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REVIEW ARTICLE

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No two classes of biosimilars: Urgent advice to the US Congress and the FDA

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Abstract

What is known and objective: The United States is the only country with legislation to approve two classes of biosimilars. One has "no clinically meaningful difference" from the reference product, and when it is tested for switching and alternating, it can receive an interchangeable status. The objective of this review is to establish whether it is possible from the switching and alternating studies to evaluate additional safety or efficacy.

Methods: Analysed published data to ascertain if the testing with switching and alternating provide additional proof of safety or efficacy. Political and scientific rationale of creating a new class of biosimilars and how this affects the confidence in biosimilars.

Results and discussion: There is no safety or efficacy concern when switching or alternating biosimilars with the reference product. Unfortunately, the rationale for interchangeability is more political than scientific, and it has brought more confusion and mistrust in using biosimilars in the United States.

What is new and conclusion: The US Congress is requested to remove the interchangeability clause from the Biological Price and Competition Act to enable faster acceptance of biosimilars and remove the threat of lack of confidence in the safety of biosimilars.

KEYWORDS
alternating, biosimilarity, biosimilars, BPCIA, clinical equivalence, EMA, FDA, interchangeability, interchangeable biosimilars, substitution, switching, US Congress

1 | INTRODUCTION

The US Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created biosimilars with "no clinically meaningful difference" with their reference product and then further tested them in a switching and alternating protocol with the reference product to declare them interchangeable.[1] However, unlike the generic chemical drugs, the biosimilars could not be substituted for the reference product.[2] While biosimilars are widely substituted for the reference product in Europe and the rest of the world, this is not the case in the United States, where the BPCIA created a separate category of Interchangeable Biosimilars, requiring a sponsor to show that the proposed interchangeable product "is biosimilar to the reference product" to support a demonstration of interchangeability. When a product is originally licensed as a biosimilar, the licensure might be used to support a demonstration of interchangeability under this statutory requirement. Furthermore, an application for an interchangeable product must include information sufficient to establish that the proposed interchangeable

product "may be expected to yield the same clinical result as the reference product in any particular patient," according to section 351(k)(4)(A) of the PHS Act. Sponsors must submit data and information demonstrating that the proposed interchangeable product would achieve the same clinical result as the reference product under all of the reference product's approved use conditions.[3]

With two classes of biosimilars in the United States, a severe challenge has arisen in making biosimilars adopted in Europe and the rest of the world. Biosimilars are approved with the FDA assurance that "there is no clinically meaningful difference" with the reference product to give confidence to stakeholders in their safety and efficacy. However, creating another class of interchangeable biosimilars has shattered the confidence in biosimilars. Not all biosimilars can comply with the testing requirements for interchangeable biosimilars, like those administered only once, or the oncology products, where such studies cannot be completed. Much worse is the race to get the interchangeable status, whether it applies merely to demonstrate superiority, as it is now widely publicized. This is a sure downfall of biosimilars.

The FDA has approved only two interchangeable products, insulin glargine and adalimumab, taken repeatedly and subject to switching and thus substitution. Both products will receive 12-month exclusivity as a convertible, while the patients have no benefit. The entire exercise will benefit the companies who can afford to spend millions of dollars securing this status. The patients and the US government pay for the higher price of interchangeable, as anticipated if a more considerable investment is made to secure the approval.

In this paper, I have provided a critical analysis of the science and the politics of interchangeability and suggest how we can overcome the provisions in the BPCIA that are defeating the purpose of the BPCIA.

1.1 | Terminology

The terminology associated with the debate around interchangeable biosimilars needs clarification. In the EU, an exchange of a reference product for a biosimilar is termed *interchange*, and it can be initiated by a physician (termed *switching*) or a pharmacist (termed *substitution*)[4]; further, *interchangeable* in the context of biosimilars means an exchange conducted via *switching*.[5] In the United States, *interchangeable* means *substitution* at the dispensing level.

1.2 | Qualified products

Interchangeability in the United States applies to the biological products dispensed in a retail pharmacy setting and self-administered, a small category of biologics to treat rheumatoid arthritis, immunoglobulin-replacement therapy in primary immunodeficiency, beta interferons in multiple sclerosis, insulins, and so forth, and TNF blockers to treat psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.[6] The European Medicines Agency (EMA) approved the self-administration of omalizumab prefilled syringes in 2018. However, in the United States, it is still required to be administered in a clinical setting to abet the risk of anaphylaxis.[7] Other candidates in this category available for self-administration include mepolizumab, dupilumab, and benralizumab. The prescriber determines the substitution for all other biological products administered in the physician's office or hospital. It is often dictated by the formularies with the patient and even the prescriber having little involvement in making a choice.

1.3 | Testing

The testing undertaken in establishing biosimilarity with the reference product is extensive. It focuses on assuring analytical similarity as the primary test and the clinical pharmacology as the second test to declare a product biosimilar. Additional clinical efficacy is needed if there remains any uncertainty about biosimilarity. It is waived for some biological products with pharmacodynamic parameters, such as erythropoietin, GCSF, insulin, and similar products. Clinical testing does not mean efficacy testing, it could be another clinical pharmacology study,[8] but most developers have offered to conduct comparative efficacy testing. However, such studies were not necessary, primarily to support the marketing plans. Further testing to secure interchangeable status requires specific protocols involving at least three switches and alternating with the reference product.

1.4 | Focus

This paper aims to motivate the US Congress to remove the status of an interchangeable biosimilar from the BPCIA based on scientific arguments and real-world data. Unless the US Congress makes this amendment, the future of biosimilars looks bleak as the FDA has now started approving interchangeable biosimilars. In addition, the US FDA is advised to continue building confidence among the stakeholders on the utility of biosimilars—something the FDA has already begun doing. There are many other suggestions for the FDA that are detailed elsewhere.[9]

2 | THE POLITICS OF BIOSIMILARS

The 22nd Amendment to the Constitution took more than 200 years to get ratified by all States to limit the term of the presidency to two terms.[10] It took less than 10 years for all States and Puerto Rico to approve new legislation to control the substitution of interchangeable biosimilars, long before the first interchangeable product was approved in 2022.[11]

State statutes and agency or board guidelines have governed the use of brand-name and generic prescription products for decades. When and how generics may be substituted for brand-name prescriptions by pharmacists or others are among the state activities.

Eight states implemented the first round of biologics and biosimilar laws in 2013–2014, 4 years after the BPCIA was passed. (North Dakota, Oregon, Utah, and Virginia) (Delaware, Florida, Indiana, Massachusetts, North Dakota, Oregon, Utah, and Virginia), and the rest followed. Within 10 years, all 50 States and Puerto Rico had established how an interchangeable biosimilar product would be substituted in their jurisdiction.[11] In 2022, the FDA approved the first interchangeable product, and the state legislature will be tested whether they deliver what they are supposed to do—help or hurt the adoption of biosimilars. This is one of the main topics of this article.

The provisions of state legislation differ, but there are a few common elements and needs:

2.1 | FDA approval

Any biological product under consideration for substitution must first be approved as "interchangeable" by the US Food and Drug Administration or FDA. Two products have gained full FDA approval as interchangeable biosimilars: insulin glargine and bevacizumab, as of May 2022.

2.2 | Prescriber decides

By stating "dispense as written" or "brand medically necessary," the prescriber (such as a physician, oncologist, physician assistant, etc.) could prevent substitute.

2.3 | Pharmacist chooses

The pharmacist or the dispenser "may substitute" in most states but "must substitute" in Hawaii, Iowa, New York, Tennessee, Vermont, Washington, West Virginia, and Wisconsin. In addition, the pharmacist "shall substitute" in Minnesota, Nevada, and Rhode Island. There is a specific legal interpretation about the use of "shall" when the US Supreme Court allowed the Sandoz petition that claimed the use of "shall" means "may." However, the Court agreed only in this context since there were repercussions for not complying with the requirement of sharing the registration dossier of a biosimilar filing with the reference product company.[12]

2.4 | "Communication" versus "notification"

In measures passed in 2013–2014, the text normally stated that any permissible substitution performed at a pharmacy "must be notified" to the prescriber. The language in most 2015 bills has been changed to "communicate with," permitting a note in an electronic medical record (EMR), PBM records, or "pharmacy record that can be electronically accessible by the prescriber." (This would allow a physician to evaluate and compare the patient's experience without delaying the transaction.) No notification is required in Idaho.

2.5 | Consent of prescriber

The pharmacist cannot substitute without prescriber consent in Alabama, Alaska, Indiana, and South Carolina, before dispensing.

2.6 | Patient notified?

A substitute or switch must be communicated to each patient individually. State law may require patient agreement before making such a move in specific situations. Some consumer experts believe that providing notification or permission may deter people from using a biosimilar that has been licensed. Patient consent is required in Alaska, Hawaii, Louisiana, South Carolina, and Utah.

2.7 | Records

For two or 3 years, the pharmacist and physician must keep records on replaced biologic drugs. No record-keeping is required in California, Connecticut, Iowa, Massachusetts, Maryland, Missouri, Montana, New Hampshire, New Jersey, New Mexico, New York, Ohio, and Vermont.

2.8 | Immunity

Some state laws grant pharmacists legal immunity if they make a substitute following state biologics laws.

2.9 | Lists on the internet

The state must keep a public or online list of FDA-approved interchangeable items.

2.10 | Cost or pricing

Some legislation requires the pharmacist to explain the cost or price of the biologic and the interchangeable biosimilar. The enacted laws in Colorado, Georgia, Illinois, North Carolina, and Texas require any authorized or allowable substitution to have the lowest cost.

2.11 | The impact of the nature of the legislation is significant

If the prescriber can control substitution, then interchangeability status has little meaning. It is always within the domain of the prescriber to decide which product gets dispensed. These provisions essentially mute the interchangeability laws for biosimilars.

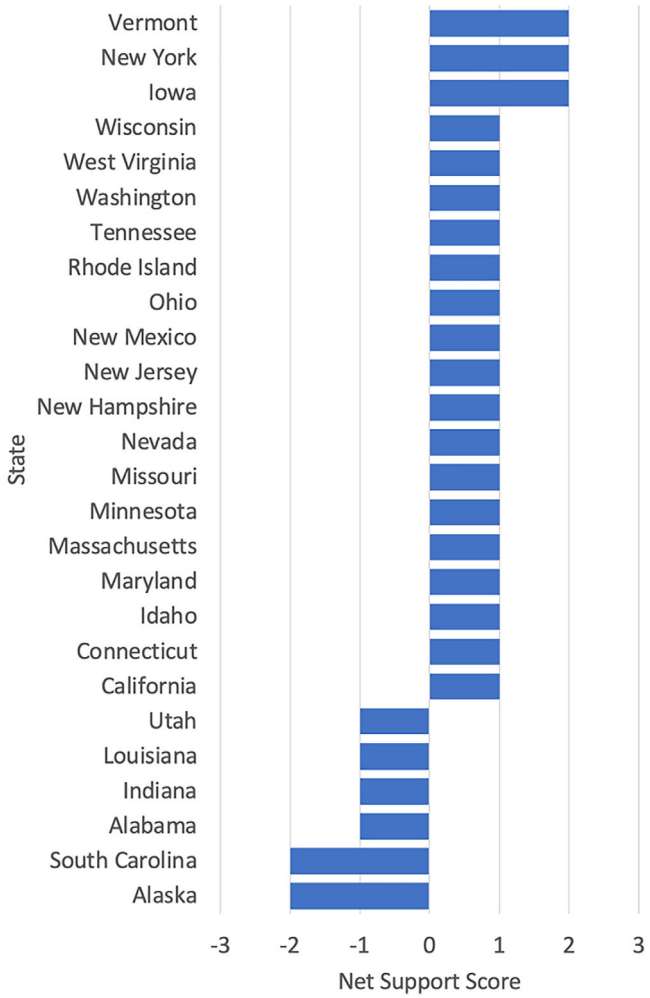

FIGURE 1 State legislation hampering or promoting the adoption of interchangeable biosimilars. States not reported are neutral with a zero score

If the patient is notified, the substitution will not occur, as the patient might assume they are getting a lower quality product. More so, where the patient is required to give consent.

Record keeping for 2–3 years becomes an additional liability for the dispenser and reduces the incentive to make the substitution.

Legal immunity is not provided to the pharmacist in all states should a substitution is made and the patient comes down with an adverse event. This risk is not worth taking for the pharmacist.

Notification after dispensing is an added burden to the dispenser and may discourage the practice.

Some state legislations encourage it, and others make it cumbersome and challenging, as shown in Figure 1. A score of zero was assigned when there was no tilt towards adoption in either direction. Reporting, prescriber consent, patient consent, and instructions for adoption were used to calculate the net score. Only those states that hamper or promote adoption are listed in Figure 1.

3 | REGULATORY FRAMEWORK

3.1 | Background

Biosimilars are expected to be highly similar to biological drugs with expired patents. The BPCIA defines a biosimilar as a product with "*no* clinically meaningful difference with its reference product." To all stakeholders, "no" means absent. Thus the two products are clinically similar, notwithstanding any allowed differences such as the formulation, or non-consequential differences in the structure or other critical quality attributes, leaving "no residual uncertainty" about the safety and efficacy of the biosimilar product as compared with the reference product. It would have been most appropriate if the legislation had stopped at this stage. Instead, the legislation went forward and created another class of biosimilar that would be acceptable for patients who are already using the innovator product—switching; and then went on to require testing multiple times switching and alternating between assuring that a biosimilar can be substituted.[13] There was no scientific or clinical evidence available to justify this regulation. It likely came out of the abundance of caution but also due to the lobbying by the industry to make it more complex; one piece of evidence of it is evident as the states have adopted different adoption rules.

While switching biologic products (at the prescriber level) is relatively common in the EU, substitution (at the dispenser level) is not common.[14] This is in contrast to small-molecule generics, which have resulted in significant cost reductions worldwide due to allowed substitution or replacement.[13,15] The perceived risk associated with biological products was a remnant of the fear of substitution when the chemical generics were introduced. Clinicians still have the prerogative to block the substitution of chemical drugs, and thus it applies to biological drugs also.[16,17] In top-down systems like Norway and Denmark, where national bodies negotiate rates for biologics used in hospitals, switching between biologics with the same active ingredient is already happening, potentially many times.[18–21] Automated transitions from reference products to biosimilars have resulted in significant cost savings in these systems.[21] Before the arrival of the BPCIA, many biological drugs that were approved as chemical drugs were substituted regularly for decades with no evidence of risk; a good example is the switching of insulin based on the insurance carrier.

3.2 | US Legislation

Since the interchangeability of biosimilars is spelled out in the legislation, the FDA does not have the authority to forego this classification. Such is not the case in many other countries where the regulatory agencies have the authority to make such decisions. The only concession the FDA could make was to allow companies to apply for an interchangeability designation for their biosimilar product simultaneously as or just after the licensing.[22,23] As stated in the BPCIA, the US FDA requires clinical studies to prove that multiple switching of the reference and biosimilar product (termed *alternating*) does not increase patient risks.[24,25] The BPCIA does not allow any concessions

for biological products administered only once, or the products with proven safety records, or where the post-market data support the conclusion that the interchangeability does not pose any risk. It must be proven.

4 | STAKEHOLDER VIEWS

The confidence of stakeholders is essential to the success of the adoption of biosimilars. In a recent systematic review,[26] one survey showed that 6%–38% of physicians believe biosimilars and reference products are interchangeable. At the same time, another study indicated that 28% of rheumatologists feel biosimilars and reference products cannot be interchanged.[27] Leaving the substitution decision to pharmacists creates an overriding power over prescribers that most do not view positively.

Nothing has done more damage than the dual classification of biosimilars to their safety and efficacy perception. When there is a choice available between an interchangeable product and one that is not interchangeable, though both are the same molecules, it is not difficult to understand why one would choose the interchangeable product and pay a higher price, a dichotomy raising serious issues of affordability of biological drugs.

5 | PRODUCT QUALIFICATION

The FDA is yet to advise how an interchangeable status would be awarded to products administered only once; the FDA suggests that the developer meet with the FDA and discuss a plan. But what would a developer discuss? Perhaps the FDA may ask for additional clinical pharmacology studies or efficacy studies without switching or alternating. But how could additional studies be of any value, having already earned the credit of having "no clinically meaningful difference." Since the patients for these products are naïve, it makes no difference as there is no switching or alternating. If the FDA has started awarding interchangeability to one-time use products, it will crash the market of those that have not spent hundreds of millions that should not have been spent in the first place. It is like the FDA asking to find a needle in the haystack when there is no needle.

Products that are subject to formulary decisions or administered in a clinical setting may have the prescriber's discretion. Still, prescribers' perception can also change if an interchangeable option is available.

6 | SCIENTIFIC RATIONALE

Every batch of a biological product, whether the originator product or a biosimilar product, is different due to the nature of the biological production process. So, every time a patient receives a different batch, it is like switching to a different product. The clinical trials conducted for the approval of the reference product do not use different batches, so there remains an uncertainty if the differences between batches will impact the safety and efficacy. The same applies to biosimilars. Post-market studies and the safety record of the originator product demonstrate that the subtle differences between the batches are not of concern; it should hold for the biosimilars.

An interchangeable product must meet three criteria, according to the BPCIA. First, the interchangeable product must meet the exact requirements as the reference product for standard or non-interchangeable biosimilar: it must be highly comparable and have no clinically relevant differences. Second, the interchangeable product in any patient must be expected to achieve the same clinical result as the reference product. Third, the danger of switching between a reference product and an interchangeable product for a product that is given more than once must not be more significant than the risk of using the reference product without switching. The FDA has concluded that a switching study is generally expected for risk assessment based on this last criterion. In such research, at least two alternating exposures of the proposed interchangeable product and the reference product are expected, resulting in at least three switches.

The FDA recommends that a switching study include at least two alternate exposures of the proposed interchangeable product, the reference product, and at least three switches. The final changeover from the reference product to the interchangeable product is described. The comparative assessment takes place after the proposed interchangeable product has been exposed for the final time. Notably, the FDA recommends including a sufficient lead-in time in which all trial participants are given the reference product. The FDA states that PK and pharmacodynamic endpoints should be included in the primary analysis, while safety, immunogenicity, and effectiveness should be included in the secondary analysis. According to a recent FDA simulation, three switches are ideal for identifying the influence of anti-drug antibodies (ADA) on PK outcomes.[28] The probability of concluding PK similarity was calculated by adjusting the percentage of ADA incidence induced by switching and the likelihood of concluding PK similarity. According to the simulation, ADA produced during the initial lead-in period were also observed to have a confounding influence on the PK analyses between the switching and non-switching arms of the study. Switching studies do not appear to be beneficial in identifying significant changes in ADA prevalence if the prevalence of ADA is already relatively high. According to the FDA researchers, actual data from a switching clinical study was unavailable for inclusion. The simulation model is based on generic PK characteristics for a monoclonal antibody. While the authors acknowledge the study's limitations, it demonstrates that various factors can influence the outcome of switching trials and emphasizes the possible difficulties in demonstrating interchangeability.

According to section 351(k)(4)(B) of the PHS Act, a switching study or studies must show that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" for a biological product that is administered more than once to an individual. A switching study determines whether switching between the reference product and the proposed interchangeable product has a greater risk of harm or lower efficacy than using the reference product without switching. The evaluation of efficacy endpoints may be

included in a switching study. However, many clinical efficacy endpoints are less sensitive at therapeutic levels to identify changes in exposure and activity due to alternating or switching, even though efficacy endpoints can be helpful.

Furthermore, the FDA suggests that integrated research be designed to support both biosimilarity and interchangeability conclusions. The study's first phase aims to see if the product meets the biosimilarity requirements. The participants in the reference arm of the trial are re-randomized to either continue receiving the reference product or switch to the proposed interchangeable product at the end of this initial period. In the switching-arm stage of the experiment, at least three switches are required. To analyse suitable outcomes for the biosimilarity and interchangeability sections of the trial, enough people must be included in the integrated study design.

Post-marketing data's worth is still a mystery. Data from the licensed biosimilar product's post-marketing surveillance, combined with data from an appropriately designed switching study, may be required in some cases, according to the FDA, to address interchangeability doubts and add to the totality of the evidence to support a demonstration of interchangeability. To resolve doubts concerning interchangeability demonstration, a post-marketing study and post-marketing surveillance data from the approved biosimilar product may be necessary for some situations.

While recent FDA publications have improved the "three-switch" approach, an interchangeability decision for all types of biosimilars other than insulins still necessitates a separate clinical trial (pending finalization of draft guidance). The time and cost of these requirements, as well as the uncertainty about the practical impact of an interchangeability designation in practice due to varying state laws and the relatively limited but growing adoption of biosimilars in the US market, are likely factors in the biosimilar market's limited use of the interchangeability approvals to date. As a result, limited acceptance has ramifications for switching, ease of entrance, capacity to gain market share, and price competitiveness in the biologics markets in the United States.

7 | INTERCHANGEABILITY TESTING FAILURES

Many studies involving millions of patients have concluded that there is no adverse effect if a biological product is switched (Table 1).

Besides the studies listed in Table 1, biological products' historic switching and alternating have a long history. For example, insulin users would be allowed a brand that the payor selects. It was not uncommon to switch and alternate for decades without evidence of safety or efficacy reduction risk. Now that insulin is part of the CDER, it is no longer considered a drug but a biological product, subject to interchangeability rules. The first interchangeable biosimilar approved by the FDA as an insulin product. How this would change the use of insulin is yet to be determined, but this interchangeable approval was not necessary—it had already been established in the real-world practice.

Thus, evidence from the reported studies, including randomized clinical trials and open-label extension trials, suggests that transitioning from a reference product to a biosimilar or vice versa poses a little risk of safety and efficacy. These results hold for many biologics, from small molecules like insulin to huge, complex biologics like monoclonal antibodies. The reason why these studies did not fail is that they cannot fail for the following reasons:

7.1 | Study power

Clinical trials are based on statistical models wherein the regulatory agency risk of approving a product when it should not be is fixed at 5%. The study power, the risk of rejection when it not be rejected, is 20%.[45] The study size is determined by the response (the effect size) and its variation, inter-, and intra-subject. A decision for a new drug tested against a placebo is made post-study if the efficacy response is justified compared to the safety risk before the product is approved. The studies listed (Table 1) compare two groups; both are expected to demonstrate the same response, making it more complex to calculate the study size. Many of these studies included a few dozen to a few hundred patients, and at this study size, the study power goes down significantly, resulting in a demonstration of equivalence. An appropriate size will be much larger than the study conducted to establish the safety and efficacy of the reference product.

7.2 | Study population

While clinical pharmacology studies for biosimilars are mostly conducted in healthy subjects, the interchangeability testing requires enrolling patients unless the FDA decides otherwise and agrees on in silico studies. It is difficult to enrol naïve patients, so the response rate is expected to be highly variable based on their prior treatment. In addition, the patient would have been exposed to the reference product, so the first treatment is already a switch unless the study is limited to new patients. For example, the study on insulin products enrols type 1 or 2 diabetics that have already been exposed to chemical drugs and insulin. This large variability of the study population further confounds the ability of any study to demonstrate a difference, if there is one.

7.3 | Likely difference

Clinical pharmacology studies establish no difference in the body's exposure to the biosimilar product compared to the reference product and vice versa. The pharmacological effects of biologicals are based on receptor binding and the side effects, an extension of the pharmacology. Thus showing PK/PD similarity is more powerful in its design than any clinical efficacy testing protocol, particularly if there are multiple switches where differences at different levels are supposed to be quantitated. The only possible difference in switching and alternating can be in the immune response due to any subtle differences in the structure of the biosimilar molecule compared to the reference

TABLE 1 Clinical studies demonstrate no difference in switching and alternating biosimilars with the reference product

Study	Plan and outcome
Ebbers et al.[27]	Erythropoietin, human recombinant growth hormone, granulocyte colony-stimulating factors; 58 clinical trials encompassing 12,039 participants and 193 adverse event summaries.
Cohen et al.[29]	Ninety studies enrolled 14,225 participants utilizing seven biological products treating 14 disease indications. Overall, 87 of the 90 studies featured only one switch.
Barbier et al.[30]	There were roughly 21,000 swapped patients in 178 studies. Seventy-nine percent of the investigations were conducted in real-world situations that were not part of the product's clinical development.
McKinnon and colleagues[28]	Fifty-seven switching studies (composed of 23 randomized and 34 observational studies); however, 38 of the 57 studies featured fewer than 100 patients.
Hadjiyianni et al.[31]	Type 1 and type 2 diabetes patients were switched between the two treatments.
Wizemann et al.[32]	Epoetin zeta and alpha Efficacy testing.
Ziextenzo[33]	Filgrastim. For six cycles, participants were divided into four therapy groups. Two of these arms switched between the reference and biosimilar goods for six cycles, resulting in five total swaps within each arm.
NOR-SWITCH trial[34]	Switching comparison of from Remicade to infliximab biosimilar product Inflectra (Remsima).
PLANETAS[35] and PLANETRA[36]	Remicade against the group that moved from Inflectra to Remicade in a single changeover.
ADACCESS[37] and ARABESC-OLE[38]	When switching between Humira and a biosimilar product, several switches indicate long-term safety, efficacy, and immunogenicity. Humira and the biosimilar medicine Hyrimoz were switched four times in the ADACCESS trial. The FDA guidelines for testing biosimilarity and interchangeability are met by one arm of this trial strategy.
VOLTAIRE-X. 202[39]	Participants with moderate-to-severe chronic plaque psoriasis treated continuously with Humira and cycled between Humira and the biosimilar product Cyltezo were compared in terms of PK similarity. No difference.
EGALITY[40]	In patients with plaque psoriasis, there were four swaps between Enbrel and a biosimilar called GP2015.
von Minckwitz et al.[41]	Kanjinti switched from Herceptin, a trastuzumab reference product for HER-2 positive early-stage breast cancer patients.
Van den Hoven[42]	As of 2017, the EU pharmacovigilance databases had tracked over 700 million patient days of biosimilar exposure.
Ingrasciotta et al.[43]	Erythropoietin
Belleudi et al.[44]	GCSF

product. The FDA has already managed this aspect by declaring that unless the differences in the immune responses affect the pharmacokinetics, no testing is required, such as for insulin products.[46] Due to their structure, most biological products trigger an immune response, not necessarily an adverse response.[47] Thus even if the switching and alternating bring a change in the immunogenicity, it is less relevant unless it alters the pharmacokinetic profile.

7.4 | Acceptance criteria

A comparative study begins with accepting a reasonable difference to account for the biological variability in clinical responses. However, if the difference is likely to be less than the arbitrary difference agreed upon, it will never be possible to conclude that a product is similar.

7.5 | Nocebo effects

Concerns that switching might have negative implications for patients can report adverse responses.[48] Unfavourable views of biosimilars and interchangeability may, in some situations, result in adverse outcomes for patients due to the "nocebo" effect.[49] a phenomenon where participants' negative perceptions of a treatment lead to adverse outcomes. For example, when told, 24% of participants stopped taking the biosimilar in a study of infliximab.[50]

7.6 | Study failure

In a rare situation, if a study demonstrates a statistical difference in clinical response or side effects upon switching and alternating, the FDA has already concluded that such a product will not be given the interchangeable status. The product can maintain the biosimilar status, still claiming that there is "no clinically meaningful difference" with the reference product, weakening the argument of similarity.

8 | RECOMMENDATIONS

The proponents of interchangeable testing argue that one or more interchangeability studies are required to assure there is no increased risk of safety or loss of efficacy to improve the confidence of providers, patients, and insurance companies.[51] However, such suggestions do not qualify as an abundance of caution. They are based on the historic thinking preferred by prescribers who wish to see the data

from the patient population, in this case, a trial, even though it cannot fail.

8.1 | Allow biosimilar substitution for naïve patient

A naïve patient has no exposure to the reference product. Since the FDA says that there is "no clinically meaningful difference," the pharmacist should be able to substitute a biosimilar if the prescriber allows substitution. There is no reason to engage the patient, no record keeping, and no liability to the pharmacist.

8.2 | The naming of biologics

If switching is left to the pharmacist, a legal issue arises from naming the active biological ingredient that now comes with a suffix, making it a different active component. The non-proprietary nomenclature of biosimilar products increases legal and conceptual ambiguity for health care professionals (because the active ingredient is not the same). While the FDA's decision to add four-letter suffixes was intended to reduce pharmacovigilance confusion, it may have caused even more.[52] While this may be a "horse out of the barn" situation, additional teaching by the FDA to justify the suffix will help. The original argument that the suffix improves traceability has been challenged. The FTC has already determined that the suffix reduces competition.[53] The FDA has not responded to the author's petition to remove the suffix system.[54] For now, we can get around this hurdle by including the statement on the prescription: "may be interchanged with a similar product."

8.3 | Amend BPCIA

Since the interchangeable class of biosimilars is mandated in the legislation, the first step should be to amend the BPCIA, removing the category of interchangeable products. Once that is achieved, using a biosimilar should be left to the prescribers, who must receive additional education. The FDA has already embarked on this project. The States already have systems to replace brand products with generic equivalents; there is no need for new legislation. Removing the category of interchangeable biosimilars will encourage competition and lower the cost to patients and the US government through the CMS programs; the payors can then enter and enforce their power through formularies to select biosimilar biologics, as they have done for decades.[55] The EC strategy[56] states plan to review the pharmaceutical legislation regarding the interchangeability of biosimilars. That absence of automatic substitution can create market barriers that influence access to biosimilars.

There appears to be bipartisan support for expanded biosimilar use to benefit patients. However, Congress should re-evaluate whether the unique US interchangeability designation is necessary or not as they consider user fee reauthorization legislation, including BsUFA III.

8.4 | Remove misconceptions

In addition to published guidance documents 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 the science-based use of biosimilars in response to the mandate for such educational materials in the Advancing Education on Biosimilars Act of 2021.[57] We need more investigations to fill in the gaps in our understanding of switching and substitution and close the gap in our understanding of the impacts of numerous switches between biologics.[58]

Biosimilars have come of age after 17 years of successful use and saving billions of dollars for patients and the payors. However, the financial impact of a biosimilar has been limited in the United States, and it is about to shrink further as the FDA has begun approving interchangeable products; two so far. There is already a discussion about the product's superiority with interchangeable status, while many other biosimilars without the interchangeable status may offer a better price advantage.

If the complex switching and alternating protocols had a chance of demonstrating a clinically meaningful difference, one could have argued the value of this testing. However, with little chance of these studies ever failing, these studies are tantamount to an abundance of misconception rather than an abundance of caution. While no other regulatory agency offers two classes of products, except the FDA, one must wonder about the rationale, particularly when none can be presented. Unlike other agencies, the FDA must follow the legislation. Even if the FDA decides there is no need to demonstrate safety and efficacy with switching and alternating, it cannot list the products as interchangeable. It will require an amendment to the BPCIA.

Once the legal language is removed from the BPCIA, the interchangeable status should be granted to all biosimilars and so dispensed, notwithstanding any objection by the prescriber. This change will also remove the bias created among the states on substituting biosimilars and provide a more uniform implementation of the law.

These actions should be taken immediately.

CONFLICT OF INTEREST

The author declares no conflict of interest. The author is also a patent law practitioner in the United States.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

DISCLAIMER

The author is not advising any legal violations when suggesting how to secure the rights to intellectual property.

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