Biosimilars in dermatology: identifying myths and knowledge gaps

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Abstract

Biosimilars are beginning to gain regulatory approval in the United States. Biosimilars are structurally near identical to the innovator and must demonstrate identical pharmacokinetics via the same binding affinity and biological function on assays. However, biologics are so complex that even the innovator company cannot produce exact duplicates; there is batch-to-batch variation. The International Psoriasis Council has outlined a biosimilarity index, which aims to standardize preclinical definitions of biosimilarity. Such an index, paired with post-approval monitoring, could provide a transparent, quantitative definition of biosimilarity. Such an index could increase trust in biosimilar medicines and the preclinical assessment process without increasing costs. As preclinical analyses are critical to biosimilar approval, manufacturers should devote proportionate resources to completing them. Dermatologists, who might reflexively look for indication-specific clinical data, might also shift their focus to preclinical variables. Finally, it should be noted that biosimilars provide more evidence of similarity than we have for different batches of the innovator product. Thus, any clinical testing standards, or lack thereof, for different batches of innovator products should also apply to biosimilars.

Keywords: biologics, biosimilars, cost-containment, dermatology, immunogenicity, psoriasis

Introduction

Biosimilars are beginning to gain regulatory approval in the United States following a decade of clinical use in Europe. Biosimilars were hailed as "generic biologics" upon market introduction [1]. However, unlike generic small molecule medications—whose active ingredients are chemically identical to the originator product—biosimilars are an imprecise match. Among other differences, companies making biosimilars do not have the original cell line used in biologic development.

Despite this difference, biosimilar drugs must be highly similar to the innovator to earn regulatory approval. Biosimilar products must have the same amino acid sequence as the originator, similar glycosylation (an integral functional modifier, particularly for antibodies and hormones) to the originator, and are subject to rigorous testing for post-translational modification differences [1]. Approved products should be as safe and effective as the original drug and use the same mechanism of action. Further, the biosimilar should be effective at the same dose as the originator biologic and for the same conditions.

The FDA has approved 35 biosimilars to date, the majority of which are used for treatment of inflammatory conditions [2]. Given the widespread use of biologics in dermatology, the use of

biosimilars for dermatologic indications is imminent. This introduction will face challenges, perhaps the foremost being patient and provider education regarding the safety and efficacy of these products.

There are major gaps in knowledge and awareness about biosimilars. Only 6% of surveyed patients and caregivers handling chronic inflammatory conditions had a basic awareness of biosimilars [3]. In addition, 80% of surveyed patients with autoimmune disease did not know what biosimilar medicines were and over half did not understand the difference between biologic and synthetic drugs [3]. Patients familiar with biosimilars were more likely to believe biosimilars were safe and to be comfortable switching from an originator biologic to a biosimilar.

Although providers are typically more aware of pharmaceutical innovations than the general population, there are still large knowledge gaps. Two-thirds of surveyed dermatologists were at least slightly unfamiliar with biosimilars [4]. Studies in other specialties have yielded similar.

Results

a third of oncologists did not believe that biosimilars have equal safety and efficacy as the reference products, even though such equivalence is critical to gaining regulatory approval [5].

Dermatologists will inevitably be called upon to advise their patients regarding the use of biosimilars. Industry has devoted much energy to developing these drugs; we must now devote some energy to learning about them. This paper aims to explore areas of success and potential for improvement in biosimilar development and regulatory approval. Providers familiar with these topics will be better equipped to counsel their patients regarding the use of these medications.

Results

Variation within innovator products

Biologic drugs are too large and complex to be exactly duplicated. Even different batches of the same innovator product—which use the same cell line and buffers—can vary. Researchers found the biochemical fingerprint of marketed etanercept produced before and after 2009 varied by 20-40% in its number of basic variants (C-terminal lysine variants) and degree of glycosylation [6]. In sum, the etanercept produced today is a variation of the etanercept originally approved by the FDA. Batch-to-batch variation in the innovator product means industry has been producing biologic variations, and regulating authorities approving them, long before the term "biosimilar" was introduced [1]. These different batches of innovator undergo no retesting, meaning they have less safety and efficacy data than biosimilar products do.

Biosimilar manufacturers argue that analytical studies should be all that is needed to approve their drugs. If innovator companies are not required to redo clinical studies with manufacturing changes, biosimilar companies should not necessarily be required to gather clinical data to earn regulatory approval [1]. To earn biosimilarity designation, manufacturers must demonstrate that a product is structurally near-identical to the innovator (e.g., has the same amino acid sequence, post-translational modifications, and end-product stability), (**Figure 1**). It must also demonstrate identical pharmacokinetics via the same binding affinity and biological function on assays (**Figure 1**). After meeting these strict preclinical testing requirements, little-to-no clinical testing may be needed, and if done, should confirm what the science predicts (**Figure 2**).

Standardizing the definition of biosimilarity

The FDA and EMA (European Medicines Agency) have issued guidelines for biosimilar manufacturers to determine preclinical biosimilarity [7-9]. These guidelines request investigation of quality factors including receptor binding and end-product stability. However, these regulatory statements are vague and do not define the types of tests required

Figure 2. *Proposed International Psoriasis Council Biosimilarity Index.*

for each quality factor or the degree of variability allowed within individual tests. Further, acceptance criteria for each quality factor are not pre-defined and the allowable difference between the innovator and biosimilar product is not set.

To provide better assurance about biosimilar quality, the International Psoriasis Council suggests that a "biosimilarity index" be defined. Such an index would provide manufacturing guidance and encourage drug developers to meet international preclinical testing standards (e.g., testing for end-product drug stability) before widespread biosimilar uptake (**Box 1**). An index would also allow prescribing dermatologists to judge a biosimilar's similarity to the originator quantitatively and integrate it into a treatment regimen if it meets the similarity criteria they deem essential to an individual patient's care [1].

If adopted, a biosimilarity index should describe batch-to-batch variation in the innovator product in addition to variation between the innovator and biosimilars. The biosimilarity index between batches of a biologic, whose complex 3D protein folding and post-translational modifications makes it impossible to exactly replicate, would be imperfect (**Figure 2**). This might give patients and providers greater reassurance when using biosimilars with similarly imperfect index scores.

Regulatory bodies still request clinical data

Although biosimilarity can be defined solely by preclinical assessment, most regulatory bodies continue to use some clinical data in their approval process [10]. However, these clinical testing requirements are far less stringent than for the original batches of innovator product that were used in the Phase 3 trials required for drug approval. Regulatory agency requirements for biosimilar approval allow for smaller sample sizes and do not need to be repeated for every indication of the originator (**Figure 1**).

Thus, unlike the original batch of innovator, biosimilars are not tested for every approved condition [1]. This decision is deliberate; lengthy clinical trials are costly, ultimately resulting in higher drug prices upon drug entry. Regulatory agencies have endorsed the principle of extrapolation to minimize costs. This practice allows manufacturers to utilize clinical study data from one condition to gain regulatory approval for a different condition (**Figure 1**), [11].

Biosimilars seeking FDA approval should undergo clinical trials in conditions sensitive enough to identify differences between the biologic and the biosimilar (**Figure 1**). For example, the International Psoriasis Council has recommended that for biosimilars of tumor necrosis factor blockers, the ideal disease model is psoriasis. Psoriasis severity can be objectively measured (unlike the more subjective criteria used to measure joint pain) and biologics are given as monotherapy for psoriasis (instead of with methotrexate, which can reduce the chance of detecting immunogenicity differences). Thus, psoriasis is the most sensitive model for detecting possible differences between a biosimilar and the current batch of innovator. If a biosimilar is approved in the psoriasis model, findings might be extrapolated to other disease conditions [12].

While extrapolation practices are closely monitored and substantially reduce cost, regulatory agencies have differed in their approach towards them. By extrapolation, the EMA approved INN-infliximab and infliximab-dyyb (infliximab biosimilars) for psoriasis, psoriatic arthritis, and inflammatory bowel diseases (IBD) after the drugs underwent clinical testing in rheumatoid arthritis and ankylosis spondylitis [13]. Health Canada disagreed with this practice; results might be extrapolated to psoriasis/psoriatic arthritis,

Box 1. *Comparing the approval process for innovator and biosimilar products.*

Similarity factors
Sequence of amino acids
Post-translational modifications
Charge
Binding affinity to target
Biologic function assays
Analysis of excipients, impurities, and aggregates
End-product stability
Delivery device

Algorithm design
The proposed algorithm would weigh each of the above factors by the relative extent to which they determine biologic similarity. Using this index, biosimilars (and different batches of the innovator) could be scored on their preclinical similarity to the original batch of the innovator.

but not inflammatory bowel diseases [14]. These approval differences can confuse patients, who might already understand little about biosimilar medicines.

Preclinical characterization contributes to indication decisions

Preclinical characterization of biological activity can contribute to approval decisions made even after clinical testing. Although INN-infliximab and infliximab-dyyb had similar clinical trial results to infliximab when tested in rheumatoid arthritis and ankylosing spondylitis patients, regulatory bodies disagreed as to whether similar results would be documented in patients with psoriatic conditions or inflammatory bowel diseases [13].

This disagreement stemmed from an international difference in preclinical testing requirements. The antibody-dependent cell-mediated cytotoxicity of TNF blockers is believed to be critical to efficacy in inflammatory bowel disease. Health Canada found that preclinical testing for antibody-dependent cell-mediated cytotoxicity was inadequate, thus denying INN-infliximab and infliximab-dyyb approval for IBD. The EMA, however, found the preclinical data sufficient for IBD approval.

Preclinical characterization predicts biosimilar activity and manufacturers should not rush into clinical testing prior to fulfilling international preclinical requirements. Unlike approval for innovator medicines, which relies heavily upon clinical testing, approval for biosimilars relies most on preclinical analyses, with clinical testing only requested for representative indications (**Figure 1**). As preclinical analyses are critical to biosimilar approval, manufacturers should devote proportionate resources to completing them. Dermatologists, who might reflexively look for indication-specific clinical data, must also shift their focus to preclinical variables (**Figure 1**).

Immunogenicity of biosimilars is a common concern among prescribers and patients

The primary safety concern with biosimilars is their potential for immunogenicity. Biologic therapies are inherently immunogenic; the molecules are large, complex, and can include host cell proteins, all of which might trigger the patient's immune system.

Because originator biologics and biosimilars are not identical, switching a patient between the two could theoretically cause an immunogenic reaction [15]. However, immunogenic concerns are not unique to biosimilars; there is potential for variation even within batches of the same biologic. This was demonstrated in Europe when a new batch of epoetin produced neutralizing antibodies, resulting in a cross-reaction that sent 200 patients into pure red cell aplasia [16].

Although such incidents call attention to the importance of maintaining strict quality standards for biologic manufacturers, no consistent correlation between switching to a biosimilar and increased risk of immunogenic reaction has been demonstrated. Long-term concerns might emerge and continued pharmacovigilance is required to ensure early detection of any such toxicity [17].

Switch trials provide an imperfect way to evaluate immunogenicity

As with biologics, rigorous evaluation of immunogenicity is a critical part of the biosimilar development process. Clinical trials increasingly incorporate a switching component, in which patients are switched from the biosimilar to the reference biologic. Trials of four biosimilars developed for use in chronic inflammatory diseases (infliximab-abda, infliximab-dyyb, etanercept-szzs, and adalimumab-atto) all included switching and demonstrated no concerns for immunogenicity [18-21].

The phase 3 Egality trial evaluated etanercept-szzs in patients with moderate-to-severe chronic plaque psoriasis. This study incorporated three switches between the biosimilar and originator and demonstrated no significant immune reactions [22]. The International Psoriasis Council states that for a biosimilar to meet criteria and be freely substituted for the reference product, an eight-sequence, three-period switching trial must be conducted to incorporate all potential switching situations a patient might encounter (**Figure 1**). However, different batches of the innovator product are freely

substituted for one another without any switch trials, despite batch-to-batch variation in the innovator. Imposing this guideline on biosimilar manufacturers has the potential to drive up cost without a reasonable increase in product safety and may reinforce misperceptions about the similarity of biosimilars to originator products.

Post-approval monitoring could increase uptake of biosimilar medicines

The FDA grants interchangeability designation to products that can be freely substituted for one another without the prescriber's approval [23-24]. Thorough preclinical evaluation of a biosimilar should prove its interchangeability with the innovator as, despite batch-to-batch variation in innovator products, different batches of the innovator product are freely substituted. Despite this, no biosimilar has been granted interchangeability designation, meaning providers have retained the final say. Many providers are wary of biosimilars, unsure how to judge their safety when the usual clinical study data is unavailable. Although limited clinical testing has reduced the cost of biosimilar medications, it has also reduced physician trust in the end-product. This reduced faith is a barrier to their uptake.

Introducing clinical or multi-switch testing requirements would prove counterintuitive by increasing the cost of and thereby limiting access to biosimilar medications. Post-approval monitoring has the potential to provide clinical safety and efficacy data without requiring the manufacturer to conduct expensive trials. Such monitoring should theoretically provide no novel data if thorough preclinical testing has already been performed. However, post-approval monitoring could serve an important confirmatory purpose, demonstrating that using biosimilar medications is much like using different batches of the innovator product (**Figure 1**).

Granting biosimilars interchangeability designation upon regulatory approval would make it difficult to conduct post-approval safety and efficacy monitoring, as prescribers could not easily track which patients were receiving innovator versus biosimilar products. Granting interchangeability after post-approval monitoring could increase faith in biosimilar medications and preclinical assessment, ultimately increasing their uptake without driving up manufacturing costs.

Conclusion

Biologic drugs are too large and complex for anyone to duplicate, including the originator company. Batch-to-batch variation in innovator products means products that have not undergone rigorous clinical trial testing have long been in use in dermatology, without ever being named as such. We must abandon the myth that industry can produce biosimilars identical to the innovator product. Left unchecked, this myth will spur fear about biosimilars and increase costs by way of extravagant clinical testing requirements.

The International Psoriasis Council has outlined a biosimilarity index, which could assure for better quality control among emerging biosimilars as well as different batches of the innovator product. If appropriately applied, such an index could provide much-needed transparency regarding international preclinical testing requirements for biologic products. Paired with post-approval monitoring, such an index could increase physician and patient trust in biosimilars and the preclinical assessment process.

Understanding the implications of the complexity of biologics is essential to understanding biosimilars. Biologics are so large and so complex that even the innovator company cannot produce exact duplicates; there is batch-to-batch variation. That variation has not caused detectable problems in the biologics used for psoriasis. Biosimilars provide far more evidence of similarity than we have for the current batch of innovator products. If we are comfortable with the current batches of innovator products, we should be comfortable with biosimilars.

Potential conflicts of interest

Steven R. Feldman has received research, speaking and/or consulting support from Sun Pharma, Amgen, BMS, Helssin, Arcutis, Dermavant, Alvotech,

Galderma, Almirall, Leo Pharma, Boehringer Ingelheim, Pfizer, Ortho Dermatology, Abbvie, Samsung, Janssen, Lilly, Novartis, Regeneron, Sanofi, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Palak Patel, Caitlin Purvis, and Ramiz Hamid have no conflicts to disclose.

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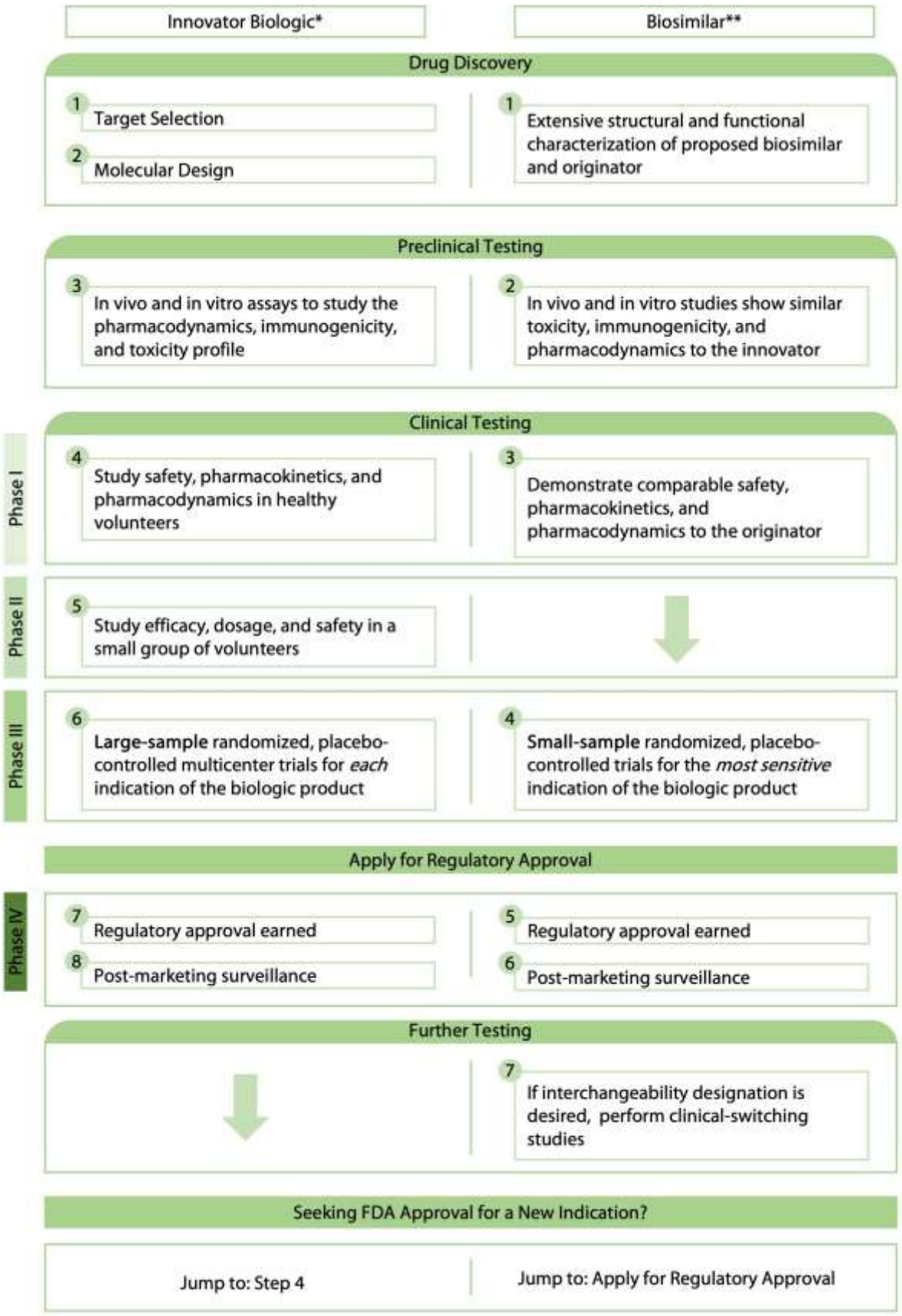

Figure 1. *Preclinical development and testing of biosimilar products.*
*FDA. Guidance, Compliance & Regulatory Information (Biologics). May 2, 2022. **FDA. Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product Guidance for Industry. February 27, 2020.