a minimum quota of certain biosimilars, encourage a certain minimum percentage of biosimilars be prescribed for treatment-naïve patients, or compel the physician to prescribe the most cost-effective product.[10, 11] There is no uniform, systematic incentive for biosimilar prescribing in the United States, where payers and pharmacy benefit managers play influential roles in pricing and availability, although biosimilar prescribing may be encouraged in some instances.[12]

Physicians also need evidence of biosimilar safety and efficacy to share with patients who may be reluctant to switch from a biologic to a biosimilar.[13] In addition, several professional medical societies explicitly state that the patient's awareness and consent are required for a physician to prescribe a biosimilar.[1]

THE ROLE OF SUBSTITUTION IN BIOSIMILAR DEMAND

Physicians are the main gatekeepers in determining whether patients receive an originator biologic or biosimilar. Unlike generic versions of small molecules, pharmacists cannot dispense a biosimilar in place of the originator biologic without the direct consent of the prescribing physician (referred to as substitution) in many markets.[14] In the United States, only the US Food and Drug Administration (FDA) can determine whether a biosimilar is interchangeable (referring to the highest degree of biosimilarity to the originator biologic as to allow pharmacist substitution) with its originator.[1] But as of May 2018, there are no FDA-designated interchangeable products,[15] and most states have passed legislation declaring that pharmacist substitution is contingent on the FDA's interchangeability approval.[16] Many professional medical societies throughout Europe, Canada, the United States, and Australia also oppose biosimilar substitution.[1]

EVIDENCE NEEDS AND CHANNELS FOR PHYSICIANS

Taken together, these survey results indicate that physicians act as a major regulator in biosimilar demand, but safety, efficacy, and immunogenicity concerns may hinder biosimilar adoption. Physicians throughout Europe, the United States, and Japan express a need for more high-quality information communicated in an ongoing manner on biosimilar safety, efficacy, comparability to the originator biologic, extrapolation, and cost.[6,9,10] But even in mature markets such as Europe, few countries provide biosimilar education specifically targeting physicians.[11]

Manufacturers can enhance biosimilar adoption by addressing physicians' widespread apprehension of insufficient biosimilar clinical data by providing additional safety and efficacy data. Physicians across Europe, the United States, and Latin America rank peer-reviewed publications, professional society guidelines, and medical conferences as their top sources for biosimilar efficacy and safety information.[6-8,17] Studies show that the source of randomized controlled trial sponsorship (any pharmaceutical treatment) has some to no effect on physicians' confidence in clinical study rigor and findings,[18] and manufacturers should feel empowered to convey valuable information by sponsoring additional clinical studies. Conversely, the least valuable information channels to physicians in these regions include prescribing information, medical science liaisons, and health insurance plans/pharmacy benefit managers.[6-8,17]

THE ROLE OF RWE IN ASSESSING BIOSIMILARS

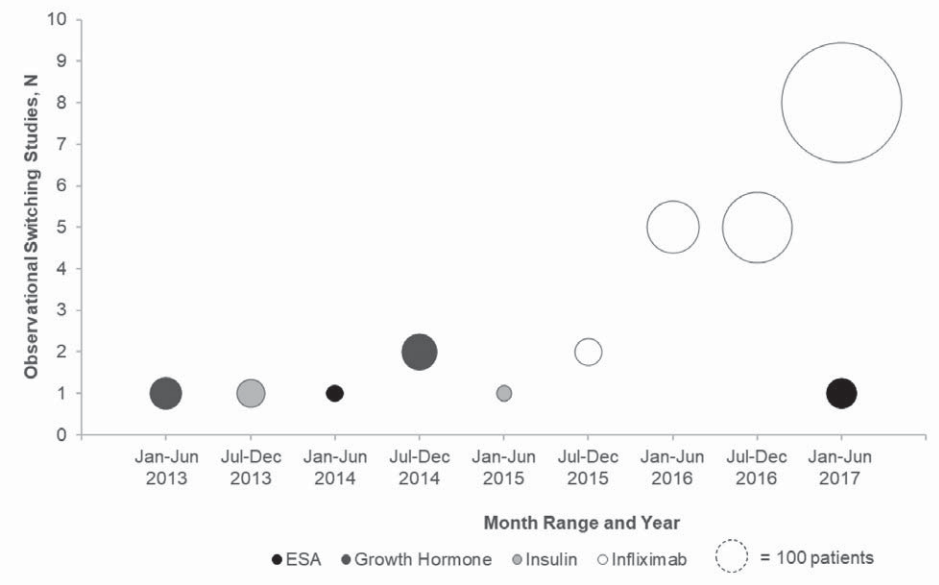
Clinical trials enabling biosimilar approval may provide insufficient evidence to support biosimilar acceptance among all physicians and patients, particularly in less mature markets. Biosimilar registrational randomized controlled trials (RCTs) provide safety and efficacy data, but may be limited by relatively short duration. Furthermore, the resource-intensive nature of RCTs prevents studying every indication in every market. Publishing postmarketing surveillance and other observational studies of real-world data (RWD) offers an important opportunity for manufacturers to provide physicians with additional effectiveness and safety evidence, particularly related to long-term safety, efficacy in extrapolated indications, and effects of switching.

Depending on the study design and objective, RWE studies can follow patients over several years, represent diverse patient populations (including children, elderly, or patients with comorbidities who may have been excluded from registrational RCTs), include patients from extrapolated indications, and focus on specific markets. These studies can also include additional outcomes, such as patient-reported information and economic evidence. Consequently, RWE studies enable generation of safety and effectiveness data demanded by clinicians and cost savings data needed by payers. Furthermore, as more biosimilars are approved, RWE studies may differentiate a single biosimilar from competing biosimilars by addressing outcomes missing in a competitor product. When stakeholders in crowded biosimilar markets perceive a class effect among many biosimilars of the same originator product, RWE studies provide useful distinctions.

DESIGNING AND CONDUCTING RWE STUDIES

Choosing the right RWE study design is critical to generating data that will best address evidence gaps and convince all stakeholders of biosimilar safety and effectiveness, including physicians and patients.[19] Identifying and prioritizing evidence gaps requires market research to determine whether efficacy, safety, immunogenicity, extrapolation, or switching is the most pressing issue, then targeting specific questions within these topics. Each biosimilar must be >

Figure 1: Publication Trends in Biosimilar Switching Studies, January 1, 2013 to June 10, 2017 [1]



Abbreviation: ESA = erythropoietin-stimulating agent. / Note: Bubble size indicates the number of patients.

examined within the context of the indicated population, existing safety and effectiveness data, product maturity, and competitive landscape. For example, prospective observational studies answer key efficacy and safety questions to help build confidence in a newly launched biosimilar, while retrospective studies examining specific populations are useful later in the product lifecycle to answer targeted questions for products with more available RWD.

Conducting RWE studies is usually less resource intensive than operating RCTs, but still may pose a substantial burden to academic groups. Manufacturers should collaborate with organizations capable of generating RWD and groups adept in analyzing, interpreting, and disseminating study findings. One such partner is the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), a United States nonprofit organization founded by managed care organizations, pharmacy benefit managers, health plans, pharmaceutical companies, and other groups. The BBCIC acts as a neutral convener to support transparent research on biologics/biosimilar safety, effectiveness, and use within populations.[20] Registries for diseases treated with biologics, such as oncology and inflammatory conditions, are also helpful partners in providing manufacturers with biosimilar RWD.

RWE IN BIOSIMILAR LIFECYCLE MANAGEMENT

It is critical that manufacturers work collaboratively with key stakeholders and regulatory agencies to sponsor and disseminate RWE studies on the value of biosimilars. To that end, RWE is an integral aspect of biosimilar lifecycle management. Most RWE studies are conducted postapproval, when launched products are available to diverse populations. These could include postmarketing surveillance of product safety, which is required in some countries, or other studies designed to answer different clinical questions. Hence, RWE is particularly useful as a tool to engage with physicians and patients following product launch until broader familiarity and acceptance of approved biosimilars is achieved. Less mature biosimilar markets should leverage existing RWD from markets with higher initial adoption of a given product to conduct RWE studies.

Although there are only a handful of biosimilars on the market in the United States and limited RWD, the landscape will evolve rapidly as more products are approved and patients gain access to these powerful therapies. There is evidence that an inflection point has been reached in publishing biosimilar RWE (Figure 1).[1] As more biosimilars of the same biologic are developed, switch studies can also address biosimilar-to-biosimilar switching.

CONCLUSION

There are unique challenges for biosimilar adoption in approval and access. Although economic incentives and regulatory frameworks both play important roles within each market, physicians are influential players in biosimilar adoption. Awareness and assurance of biosimilar safety and effectiveness among physicians varies based on market maturity and local experience, but there is a global need for improved communication and dissemination of biosimilar research with physicians. Physicians need more evidence of biosimilar safety and effectiveness—including the effects of switching and effects on extrapolated populations—in high-quality studies reported in peer-reviewed publications. RWE provides useful sources for biosimilar information not captured in registrational trials leading to approval. Biosimilar manufacturers and their collaborators have opportunities to address physicians' concerns by strategically designing RWE studies to fill knowledge gaps in biosimilar safety and effectiveness and increase biosimilar adoption.

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