

Realizing the Benefits of Biosimilars: REVISITING INTERCHANGEABILITY

Revisiting Interchangeability to Realize the Benefit of Biosimilars

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Executive Summary

Issue: The approval, by the U.S. Food and Drug Administration (FDA), of an interchangeable biosimilar product, in July 2021, culminated an 11-year process that began in 2010 with the passage of the Biologics Price Competition and Innovation Act. While there are now two interchangeable products that can be automatically substituted in a retail pharmacy setting (the primary benefit of pursuing an interchangeable designation), there is still uncertainty as to what effect the unique U.S. regulatory construct of interchangeability should have on use and development of biosimilars in the U.S. This issue brief explores the current landscape of scientific evidence on switching between biosimilar and reference products as well as issues affecting the perception of biosimilar and interchangeable products. Consideration is given to studies that came close to following the recommended “three-switch” guidance. There is also a focus on product-class specific switching evidence.

Key Findings: The overwhelming majority of trials conducted during biosimilar development support the fact that there is no evidence of safety and efficacy concerns when switching from or to a reference product. The absence of evidence for safety and efficacy of concerns is mirrored in real-world settings as well. This growing evidence base has implications for regulatory requirements to demonstrate interchangeability while also revealing the continued difficulty of demonstrating interchangeability via a substantial clinical comparative assessment.

Policy Recommendations: To help advance biosimilar development, the FDA should consider opportunities for increased regulatory flexibility in interchangeability determinations for well understood products. Starting with drug classes where the evidence of clinical equivalence supporting interchangeability is strongest, FDA should consider a pathway to market that does not require switching studies on top of requirements to demonstrate biosimilarity. Working with international regulatory bodies, the FDA should explore how to further utilize post-market data from the U.S. and elsewhere in the world, including requiring post-market studies using real-world data on the approved interchangeable product, which would further ensure that the product is safe and effective for switches. Alternatively, outlining a clear process of demonstrating biosimilarity then utilizing post-market real-world data collection to demonstrate interchangeability could be considered. FDA should also consider a clear path to reduce the need

for bridging studies for reference products from other countries and work closely with international regulators to harmonize regulatory requirements for biosimilar products. FDA can continue to work with other federal agencies, disease specific professional societies, and patient organizations to develop succinct and easily understandable education material to increase provider and patient comfort with these products. Additionally, educational material should clarify that interchangeability is only relevant for products dispensed in retail pharmacy settings.

Congress has demonstrated bipartisan interest in seeing increased adoption of biosimilars to benefit patients. As they evaluate user fee reauthorization legislation, including BsUFA III, Congress should also re-evaluate whether the unique U.S. interchangeability designation is accomplishing its desired goals. An alternative regulatory model, more in line with the rest of the world and the growing U.S. and global experience with biosimilars, would focus on biosimilarity and have a clear scientific foundation for any restrictions on interchangeability.

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Introduction

Biologic drugs are medical products developed from living organisms and include treatment classes such as monoclonal antibodies, insulin, vaccines, and other products. The Biologics Price Competition and Innovation Act (BPCIA) 2009 provided a pathway for the United States Food and Drug Administration (FDA) to approve biosimilars for biologics already approved, known as reference products.¹ Approval through the abbreviated regulatory process permits the biosimilar to be used for any indication present on the reference product label subject to existing patent and exclusivity protections. The typical mechanism for this approval process is through the 351 (k) pathway. Biosimilars are evaluated against an approved reference biological product using two criteria. The first is whether the biosimilar is “highly similar” to the reference product. The second is whether the biosimilars possess “no clinically meaningful differences” to the reference product. As of September 2021, the FDA has approved 31 biosimilars for 11 reference biologics.²

Biosimilar manufacturers can also choose to apply for an interchangeable designation. Achieving the interchangeable designation permits the biosimilar to be substituted for the reference product in the retail pharmacy setting. Interchangeability designations are a potential path for increased biosimilar adoption and may help lower healthcare spending. However, until recently biosimilar developers did not use this pathway because the requirements and benefits for developers were uncertain, the process takes longer, and the costs are higher.

The BPCIA requires that an interchangeable product satisfies three criteria. First, the interchangeable product must meet the previously mentioned criteria for biosimilar approval to the reference product—being highly similar and possessing no clinically meaningful differences. Second, the interchangeable product must be expected to produce the same clinical result as the reference product in any given patient. Third, for a product administered more than once, the risk of switching between a reference product and an interchangeable product must not be greater than the risk of using the reference product without switching. FDA has interpreted this last requirement by concluding that a switching study is generally expected for risk assessment. Such studies are expected to contain at least two alternating exposures of the proposed interchangeable product and the reference product resulting in at least three switches.

In effect, the BPCIA provided a mandate to FDA to assure that any approved biosimilar is clinically equivalent to the reference product, yet to also describe a further process for demonstrating that patients can switch safely and effectively between a biosimilar and the reference product.

In facilitating development and regulatory approval of interchangeable products, the FDA has issued various guidance documents clarifying the requirements for achieving interchangeability. These guidance documents have been released in part due to biosimilar developer and other

stakeholder feedback that clear guidance from the FDA was needed. In December 2018, in response to industry questions on biosimilar and interchangeable product development as outlined in the BPCIA, the agency disseminated a guidance as a series of questions and answers.³

In 2019, the FDA released a general guidance on demonstrating interchangeability for industry sponsors.⁴ Notably, this guidance sets the agency's expectation that a switching study or studies will be presented as part of an application for a new interchangeable product. The next disseminated FDA guidance, a draft guidance released in November 2019, applied only to insulin products seeking biosimilarity and interchangeability approval.⁵ These recommendations included a suggestion that comparative clinical immunogenicity studies were unlikely to be needed for a proposed interchangeable product that already demonstrated biosimilarity to a reference product.

Subsequently, in February of 2020, the FDA helped to clarify the process for applying for a biosimilar or interchangeable product that has fewer indications than the reference product.⁶ In November 2020, the FDA published a Q&A formatted guidance document that addressed questions related to the regulatory review process specifically on interchangeable biosimilar products.⁷ Most recently, in September 2021, the FDA released an update to the Q&A guidance originally published in December 2018.⁸ In the updated Q&A the agency noted that sponsors of a proposed injectable biosimilar or interchangeable product can show their product has the same strength by showing their product has the same total content and concentration of drug substance as the reference product.

The first approval of an interchangeable product occurred in July 2021. SemGlee, a biosimilar product to insulin glargine reference product Lantus, had been previously approved as a biosimilar in June 2020 under the generic 505(b)(2) pathway.⁹ Based on the draft FDA guidance for proposed interchangeable insulin products, this approval would not require a switching study. However, the sponsor for SemGlee, Mylan (now Viatris), had previously supported a Phase 3 study to assess the efficacy and safety of switching between a reference insulin glargine product and SemGlee (INSTRIDE 3).¹⁰ INSTRIDE 3 was conducted prior to the FDA guidance being released and was used as supplementary data for demonstrating interchangeability by Viatris. Analytic data and pharmacokinetic (PK) and pharmacodynamic data comprised the majority of evidence reviewed by the FDA for approval of the interchangeability designation.

More recently, in October 2021, the FDA approved Cyltezo, a biosimilar product to adalimumab reference product Humira.¹¹ Cyltezo was previously approved as a biosimilar in August 2017 and will be commercially available beginning July 2023. It is the first interchangeable monoclonal antibody product approved by the FDA. The sponsor for Cyltezo, Boehringer Ingelheim, conducted a Phase 3 switching study – VOLTAIRE-X, a randomized clinical trial that examined differences in PK, safety, immunogenicity, and efficacy after multiple switches between Humira and Cyltezo.¹² Results from VOLTAIRE-X were used as supporting evidence by Boehringer Ingelheim in seeking approval by the FDA for the interchangeability demonstration. Another biosimilar product to Humira, AVT02, also underwent a Phase 3 switching study as part of its development by Alvotech.¹³ Alvotech announced top line results for the Phase 3 trial, which

assessed differences in PK, safety, immunogenicity, and efficacy after multiple switches between Humira and AVT02.¹⁴

While there are now two interchangeable biosimilars, there are still many lingering questions regarding interchangeability in the broader discussion surrounding use of biosimilars in the U.S. So far, no interchangeability designations have been granted to biosimilars that did not conduct Phase 3 switching studies that tracked clinical outcomes for randomized patients – a costly step. Especially in areas besides insulins, among the simplest biologics, there is uncertainty about the evidence of switching between biosimilars and reference products and what gaps exist in the research. The necessity of requirements to demonstrate interchangeability is also subject to scientific debate, especially as more evidence on biosimilar substitution accumulates worldwide. Furthermore, the existence of both the interchangeability and biosimilarity designations has created perception issues among patients and providers. Additionally, interchangeability is only relevant for products dispensed in a retail pharmacy setting and such products represent only a subset of biologic products. Concerns about non-medical switching, formulary driven changes that occur for reasons other than safety, efficacy, or compliance by the patient, also contribute to uncertainty around interchangeable products. All of this uncertainty has implications for biosimilar development and adoption.

While the intent of BPCIA may have been to set a national science-based standard for interchangeability, with some uncertainty about the importance of the distinction between clinical equivalence and interchangeability, states have taken action. Since 2013, at least 45 U.S. states have passed laws governing interchangeable substitution in different ways.¹⁵ Most of these regulations generally allow the substitution of interchangeable products, but place more stringent requirements than those instituted for generic drugs. These more stringent requirements permit the prescriber to prevent pharmacy substitution and, in at least 20 states mandate patient notification before switching as well. Individual state statutes are worded differently and some require that providers “must be notified” while others stress pharmacists will “communicate with” providers.

The regulatory agency-based interchangeability designation being linked to automatic substitution in the retail pharmacy setting is unique to the U.S. The European Medicines Agency (EMA) approves biosimilars but does not have authority on automatic substitution in the pharmacy setting. The EMA leaves the approval of biosimilars as interchangeable and policymaking on substitution to individual European Union (EU) member states. Some European countries have embraced biosimilar development—chief among them is Norway, where the NOR-SWITCH trial took place.¹⁶ Automatic pharmacy substitution in EU member states is mostly left to the prescribing physician, meaning switching often occurs only with medical supervision.¹⁷ The Therapeutic Goods Administration in Australia designates authority on switching to the Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC permits automatic substitution of a reference product to a biosimilar so long as the reference product is explicitly indicated on the Schedule of Pharmacy Benefits. The pharmacist communicates only with the patient but the prescriber may intervene requiring the pharmacist to contact the prescriber before substituting even a highlighted reference product. Health Canada approves biosimilars and takes an official

position that switching between a reference product and biosimilar should result in no change in safety or efficacy for the patient.¹⁸ Large scale switches have been occurring in Canada on a province-by-province basis. Brazil and Japan's regulatory agencies hold that interchangeability is a matter of clinical practice with physicians directly involved in any switching.

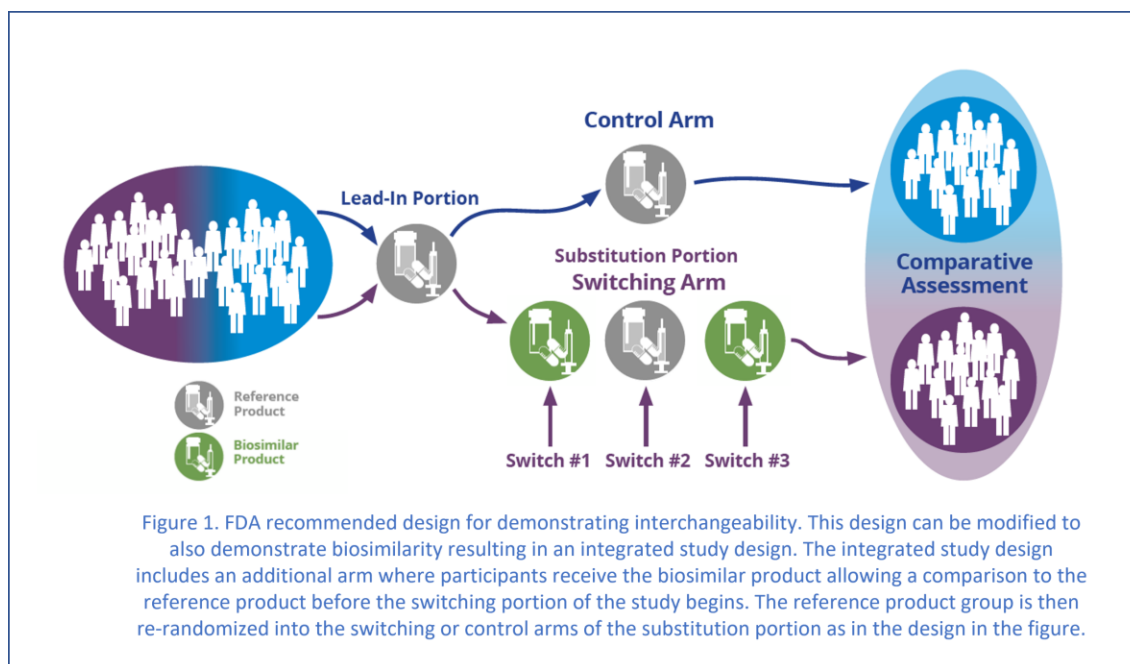
FDA has taken other actions relevant to interchangeability and biosimilar adoption and switching. In March 2019, the FDA clarified that nonproprietary names for all new biologics should contain a unique four-letter suffix.¹⁹ A biosimilar and its reference product would share a core name as they both contained the same originator product. However, the four-letter suffix would help distinguish between the biosimilar and reference products. This was intended to support pharmacovigilance and to ensure that biosimilar and reference products were not mistaken for one another. Applications for proposed interchangeable products are required to have a nonproprietary name containing a four-letter suffix.

In addition to published guidance document related to interchangeability, the FDA has also recently produced a suite of new educational materials for health care providers intended to provide information and support science-based use of biosimilars,²⁰ in response to the mandate for such educational materials in the Advancing Education on Biosimilars Act of 2021.²¹ The FDA timed the release of the educational materials to coincide with the first interchangeable biosimilar approval.

This issue brief highlights the expanding scientific evidence regarding biosimilar substitution in retail pharmacies, and the appropriate role of interchangeability as a regulatory standard. With relatively little experience with biosimilars, especially complex molecules like monoclonal antibodies with complex manufacturing processes, patient and clinician concern about switching was understandable at the time of the BPCIA. Since that time, considerable clinical evidence has accumulated related to the biosimilarity requirement of clinical equivalence, alongside experience with the practical impact on biosimilar adoption and cost and patient outcome implications of different approaches to interchangeability around the world. The review of this evidence is divided into four parts. The first part explores the FDA three-switch design for demonstrating interchangeability. The second part provides an overview of four major literature reviews on the safety and efficacy of switching between reference products and biosimilars. The third part breaks down the scientific evidence on switching for individual biosimilars grouped by the diseases the reference products were developed to treat. Finally, the fourth part explores evidence from real-world data sources. Our analysis follows on and expands Duke-Margolis brief detailing what the U.S. can learn from biosimilar adoption, development, and regulation in Europe.²² Based on this accumulating evidence, the brief provides recommendations for potential regulatory or legislative reforms for the current interchangeable biosimilar designation and discusses how regulatory approaches to interchangeability affect the clinical acceptance of biosimilars. This brief is intended for FDA and congressional policymakers to utilize for future decision-making on preserving, reforming, or removing the BPCIA-defined interchangeability designation.

Current Landscape for Evaluating Switching

Three-switch design



Current FDA guidance on demonstrating interchangeability is clear on its recommendations for switching studies. The agency suggests a switching study should contain at least two alternating exposures of the proposed interchangeable product and the reference product resulting in at least three switches (Figure 1). The final switch is specified to occur from the reference product to the interchangeable product with the comparative assessment occurring after the final exposure period to the proposed interchangeable product. Importantly, the FDA also advises to include a lead-in period of sufficient duration, where all study participants are given the reference product. Concerning the comparative assessment, the agency notes that PK and pharmacodynamic endpoints should comprise the primary analysis while safety, immunogenicity, and efficacy comprise the secondary endpoints. A recent simulation published by the FDA concludes that three switches are optimal for detecting the impact of anti-drug antibodies (ADA) on the PK endpoints.²³ This conclusion was based off varying the percentage of ADA incidence caused by switching and then calculating the probability of concluding PK similarity. The simulation also found that anti-drug antibodies induced during the initial lead-in period can have a confounding effect on the PK analysis between the switching and non-switching arms of the trial. It also appears that if the prevalence of anti-drug antibodies is already quite high then switching studies may not prove useful in detecting significant changes in anti-drug antibody prevalence. The FDA researchers note that actual data from a switching clinical study were not available for inclusion and that the simulation model is based on general PK characteristics for a monoclonal antibody. While the authors acknowledge this study had several

limitations, it suggests that a range of factors can influence the outcome of switching studies and highlights the potential complications in demonstrating interchangeability.

Furthermore, the agency recommends a design for an integrated study to support determinations of both biosimilarity and interchangeability. The initial time period of the study is intended to determine if the product satisfies the biosimilarity requirements. Following the end of this initial time period, the participants in the reference arm of the trial are re-randomized to either continue receiving the reference product or switched to the proposed interchangeable product. At least three switches are needed in the switching-arm portion of this part of the trial. Enough participants have to be enrolled in the integrated study design in order to evaluate appropriate endpoints for the biosimilarity and the interchangeability portions of the trial.

While these recent FDA publications have refined the “three-switch” design, an interchangeability determination continues to require an additional clinical study to evaluate switching for all types of biosimilars besides insulins (pending finalization of draft guidance). The time and cost of these requirements, alongside the uncertainty about the practical impact of an interchangeability designation in practice given varying state laws and relatively limited but growing adoption of biosimilars in the U.S. market, are likely contributors to the limited use of interchangeability approvals in the U.S. biosimilar market to date. In turn, this limited adoption has implications for switching and thus for ease of entry, ability to gain market share, and price competition in U.S. biologics markets.

Literature reviews of switching

As noted above, despite limited adoption of interchangeability approvals in the U.S., substantial switching from originators to biosimilars has occurred, especially outside the U.S. Four wide-ranging reviews have examined this growing evidence. A 2012 review by Ebbers *et al.* examined the safety of switching between biosimilar and reference products in the following product class categories: human recombinant growth hormone, erythropoietin, and granulocyte colony stimulating factors.²⁴ The authors reviewed 58 clinical trials encompassing 12,039 participants and 193 adverse event summaries. They did not find evidence of safety risks resulting from switching between reference and approved biosimilar products. A 2018 comprehensive review by Cohen *et al.* of studies featuring single or multiple switches from reference biological products to biosimilars also found no evidence of safety concerns, risk of immunogenicity or loss of efficacy for switching.²⁵ The review evaluated 90 studies that enrolled 14,225 total participants utilizing seven biological products treating 14 disease indications. Overall, 87 of the 90 studies featured only one switch. The most recent systematic review evaluating switching between biosimilars and references products, by Barbier *et al.*, compiled 178 studies totaling nearly 21,000 switched patients. Seventy-nine percent of the studies originated from real-world settings defined as being generated from outside the clinical development of the product.²⁶ Once again, most of the studies consisted of a single switch with only six studies having a multiple switch design. Ultimately, the authors agreed with these two previous landscape review groups that there is no direct evidence that switching from a reference product to a biosimilar results in major safety

issues. In addition, this more recent review also agreed with Cohen *et al.* that there is no direct evidence that switching contributes to major differences in efficacy or increases the risk of immunogenicity.

On the other hand, a review published in 2018 by McKinnon and colleagues takes a different point of view on the safety of switching.²⁷ After examining 57 switching studies (composed of 23 randomized studies and 34 observational studies), the authors noted that the majority of studies found no safety issues between switching but also that 38 of the 57 studies featured fewer than 100 patients. The reviewers concluded that there are major evidentiary gaps surrounding the safety of switching between biosimilars and reference products. Specifically, they highlighted the need for larger cohorts and more long-term studies that generate sufficient statistical power for efficacy, immunogenicity risk, and safety considerations. In particular, only nine of the 34 observational studies reviewed by the authors evaluated immunogenicity.

These four reviews of switching between reference products and biosimilars suggest a set of high-level conclusions. The first is related to the quality of many published switching studies. Most studies only look at one switch and therefore do not match FDA recommended guidance including the utilization of three switches, and do not assess immunogenicity. Furthermore, these studies enroll smaller numbers of patients and may lack long-term follow-ups, and many are not randomized so may be more likely to be confounded (e.g., more or less stable patients may be more likely to switch). This complicates reaching definitive conclusions, including with regard to whether patients living with chronic conditions who may face multiple switches can do so without clinical consequences. Second, the heterogeneity in design of switching studies highlights the value of further, more standardized product-specific and disease-specific studies. Switching studies to date are often descriptive and are thus not well designed to detect small but meaningful changes in efficacy or safety. They may also lack randomization or even a control treatment arm. These one-switch observational studies consequently have important limitations in assessing the safety, efficacy, and immunogenicity when taking patients off a reference product and putting them on a biosimilar.

Further, a loss of efficacy is commonplace for specific products and in the treatment of certain diseases. Parsing out whether changes in efficacy are due to switching or are product-specific is only accomplished with intentionally designed studies or trials.

Finally, prospective and retrospective observational cohorts makeup a substantial chunk of the available evidence. Most of these studies were conducted in Europe, where biosimilar adoption is more widespread, have health care systems and data collection well-suited for observational studies. In addition, manufacturers may be hesitant to conduct and patients hesitant to enroll in clinical studies assessing switching between reference and biosimilar products. For the former, as we have noted the effort needed to achieve an interchangeability designation may not be worth the time and cost. For the latter, there may be hesitation to shift off a product that is working for them – and more willingness to participate if it does not seem to be. Overall, while the growing body of switching studies contribute to an evidence base that has detected little evidence of serious or even minor impacts of switching on safety and effectiveness, these

switching studies largely do not approach the regulatory standards suggested by the FDA for an application for a proposed interchangeable product.

Product-class specific switching evidence

Evidence on the impact of switching is considerably more extensive for a limited set of product classes with relatively early and substantial biosimilar penetration, with more product-specific randomized controlled trials and open-label extension trials. There are two randomized controlled trials that examined switching between reference insulin glargine product Lantus and two different biosimilar products. The first of these switching trials was between Lantus and biosimilar product LY IGLar.²⁸ No difference in efficacy or safety outcomes was demonstrated when switching type 1 or type 2 diabetes patients between the two products. The other switching trial with Lantus was the aforementioned INSTRIDE 3 trial. This trial found that patients can switch between Lantus and biosimilar product, SemGlee without harm.²⁹ This phase 3 trial assessed the safety and efficacy of switching between the two products and employed the FDA three switch design. The non-switching arm received the reference product and the switching arm began on reference product, were switched onto SemGlee, subsequently switched back to the reference product, and finished the study on SemGlee. Differences in glycated hemoglobin (HbA1c) were used as primary endpoint with no changes seen between the two treatment arms.

Furthermore, trials administering participants reference products for smaller biologics somatropin (Omnitrope), epoetin alfa (Eprex), filgrastim (Neupogen), and follitropin alfa (GONAL-f), all found no differences in safety and/or therapeutic efficacy compared to participants switched to biosimilar products. Two of these trials included multiple switches with one designed to assess the efficacy and safety between an epoetin alfa reference product, Erypo, and a biosimilar Retacrit.³⁰ Another multiple switch trial examined the efficacy, safety and immunogenicity of switching between Neupogen and biosimilar product Ziextenzo.³¹ Participants were stratified into four treatment arms for six cycles. Two of these arms alternated between the reference and biosimilar products, for six cycles, leading to five total switches within each arm.

The most prominent product class for studies involves switching from reference products to biosimilars are monoclonal antibodies – specifically those that act against Tumor Necrosis Factor alpha (TNF-alpha) in participants with auto-immune diseases. Infliximab reference product Remicade is an antibody targeting TNF-alpha that has been subjected to nine randomized controlled or open-label extension trials designed to evaluate safety related to switching from Remicade to several biosimilars. The most notable study is the NOR-SWITCH trial that looked at efficacy and adverse effects over time in participants after switching from Remicade to infliximab biosimilar product Inflectra (also known as Remsima in the EU).³² Disease worsening was found to be similar in the participants treated with Remicade as compared to the group switched to Inflectra. Likewise, the single-switch trials PLANETAS³³ and PLANETRA³⁴ demonstrated no loss of efficacy or increase in adverse effects for rheumatoid arthritis and ankylosing spondylitis participants treated with Remicade or Inflectra.

Other TNF-alpha inhibitors with a wide range of indications that have also been examined in several switching studies include adalimumab reference product Humira and etanercept reference product Enbrel. Adalimumab has been examined in eight switching studies that are randomized controlled trials or open label-extension trials. Five of the studies involved only one switch and all of them found no difference in safety, efficacy, and immunogenicity when switching between Humira and a biosimilar. Two of the trials including multiple switches, ADACCESS³⁵ and ARABESC-OLE³⁶, demonstrate evidence for long-term safety, efficacy, and immunogenicity when switching between Humira and a biosimilar product. The ADACCESS trial involved four total switches between Humira and the biosimilar product Hyrimoz. One arm of this trial approach meets the FDA guidance for assessing biosimilarity and interchangeability. The third and most recent trial, VOLTAIRE-X, was a randomized clinical trial that primarily examined the PK similarity between participants, with moderate-to-severe chronic plaque psoriasis treated continuously with Humira and those who alternated between Humira and biosimilar product Cyltezo.³⁷ Secondary outcomes for the trial assessed the safety, immunogenicity, and efficacy of alternating patients between the two products and treating patients continuously with Humira. The trial design for VOLTAIRE-X followed the FDA recommended three-switch design with the switching arm beginning on Humira before being switched to Cyltezo, switched back to Humira and switched for the final time to Cyltezo. Results from VOLTAIRE-X found similar primary and secondary outcomes between Humira and Cyltezo.

Etanercept is approved for treatment of five indications and has been investigated in five switching studies that are either randomized clinical trials or open-label extension trials. Four of the five switching studies enrolled participants with rheumatoid arthritis finding no safety or efficacy disparities when participants were switched once from Enbrel to a biosimilar product. The fifth study was the EGALITY trial that involved four switches between Enbrel and a biosimilar GP2015 in participants with plaque psoriasis.³⁸ No differences in safety or immunogenicity were found due to the repeated switches reinforcing the findings of the four single switch studies in participants with rheumatoid arthritis.

In addition to TNF-alpha inhibiting monoclonal antibody products, biosimilars of certain monoclonal antibodies used to treat cancer have also demonstrated safety and efficacy when compared clinically to their reference products. Five trials have examined switching between rituximab reference product Rituxan and four different biosimilars. All of the switching trials enrolled participants with rheumatoid arthritis and no difference in safety or efficacy was found when switching participants from Rituxan to a biosimilar product. Likewise, in patients with HER-2 positive early-stage breast cancer, no safety concerns were found when switching from a trastuzumab reference product, Herceptin, to biosimilar product, Kanjinti.³⁹

Thus, for a more limited set of biologics where there is relatively extensive evidence from trials with regulatory implications, including randomized clinical trials and open-label extension trials, there is evidence supporting little risk of substantial safety and efficacy issues with switching from a reference product to a biosimilar or vice versa. These findings are consistent across a wide range of biologics, from relatively small molecules like insulins to large, complex biologics like monoclonal antibodies.

Global Real-World Data on Substitution

With improving data quality and methods, thoughtfully designed observational studies using well-understood real-world data present a promising avenue for augmenting the evidence on switching. Many biosimilars are already approved in the EU and undergo robust pharmacovigilance in a system that encompasses quality planning, quality adherence, quality control and assurance, and quality improvements.⁴⁰ Europe's leading experience in biosimilar development can inform real-world evidence on interchangeability in the U.S. For example, as noted above, in their review on switching between biosimilar and reference products, Ebbers and colleagues noted that they found no difference in safety disparity between clinical trial data and data mined from pharmacovigilance databases monitored by the EU.⁴¹ This review was specific for recombinant growth hormones, erythropoietins, and granulocyte colony stimulating factors. Its findings are consistent with the current EMA assessment that there has been no documentation of differences in adverse effects between biosimilars and reference medical products.⁴² The EU pharmacovigilance databases have monitored over 700 million patient days of patient exposure to biosimilars as of 2017.⁴³ Observational studies on descriptive biosimilar usage and switching in Italy from local health units also showcased widespread and increasing usage of biosimilars and switching to and from reference medical products for both erythropoietins⁴⁴ and granulocyte colony stimulating agents.⁴⁵ In addition to observational usage studies, regional health databases in Italy have shown switching from reference products to biosimilars to be safe and effective for erythropoietins for patients living in Treviso⁴⁶, Lazio⁴⁷, and four distinct Italian geographical areas.⁴⁸

The most recent assessment of the real-world evidence landscape for switching between reference and biosimilar product was also performed by Barbier and colleagues.⁴⁹ A total of 140 of the 178 studies reviewed by the authors were nonrandomized studies generated from real-world use of the biosimilar candidate. Some of the study designs included parallel arm, nonrandomized, nonblinded controls, but most studies utilized a single arm design switching patients from a reference product to a biosimilar. This single arm design was often influenced by purchasing decisions made by health care facilities. The bulk of these studies, 91 in total, analyzed switching from reference infliximab product Remicade to a biosimilar product. Most of the time that biosimilar product was Inflectra. Ultimately, the reviewers found the majority of studies supported switching from reference products to biosimilars to be safe with no loss in efficacy or risk of immunogenicity. Real-world data referencing pharmacovigilance databases, registries, and electronic health records along with prospective multicenter studies present many mechanisms for screening of safety, effectiveness, and potentially immunogenicity when switching between a reference medical product and a biosimilar. Having surveillance infrastructure in place for biosimilar and interchangeable products will provide the opportunity to learn from multiple switches if they occur or help note if they do not happen that often.

Clinical Perception of Biosimilars and Interchangeability Designation

Distinct biosimilarity and interchangeability designations were created in response to concerns that switches might have consequences for patients. But the challenges in developing a clinical foundation for the distinction, beyond simply requiring randomized studies of multiple switches, has potentially contributed to perceptions of safety issues among providers and patients, even as multiple types of evidence supporting the safety of switching among clinically equivalent products continues to accumulate.⁵⁰ In addition to obstacles from technical and regulatory concepts, other factors further complicate perceptions of biosimilar and interchangeable products. Namely, that the interchangeability designation is only relevant for retail pharmacy settings. The non-proprietary naming of biosimilar products is also an added wrinkle to process for health care providers. While the FDA guidelines to add four letter suffixes were designed to alleviate pharmacovigilance confusion, they may also contribute to additional confusion.⁵¹ If the additional requirements to demonstrate interchangeability do not have a clear scientific foundation, the existence of the additional designation will understandably continue to create concerns about the true equivalence of biosimilars to their reference products.

The negative perceptions surrounding biosimilars and interchangeability may ultimately lead to negative outcomes for patients. Participants in trials switching between a reference medical product and biosimilar have demonstrated these concerns, which are known as the nocebo effect. Using the DANBIO registry, an infliximab biosimilar was not associated with a negative impact on disease activity, yet the retention rate for the biosimilar was lower than the reference medical product; the authors suggested this might be due to the “nocebo” effect.⁵² The nocebo effect is a phenomenon where participants have negative perceptions of a treatment leading to negative outcomes. Also, during a multicenter prospective study evaluating safety and effectiveness of switching from infliximab to a biosimilar (BIO-SWITCH), 24% of participants stopped taking the biosimilar.⁵³ These negative perceptions may lead to languishing acceptance of biosimilar and interchangeable products in the U.S.

Discussion and Policy Implications

Evidentiary needs and potential for regulatory reforms

Growing clinical evidence generally suggests that switching from a reference product to a biosimilar is safe, particularly in the most likely scenario of a single switch from a reference product to a biosimilar. Randomized trial data on multiple switches are much less available, but limited evidence from these studies also suggests that switching is safe. At the same time, improvements in analytical methods and technologies are enabling ever more specific and precise characterization of biologics. These advancements help to reduce residual uncertainty, further limiting the additional value of clinical studies. In a recent policy update⁵⁴, regulators in the UK said that comparative efficacy trials are usually not required for demonstrations of biosimilarity. In the U.S., FDA guidance on interchangeability already allows for sponsors to justify not conducting a switching study. Starting with drug classes where the evidence of clinical equivalence supporting interchangeability is strongest, FDA could clarify that switching studies

may no longer be required for interchangeability on top of the requirements to demonstrate biosimilarity and provide guidance to sponsors on how to justify this. This approach would essentially establish a product as biosimilar and interchangeable at the same time based on the data submitted to demonstrate biosimilarity. FDA has already taken steps to recommend this approach in the draft guidance for insulin products. For products with more complex biosimilars or manufacturing processes, or where specific evidence of immunogenicity issues has emerged, studies with at least three switches could be more clearly justified as contributing potentially valuable evidence for the use of the product in the U.S. health care setting.

Pairing an evidence-based expansion of aligning the clinical equivalence and interchangeability determinations with requirements and supports for collecting post-market, real-world data on the approved interchangeable product could provide a more efficient approach to assuring that the biosimilar is safe and effective for switching. Alternatively, outlining a clear process of approving a product as a biosimilar then utilizing post-market real-world data collection to demonstrate interchangeability could be considered. Sponsors already collect real-world data to justify why payers should use their products so formal post-market regulatory requirements to collect real-world data would not be a significant additional burden.⁵⁵ These approaches may offer a compromise by providing data to clinicians that want to ensure therapies are safe and effective while minimizing the need for burdensome and perhaps unnecessary clinical trials. The U.S. should develop post-market monitoring capacities building on existing programs like the FDA's Sentinel Initiative and Biologics Effectiveness and Safety System (BEST). These programs are already conducting safety surveillance and increasingly sophisticated observational comparisons.

Similarly, the barrier to entry created by requirements that would-be biosimilar and interchangeable products be compared to U.S. based reference products or be subject to additional bridging studies could also be modified, building on the rigorous processes already in place to ensure manufacturing changes do not impact the safety or efficacy of a biologic product.⁵⁶ FDA could reduce requirements for bridging studies for reference products from other countries, especially in conjunction with further collaboration with non-US regulators to harmonize regulatory requirements for biosimilar products.

The recently released Biosimilar User Fee Amendments III (BsUFA III) commitment letter offers resources and avenues to consider these and other approaches to streamline the approval of interchangeability products.⁵⁷ In addition to guidance on interchangeable packaging, labeling, advertising considerations, and post-approval manufacturing changes to approved biosimilar and interchangeable products (several of these documents are not scheduled to be issued until FY 2024/2025), FDA will also pilot a regulatory science program, beginning in FY2023, intended to facilitate the development of biosimilar and interchangeable products. Specifically, for interchangeable products, this program will "investigate and evaluate the data and information (including Real World Evidence) needed to meet the safety standards for determining interchangeability." This work is slated to include evaluating methodologies to predict immunogenicity by advancing the knowledge of analytical, pharmacological, and clinical

correlation as they relate to interchangeability. This pilot program should be used to consider and advance the recommendations outlined here.

Potential legislative reforms

Since creating the biosimilar and interchangeable pathways, Congress has expressed interest in seeing increased adoption of biosimilars to benefit patients. As they evaluate user fee reauthorization legislation, including BsUFA III, they should also re-evaluate whether the unique to U.S. interchangeability designation is accomplishing the desired goal, in light of the extensive experience and evidence on the general safety of switching over the past decade. With only two interchangeable products approved in 10 years, the current designation does not appear to be contributing much to the adoption and use of biosimilars.

Addressing perception challenges

Perception challenges remain a significant barrier to the increased adoption of biosimilar and interchangeable products. The ability of biosimilar and interchangeable products to offer lower prices is a powerful driver for adoption, but safety and efficacy concerns understandably remain paramount. With growing evidence available on both equivalence and the safety of switching, the regulatory distinctions between “biosimilar” and “interchangeable” likely reinforce concerns that biosimilars may not be clinically equivalent in a critical respect – the ability to switch between them. Without more direct efforts to clarify the science-based meaning of the distinction, it is unlikely that educational initiatives will substantially change these perceptions. FDA should continue to work with other federal agencies, disease specific professional societies, and patient organizations to develop succinct and easily understandable education material to increase provider and patient understanding about the practical clinical distinctions between clinical equivalence and interchangeability. Additionally, educational material should clarify for patients that interchangeability is only relevant for products dispensed in pharmacy settings. Sponsors should also strive for clear communication about their biosimilar and interchangeable products and the FTC should continue to reign in sponsors that produce misleading material on biosimilarity and interchangeability.

FDA’s suffix policy may also contribute to perceptions that are not aligned with the latest scientific evidence on clinical equivalence and interchangeability. Under the current paradigm, two products have different non-proprietary names even if they are interchangeable. This is in contrast to generic drug naming standards. While the ability to track particular products is important to assess manufacturing issues, the agency should evaluate whether there are now other ways to support pharmacovigilance that do not suggest equivalent products have significant clinical differences, especially for interchangeable products.

Conclusion

While the U.S. biosimilar market is expanding, it continues to lag behind that of Europe, and appears to lag behind the growing evidence on the safety of switching and the clinical equivalence of biosimilars and originator products. This issue brief provides recommendations intended to address features of the unique U.S. interchangeability designation to further advance biosimilar adoption based on this growing evidence. Implementing appropriate regulatory flexibilities for well understood therapies, expanding the use of real-world evidence to collect post-market data, and re-evaluating the current suffix-based naming policy are potential avenues for the FDA to consider. Meanwhile, the FDA and the FTC must continue working together to address deliberate misinformation in advertising about biosimilar and interchangeable products. As Congress considers the next round of user fee reauthorization, it should consider whether the interchangeable designation is accomplishing the desired goal.

These recommendations may help streamline the regulatory processes for biosimilar and interchangeable products and thereby advance the development of these products. However, significant barriers also exist within the payment realm. Companion briefs in this series will explore some of these issues, including rebate walls and how interchangeability might play a role at lowering those walls. Interchangeable product developers may also have to contend with reference product developers shifting their formulations or concentrations to move the market away from the interchangeable version, potentially limiting the uptake of the interchangeable product.

Disclosures

Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomiQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

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