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EDITORIAL

The Clinical and Economic Value of Follow-on Biologics: Biosimilars, Biobetters, and Bioparallels

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Abstract

The advent of biosimilars into the market of biologic treatments less than 20 years ago in Europe and about 10 years ago in the United States heralded a period of rapid and profound changes in biological therapies. While biosimilars where the first disruptors to the biologics market and some lingering concerns have been addressed, they have since been joined by biobetters and bioparallels in a powerful aggregate of follow-on biologics (FOB) competing with originators biologics. Biobetters are drugs derived from existing biological agents, either by design or by coincidence, with improved pharmacological properties or outcomes. Bioparallels are distinct biologic agents in established classes of biological therapeutics (for instance, Programmed Death 1 (PD-1) inhibitors) that mainly compete on price without the burden of demonstrating equivalence in efficacy and safety. Lingering clinical concerns about biosimilars have been addressed. The economic dynamics of a biologics market that includes lower-priced FOBs continues to be demonstrated, especially how the cost-efficiencies from treatment with FOBs enable expanded patient access to and patient equity in biological therapy on a budget-neutral basis. However, this must be considered within a broader context of potential excess FOB capacity in countries with relatively well-funded healthcare systems, the commoditization of FOBs, and associated downward pricing pressures. Positively, however, is how this excess FOB capacity can be parlayed into increased access to biological therapeutics in low- and middle-income countries.

Key words: biosimilar; biobetter; bioparallel; pharmacoeconomics; expanded access

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Introduction

Twenty years ago, the first application for a biosimilar was submitted to the European Medicines Agency (EMA). The initial wave of biosimilar approvals, which included somatropin (2006), epoetin-alfa (2007), and filgrastim (2009), was met with considerable resistance. The manufacturers of the originator products had innovations and markets to defend, especially in the lucrative area of growth factors. Competition was fierce and, at times, foul.

Some concerns among clinicians were fair but have abated. Similarly, some tactics were questionable but have ceased. Payers came to recognize potential savings and clinicians were reassured by the equivalence of quality, safety, and efficacy standards. More patents of biologics in other classes expired, generating more biosimilar alternatives.

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Biosimilars: Lingering Concerns

Over time, the regulatory pathways for biosimilars in highly-regulated jurisdictions changed fundamentally. The first biosimilars were approved on the basis of pre-clinical studies and clinical trials. In contrast, the 2022 revised World Health Organization (WHO) guidelines (Kang et al, 2023), mirrored also by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, the EMA, and the Food and Drug Administration (FDA) in the USA, recommend that biosimilar approval should be limited to establishing biosimilarity by means of analytical and *in vitro* tests, foregoing *in vivo* animal studies if possible, and conducting a bioequivalence study to demonstrate comparability in pharmacokinetics and/or pharmacodynamics, immunogenicity, and safety-signs of a gradually-acquired high degree of confidence among regulators.

The most needed evidence about biosimilars has moved to daily clinical practice, i.e., real-world clinical evidence. The prospective observational post-approval studies evaluating biosimilar treatment patterns and outcomes in real-world clinical settings were replaced by less granular database analyses, overlooking novel modeling methods simulating trials in the real-world setting. An excellent example, from the UK, used a target trial emulation methodology to simulate two real-world trials of reference adalimumab versus two adalimumab biosimilars in patients with psoriasis using highly credible patient registry data (Phan et al, 2025). One trial focused on treatment initiation, the other on switching; neither study found statistically significant differences in psoriasis outcomes between reference and biosimilars.

This empirical confidence may not be shared by all. Arguments, mainly from a reactionary perspective, over the interchangeability of biosimilars and their reference biologics persist, and calls for switching studies remain (Reilly, 2024). Here too, a viable alternative is available: extensive statistical simulations of various interchangeability regimens, many more than would be feasible in a clinical trial, at a fraction of the cost of a redundant trial (Available from the corresponding author).

Remains patient and clinician engagement. A recent qualitative study in the UK involving 5 consultants who had never prescribed biosimilars and 9 patients being treated with originator products revealed an interplay between lack of understanding and confidence in biosimilars (Rosembert et al, 2024). Consultants recognized the financial benefits to the National Health Service (NHS) but emphasized that savings should be redirected to increase patient access to treatments. They stressed the importance of efficacy and safety evidence, but generally trusted regulatory approvals by the FDA and EMA. They recommended that physicians or specialist nurses communicate switching to biosimilar treatment to patients. Patients and consultants concurred that patients should be given sufficient time to review the information given about switching, and that patients should have the option to revert to the originator product.

Beyond Biosimilars: Biobetters and Bioparallels

Accountable and transparent adoption of biosimilars serves as both foundation and experience for integrating two other follow-on biologics (FOBs).

Biobetters are generally drugs designed from existing ones with improved pharmacological properties or outcomes (Torres-Obreque et al, 2022; Weise et al, 2011). Considered new drugs by regulators, they hold patent exclusivity, don't have to wait for the reference's exclusivity to expire, and, importantly, could "beat a biosimilar to market" (Dotmatics, 2024). Alternatively, biobetters may be biosimilar candidates that "failed" biosimilarity. One already-approved intravenous infliximab biosimilar was reformulated into a subcutaneous version and gained EMA biosimilar approval in 2019 across a broad spectrum of indications. This confers the convenience of self-injection at home as well as patient comfort, quality of life, and adherence. In contrast, concerned that a different administration route might affect pharmacokinetics and pharmacodynamics, the FDA requested two placebo-controlled phase III trials in moderate to severe active Crohn's disease and ulcerative colitis (the FDA approved the subcutaneous version in 2023). Rather ironically, while in the US the intravenous biosimilar infliximab is indicated for a broad range of diseases, the subcutaneous formulation is limited to the Crohn's disease and ulcerative colitis indications from the trials. This confers clinical and patient-centric benefits to a limited segment of otherwise eligible patients. Moreover, the subcutaneous formulation is priced much higher, largely due to the cost of the trials.

Bioparallels, a term we proposed recently to differentiate yet another FOB (Abraham, 2023), are FOBs that compete mainly on price for the clinical benefit they bring, without the regulatory biosimilarity constraints of needing to be equivalent in efficacy and safety (Abraham and MacDonald, 2025). Case in point: the Programmed Death 1 (PD-1) inhibitors toripalimab and tislelizumab, developed by the Chinese companies Junshi Biosciences and Beigene (soon known as BeOne Medicines), respectively, were approved recently by the MHRA, EMA, and FDA, in two low-incidence advanced cancers—both being unmet medical needs. The major differentiator is that both agents are priced markedly lower than, for instance, pembrolizumab, and that they could beat biosimilars to the FOB market. Of note, certainly in the US, there is quite some anti-China sentiment. This ignores the innovation in human therapeutics in China. Its regulatory agency joining the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) signaled the country's intent to be both innovator and competitor. More generally, it reflects the country's growing scientific output and impact in many areas, as documented recently in The Economist (2024).

The Economics of FOBs

With FOBs generally priced lower, there are, of course, savings to be generated to payer organizations (Mulcahy et al, 2022). Yet, savings from the use of biosimilars do not systematically lower patients' out-of-pocket costs (Feng et al, 2024). The value of FOBs to payor organizations and society at large goes well beyond cost-minimization and lies in the cost-efficiencies generated: the most efficient cost-structure contributing to the value equation of biological therapy with FOBs (Abraham et al, 2024). Practically, cost-savings can be re-allocated to provide expanded access to biological therapy to more patients on a budget-neutral

basis (Roth et al, 2025). In practical terms, it addresses the question of "how many more patients can be treated from the savings without impacting budget and requiring additional financial resourcing". In turn, and of significant public interest, this could increase patient equity.

Alternately, as the biosimilars market has shown, the FOBs confront major challenges. The likelihood of commoditization is real: as more FOBs aligned with certain originators enter the market, product differentiation ceases. FOBs will be bought for what they do, not for who they are (Abraham, 2022a). Price erosion is a reality, especially as more biosimilars enter the market and also as originator manufacturers lower their prices: the cost structure for them to stay in the market with their "old" product is fundamentally different from that of FOB manufacturers, which must still recuperate their development, regulatory, and market entry costs, among many other costs (Frank et al, 2022).

In the end, the Western world may end up with too much choice but too little market for FOBs. Here too, the biosimilar market may foreshadow a challenge and a responsibility (Abraham, 2022b). Current market offerings and FOB pipelines may be too large to be financially viable to the roughly 1 billion people in the Western world. The future of FOBs may indeed lie in also serving the other 7 billion people in low- and middle-income countries.

Conclusion

Disruptors of the biologics market they may be, biosimilars are not the only ones as biobetters and bioparallels join the FOB arena. FOBs are cost-responsible channels for improving patient access and patient equity in biological therapy. The competition may well be fiercer than it is today. Biosimilars, biobetters, and bioparallels not only compete with originator products, they also compete between and among themselves. Patients, providers, and payers will benefit – as will the smart producers.

Key Points

- The advent of biosimilars gradually changed the landscape of biological therapeutics, mainly through price competition while offering products that are similar in quality, safety, and efficacy.
- Biobetters are biological agents derived from existing biological agents, either by design or by coincidence, with improved pharmacological properties or outcomes. Bioparallels are distinct biologic agents in established classes of biological therapeutics. They compete mainly on price without the burden of needing to demonstrate equivalence in efficacy and safety to a reference product.
- The cost-efficiencies of treating patients with lower-priced follow-on biologics (FOBs) can be used to provide more patients with access to treatment on a budget-neutral basis and this increase patient equity.
- Together, these FOBs provide patients, clinicians, and payers with affordable alternatives to higher-priced originator products. However, the likelihood of commoditization and further downward pricing pressure must be considered.
- The potential excess capacity of FOBs in countries with relatively well-funded healthcare systems creates opportunities for the biological treatment of patients in low- and middle-income countries.

Availability of Data and Materials

Not applicable.

Author Contributions

IA was responsible for conceptualization and design of the work; acquisition, analysis, and interpretation of literature sources, and drafting and critically revising the manuscript for important intellectual content. ANB was responsible for acquisition, analysis, and interpretation of literature sources, and critically revising the manuscript for intellectual content. KMM was responsible for conceptualization and design of the work, acquisition, analysis, and interpretation of literature sources, and drafting and critically revising the manuscript for intellectual content. All authors contributed to important editorial changes of important content in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

Ivo Abraham and Karen Michelle MacDonald hold equity in Matrix45, LLC.

Matrix45 and predecessor companies in which Ivo Abraham and Karen Michelle MacDonald hold or have held equity, have been contracted for research, analytics, dissemination, consulting, and training services related to biologics and follow-on biologics by Janssen/Johnson & Johnson, Amgen, Novartis, and Roche on the originator side; and by Sandoz/Novartis, Coherus Biosciences, Mylan/Viatris/Biocon, Hospira/Pfizer, Teva, and Celltrion on the follow-on biologics side.

Ivo Abraham is the Quantitative Methods Editor of *JAMA Dermatology,* which is a compensated editorship contracted to Matrix45. He is Editor-in-Chief of the *Journal of Medical Economics*, which is an uncompensated editorship but for which he receives an annual allotment of submissions free of article publication charges.

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