



Biosimilars: A Virtuous Cycle of Sustainability and Innovation

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Abstract

A biosimilar is a biological medicinal product developed to replicate a licensed originator—i.e., the reference product—with which it shares quality, efficacy, and safety. Marketed following expiry of the reference product's patent protection, biosimilars introduce competition that benefits patients and foster sustainability. In addition to such sustainability of healthcare systems, biosimilars confer a less widely recognized yet equally important benefit: they stimulate innovation. The European regulatory framework, pioneered by the European Medicines Agency and reinforced by other reference regulatory bodies, has unlocked this innovative potential. This paper examines how the development, manufacturing, commercialization, and clinical use of biosimilars generate advances in healthcare delivery. Drawing on available evidence and market experience, it proposes a classification of biosimilar-driven innovation into three domains: pharmaceutical innovation, technological innovation, and therapeutic innovation. Benefits wholly or partially attributable to biosimilars encompass both incremental and disruptive improvements within each domain. These include, for instance, the reinvestment of resources into novel therapies and technologies; therapeutic paradigm shifts supported by evidence and increasingly reflected in clinical guidelines; and enhanced formulations and delivery devices. Although relevant to all healthcare stakeholders, this paper is primarily directed at physicians. As key facilitators of biosimilar adoption, they will find that the innovative aspects of these medicines offer both compelling arguments to support broader prescribing and practical examples of how biosimilars can enhance clinical practice and improve patient outcomes.

Key Points

Although developed to replicate a licensed reference product, biosimilar medicines may foster innovation that benefits patients, healthcare professionals, and healthcare systems.

Biosimilar medicines drive pharmaceutical innovation by incentivizing both disruptive and incremental improvements in drug development.

Biosimilar medicines promote technological innovation by advancing technical and methodological processes and facilitating the adoption of new healthcare equipment.

Biosimilar medicines contribute to therapeutic innovation by supporting the evolution of therapeutic paradigms through multiple pathways.

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1 Background

A biosimilar is a biological medicinal product developed to replicate an originator, known as the reference product. Biosimilars share essentially the same active substance, route of administration, dosage, and indications as their reference counterparts and must demonstrate comparable quality, efficacy, and safety [1, 2]. Although, essentially versions of the same medicine, biosimilars may evolve and differentiate after authorization within the European Medicines Agency (EMA) regulatory framework. Such differentiation may involve features, such as the route of administration or, theoretically, even therapeutic indications, although regulatory flexibility regarding the route of administration may vary across jurisdictions. Their approval requires demonstration of biosimilarity, i.e., high similarity or essential sameness, based on a rigorous evaluation of the totality of the scientific evidence. The cornerstone of this process is a comprehensive analytical comparability exercise—including structural and functional characterization—supplemented by clinical comparison. The EMA pioneered the biosimilar regulatory framework in 2005. Its scientific principles were subsequently adopted by other agencies designated by the World Health Organization (WHO) as Stringent Regulatory Authorities (SRAs) and, more recently, as WHO-Listed Authorities (WLAs), based on performance-based evaluation [3, 4].

The value of biosimilars for healthcare systems is most evident in settings where their adoption has been substantial and where patients, whether stabilized or not, have been transitioned from treatment with the originator to a corresponding biosimilar. The cumulative European experience with anti-TNF biosimilars has enabled multiple analyses of their beneficial impact [5]. Conversely, in jurisdictions or specifically in therapeutic areas with limited penetration—often justified by arguments lacking scientific support—patients face a detrimental opportunity cost. Building on this reluctance, some healthcare professionals and administrators still view biosimilars merely as “market regulators” [6], referring primarily to their impact on pricing. Such a reductionist perspective is problematic, as reliance on price competition alone risks creating even more unsustainable market conditions that may ultimately discourage biosimilar presence in a given market [7]. It is therefore essential for healthcare professionals to understand the full scope of biosimilar benefits.

Biosimilars introduction frees resources that can be reinvested in expanding patient access to biological therapies, reducing inequities even in highly regulated jurisdictions, or recruiting additional healthcare personnel, among other uses [7–11]. However, the value of biosimilars extends far beyond their economic impact. They may

also mitigate the risk of medicine shortages, thereby supporting continuity of care, and facilitate access to biological therapies through clinical trials conducted in countries with less consolidated healthcare systems. In addition to these benefits—and although frequently underestimated—biosimilars are increasingly recognized for their capacity to generate either incremental or disruptive innovation that directly or indirectly produce benefits for patients. The large-scale entry of biosimilar versions of medicines bearing certain monoclonal antibodies, for instance, together with growing evidence of their impact on clinical practice, now justifies a systematic evaluation of their innovative potential. This paper proposes a classification of innovation arising from biosimilar development and use into three domains—pharmaceutical, technological, and therapeutic—and illustrates, with concrete examples, how these advances translate into tangible improvements in clinical outcomes. Given the limited scientific literature specifically addressing biosimilar-driven innovation with a direct or indirect impact on clinical practice, this article does not follow a conventional systematic review approach. Instead, three areas of potential innovation were first identified and conceptually classified and discussed on the basis of institutional, industry, and, where appropriate, regulatory evidence, using the EMA position as the regulatory baseline. Scientific publications and other relevant sources were then sought to provide factual examples supporting the proposed framework.

2 Classification of Biosimilar-Driven Innovation

The link between biosimilars and innovation can be analyzed from several perspectives. This paper proposes a classification that highlights the domains in which innovation is primarily realized. (1) Pharmaceutical innovation, encompassing either improved medicines or the development of innovative products; (2) technological innovation, referring to technical advancements, primarily in manufacturing processes; and (3) therapeutic innovation, referring to direct improvements of treatment practices. For each category, the mechanisms underlying the innovative outcomes are described, along with examples illustrating how the innovative effects associated with biosimilars ultimately translate into clinical advances that benefit patients.

2.1 Pharmaceutical Innovation

Pharmaceutical innovation refers to research and development activities incentivized by the commercialization—or anticipated commercialization—of biosimilar versions of

a given reference biologic. Several biosimilar-driven pathways leading to either disruptive or incremental pharmaceutical innovation may be identified.

2.1.1 Disruptive innovation: drug repurposing (repositioning) and target optimization

The commercial threat posed by the launch—or anticipated launch—of one or more biosimilars may prompt marketing authorization holders of reference medicines to investigate new therapeutic applications for existing products (repurposing). The biopharmaceutical industry may thus address the need for continuous improvement in clinical practice by exploring therapeutic alternatives for already marketed medicines, while seeking to extend and maximize economic returns. Research and development conducted in the context of actual or anticipated biosimilar competition may include evaluation of the therapeutic potential of originator products in additional indications. Although such development may be driven by several scientific and commercial factors, biosimilar competition may provide an additional incentive, particularly as part of broader life-cycle management strategies. Importantly, expansion into a new indication does not in itself prevent biosimilar development or market entry, but may allow the originator to generate additional returns, either through limited indication-specific regulatory protection where applicable or simply through the commercial value of an expanded market. A direct causal relationship is rarely disclosed or demonstrable in individual cases, but the approval of Xolair® in nasal polyps [12] and the clinical development of Humira® in Dupuytren's disease [13] may illustrate this type of biosimilar-associated innovation. The threat of biosimilar competition may also stimulate innovation around therapeutic targets that have already been clinically validated, with the aim of improving efficacy, safety, selectivity, or other clinically relevant properties of the original therapeutic approach (optimization). Rather than identifying an entirely new target, this type of innovation builds on an established mechanism of action and seeks to improve its clinical performance. The development of newer anti-CD20 monoclonal antibodies following rituximab illustrates this approach, with subsequent agents designed to modify target binding and/or effector functions in an attempt to improve therapeutic outcomes in CD20-positive B cell malignancies [14, 15]. Similarly, trastuzumab emtansine (T-DM1) retains HER2 as the validated therapeutic target while coupling trastuzumab to a cytotoxic agent, thereby adding targeted intracellular delivery of chemotherapy to the established anti-HER2 strategy [16]. Whether these developments were directly driven by biosimilar competition cannot generally be established, but they illustrate the type of target-based optimization that such competition may further encourage. Together, the acceleration of efforts to

foster disruptive forms of pharmaceutical innovation, including the development of new molecules targeting novel pathways, may in some cases have occurred in the context of the market expansion associated with biosimilars, although a direct causal relationship is difficult to establish. Accordingly, recent reports indicate a temporal overlap between the launch of biosimilars and the approval of new medicines [17, 18]. In this regard, evidence supports that originator companies may increase innovation activity following loss of exclusivity and the subsequent entry of generic competition to protect revenues [19]. Similarly, biosimilar competition may stimulate disruptive pharmaceutical innovation, with clear and meaningful benefits for patients.

2.1.2 Incremental innovation: evolution of marketed reference biological medicines

The improvement of medicines approved by regulatory agencies represents a form of innovation pursued by biopharmaceutical companies to provide added clinical value and differentiate their products. Such initiatives in originator products may coincide with the imminent approval or launch of biosimilars. Overall, the presence of multiple versions of a product in the market increases the likelihood that at least one will evolve into a clinically improved variant. Examples of improvements to originator medicines, likely stimulated at least in part by the development of biosimilars, include changes to the excipients and concentration of adalimumab in Humira® [20]; formulation modifications to Xolair® and Ilaris® designed to facilitate patient self-administration [21, 22]; and pegylated erythropoietin (EPO)-beta [23], whose longer half-life compared with nonpegylated EPO-beta was intended to allow less frequent dosing in patients with renal insufficiency or in oncology settings. Another improvement, possibly reactive in part to the emergence of biosimilars, is the reformulation of originator medicines to modify their route of administration. The development of subcutaneous trastuzumab represents a clinically relevant pharmaceutical innovation that appears to have been stimulated, at least in part, by the anticipated entry of trastuzumab biosimilars [24, 25]. Other examples include the pharmaceutical development and approval of subcutaneous (SC) formulations of Mabthera® [26], as well as the development of Eylea® 8 mg [27], which allows more widely spaced intravitreal administration in patients with AMD. It is also reasonable to assume that the anticipated launch of biosimilars has prompted the marketing authorization holders of originator natalizumab (used in relapsing–remitting multiple sclerosis) and vedolizumab (used in ulcerative colitis and Crohn's disease) to develop SC formulations [28–30]. Albeit incremental, improvements of this nature may require substantial experimental and financial investment and are not devoid of risk. This is illustrated by the fact that, in the USA, the

subcutaneous (SC) formulation of trastuzumab was granted a new brand name solely because of the inclusion of hyaluronidase—considered by the Food and Drug Administration (FDA) to be an active substance despite functioning as an excipient [31]. Irrespective of whether they are prompted by market dynamics, these innovative developments clearly contribute to improved patient care. The stimulation of improvements in originator products used as reference medicines for biosimilar development, such as new formulations, reduced injection volume or pain, and modified dosing regimens, constitutes incremental pharmaceutical innovation of considerable value in clinical practice. Such developments may form part of broader lifecycle-management strategies undertaken by originator companies around or after loss of exclusivity to maintain product differentiation and market competitiveness. Although a causal relationship cannot be firmly established, as already noted, available indications and experience from the generic medicines market suggest that actual or anticipated biosimilar competition may provide an additional incentive for such developments. The extent to which originators can capture additional commercial value from these innovations is variable and may derive from market differentiation and uptake, as well as, where applicable, from patent or regulatory protection. Such protection may be limited or short-lived, but this does not preclude the generation of meaningful market value. Importantly, whatever the commercial motivation, these innovations may ultimately translate into meaningful benefits for patients and healthcare providers. Similar innovative developments may also occur with biosimilars.

2.1.3 Innovative developments within the biosimilar

Once marketed, a biosimilar is added to the therapeutic armamentarium for one or more indications, becoming an alternative to the originator product and to other biosimilars with which it also competes. Thus, as with originator medicines, authorized biosimilars may themselves undergo post-approval improvements. To date, the only documented example is the infliximab biosimilar Remsima®. In this case, the excipients and concentration of the active ingredient in the initially approved intravenous (IV) biosimilar preparation were modified to develop a subcutaneous (SC) formulation (Remsima SC), providing substantial patient benefit [32, 33]. This evolution had not occurred with the originator product bearing infliximab after 13 years on the market, probably because its exclusive position provided little incentive for innovation.

Finally, a product initially developed in the context of a biosimilar program may also seek approval for a disease for which the original reference medicine was never formally authorized. Ipique, a bevacizumab-containing medicine, was submitted separately to the EMA for the treatment of

age-related macular degeneration (AMD), an indication in which bevacizumab had already been extensively used off-label. The application relied largely on published clinical experience with other bevacizumab-containing medicines. The CHMP ultimately issued a negative opinion [34], primarily because an adequate bridge had not been established between Ipique and the bevacizumab products from which the clinical evidence had been generated; therefore, the efficacy and safety evidence could not be directly attributed to Ipique. Notably, the negative opinion was not supported by all CHMP members. The case nevertheless illustrates the regulatory possibility of developing a biological medicine for an indication not authorized for the original reference product, particularly where substantial off-label experience already exists. This possibility was subsequently realized with Lytenava (bevacizumab gamma), which, following product-specific clinical development, received EU marketing authorization in 2024 for neovascular AMD [35].

2.2 Technological Innovation

Technological innovation refers to technical, methodological, or equipment-related advancements driven by the development, production, or use of biosimilars. Three forms of innovation within this domain are outlined below, illustrating how each contributes to concrete improvements in healthcare delivery.

2.2.1 Innovation in healthcare technologies and methodologies

As noted earlier, the increased healthcare efficiency generated by the introduction of biosimilars enables, among other benefits, the reinvestment of resources into new healthcare capabilities [36], as highlighted by leading rheumatologists [37]. While the redistribution of part of these savings toward the acquisition of innovative medicines will be addressed in a later section, these resources may also be allocated to support investment in innovative health technologies, for example, new diagnostic or therapeutic equipment. Proactive European health authorities that incentivize the use of biosimilars provide clinical centers with the opportunity to channel the resources generated through biosimilar adoption into the technological renewal of their services, through mechanisms known as Gainsharing Agreements. These investments have an immediate impact on healthcare delivery and directly benefit clinical services.

The development of new tools for monitoring clinical response can also be considered part of the technological innovation fostered by the introduction of biosimilars. Examples include infliximab immunogenicity testing kits [38], which were not marketed until biosimilar versions of infliximab entered the market and have since become available

to rheumatologists in clinical practice [39]. Likewise, new monitoring tools prompted by the arrival of biosimilars [40] provide more objective methods for clinically assessing the outcomes of switching in rheumatology patients.

2.2.2 Innovation in pharmaceutical (galenic) technology

Galenic modifications within a biosimilar may also constitute a form of clinically valuable innovation. From a regulatory perspective, qualitative or quantitative differences in excipients relative to the reference product are acceptable, provided that efficacy and safety are not compromised [41]. Such modifications may, for example, improve stability by reducing the tendency for aggregate formation, which may translate into clinically relevant consequences as discussed below. Although these enhancements do not always translate into changes in clinical use, increased stability may have desirable practical consequences. In the context of procurement and medicine management, it may enable healthcare institutions to purchase larger volumes, thereby simplifying administrative processes and potentially strengthening bargaining power in bulk purchasing. These potential logistical and commercial advantages derived from galenic reformulation may also be accompanied by pharmacological benefits. Reducing the risk of aggregate formation through reformulation, for example, may influence pharmacological behavior (see [Therapeutic Innovation](#)). Despite the regulatory latitude for such formulation enhancements, no marketed biosimilar has been explicitly described as incorporating them. Although not directly categorized as galenic incremental innovation, improvements have been documented for a follitropin alfa biosimilar [42] and suggested for infliximab [43] and trastuzumab [44] biosimilars. What has been reported are improved specifications regarding stability of biosimilars bearing bevacizumab [45–48]. However, it remains unclear whether they reflect a formulation change or simply more extensive stability data generated by the manufacturer. Excipient modifications may, in theory, also be introduced for other purposes, for example, to facilitate or accelerate reconstitution from a lyophilized presentation by the patient.

2.2.3 Methodological and process engineering innovation

The development and manufacture of biosimilars often benefit from more advanced manufacturing and analytical technologies than those available when the reference product was originally developed. Such advances may result, for example, in tighter process control and greater batch-to-batch consistency [49–51]. Greater manufacturing consistency may, in turn, reduce batch-to-batch variability and potentially allow tighter specification ranges to be established over time, thereby contributing to an overall improvement in manufacturing quality. This may also progressively

limit physicochemical drift throughout the product lifecycle and further reduce the already low risk of such variability becoming clinically relevant.

When these technological advances represent a meaningful improvement, they may become more broadly adopted within the industry and contribute to progress in the development and manufacture of biologics overall [52]. Technological innovation is, of course, also driven by manufacturers of originator biologics; the point here is that biosimilar development provides an additional opportunity to introduce and consolidate improved manufacturing and analytical technologies. It will therefore be of interest to determine the extent to which improved process control and manufacturing consistency can mitigate physicochemical drift over the product lifecycle [53], a phenomenon that has so far been studied predominantly in originator biologics [54–56]. Drift is closely monitored by regulators and industry alike and is generally well managed through stringent in-process controls and clearly defined specifications. Notably, significant deviations were observed in an original reference product during the development of a biosimilar. Indeed, the comparability exercise between the biosimilar candidate SB3 (Ontruzant[®]) and trastuzumab (Herceptin[®]) revealed previously unidentified and unreported variations in the glycosylation profile of the reference medicine. These variations led to functional changes in antibody-dependent cellular cytotoxicity (ADCC) across several lots of the originator, and patients with breast cancer treated with these lots received products with reduced potency [57, 58]. The marketing authorization holder of Ontruzant[®] reported this drift in Herceptin[®], which likely would not have come to light without the exhaustive analytical characterization of the reference product undertaken during the biosimilar development.

2.3 Therapeutic Innovation

Therapeutic innovation, as used in this paper, refers to improvements in specific treatments that arise as a direct cause–effect consequence of the cumulative use of biosimilars. Although this may seem paradoxical—given that a biosimilar’s purpose is to replicate the reference product with a high degree of fidelity—their use in clinical practice can nonetheless generate incremental or even disruptive therapeutic advances, either immediately or over time, through several pathways. To illustrate how biosimilars may lead directly to therapeutic innovation, three subcategories are proposed.

2.3.1 Therapeutic innovation incorporated into the biosimilar

As noted in the section on Pharmaceutical Innovation, regulatory frameworks allow certain innovations to be

incorporated into a biosimilar, provided they do not alter its highly comparable quality, efficacy, or safety relative to the reference medicine. These intentional modifications are designed to provide additional value and are typically incremental, as they enhance specific features relative to the originator product. Accordingly, biosimilar developers often design administration devices to improve patient convenience [59–61]. Such devices aim to facilitate preparation or administration and, in some cases, may maximize the usable content of pens or syringes by reducing dead volume and thereby limiting product waste. Examples include the introduction of a new autoinjector for an etanercept biosimilar, perceived as easier to handle than the reference device [62]. Likewise, Omlyclo®, a biosimilar containing omalizumab, has been developed as both a prefilled syringe and a pen—a device not available in Europe for the reference medicine. The prefilled pen offers a more automated, user-friendly delivery mechanism, often preferred for self-administration [63].

As already noted, innovation can also be introduced at the level of biosimilar formulation to reduce certain clinical risks. Reformulation may be theoretically justified by lowering injection-site pain or by mitigating extrinsic immunogenicity, for example by reducing the tendency to form aggregates (regulatory authorities would not allow differences in intrinsic immunogenicity attributable to the active substance itself) [64]. To date, no biosimilar has demonstrated a meaningful reduction in immunogenicity, although some reports suggest that certain biosimilars containing etanercept as the active substance induce anti-drug antibodies (ADA) in a smaller proportion of patients [65, 66]. The clinical relevance appears limited, given the weak immunogenicity of etanercept, but the observation is noteworthy because the biosimilar's formulation differs from that of the reference product. Importantly, such improvements are legally permissible and may increasingly be adopted by developers.

2.3.2 Therapeutic innovation fostered by biosimilars

As previously discussed, much of the value delivered by biosimilars stems from the price reductions in biological therapies driven by market competition [7, 67, 68]. This improvement in cost-effectiveness enables more efficient resource allocation without compromising quality of care. A portion of the freed resources can be reinvested in acquiring new medicines that offer added therapeutic value. The enhanced access to innovative therapies resulting from biosimilar use constitutes a disruptive form of therapeutic innovation, as it meaningfully improves treatment for eligible patients. In this way, a direct relationship can be established between biosimilar uptake and accelerated access to therapeutic advances in clinical practice. For example, in Canada,

increased biosimilar use facilitated access to Janus kinase inhibitors (JAKi) for the treatment of rheumatoid arthritis [69].

2.3.3 Therapeutic paradigm shift

The substantial improvement in the cost–benefit ratio of certain biological therapies in therapeutic areas where originators coexist with at least one biosimilar has accelerated the implementation of alternative therapeutic strategies, sometimes in off-label contexts. These strategies include earlier initiation of biologic therapy in patients with insufficient response to first-line treatments and faster escalation of such therapies. Improved cost–benefit ratios also support the broader use of one or more biologics within a given indication. Therefore, a significant increase in the number of patients treated with different versions of a given product further drives a shift in the therapeutic paradigm. Patient numbers can be quantified using defined daily doses (DDD), as defined by the WHO, or equivalently, days of treatment [70]. Greater patient exposure leads to expanded therapeutic experience and knowledge accumulation, which in turn increases the likelihood of identifying alternative uses or optimized strategies for a given medicine. Importantly, wider use also refines safety knowledge through increased reporting of adverse reactions, thereby contributing to treatment optimization. Certain modifications may ultimately be incorporated into clinical guidelines or reflected in product labeling once sufficient evidence becomes available.

Transition toward new treatment paradigms is generally gradual but ultimately inevitable, as leading rheumatologists have noted [37]. A case highlighted by the European League Against Rheumatism (EULAR)—the most influential rheumatology body in Europe—is illustrative. In 2019, prompted by the arrival of biosimilars, EULAR recommended the earlier use of biologic or synthetic disease-modifying antirheumatic drugs (DMARDs) after failure of first-line therapy in patients with poor prognostic factors, in contrast to its prior stance, which merely advised “considering” their addition [71]. Paradigm shifts may also involve demonstrating the utility of biologics in patients with certain comorbidities, extending their use to individuals with milder disease forms, or improving outcomes when combined with other agents. This is not a theoretical prospect. The improved cost–effectiveness of certain therapeutic groups driven by biosimilars is already reshaping health technology assessment recommendations. For example, National Institute for Health and Care Excellence (NICE) in the UK recently recommended anti-TNF agents for more moderate forms of rheumatic disease [72–74], and endorsed trastuzumab plus pertuzumab for early-stage HER2-positive breast cancer in node-positive patients [75]. Other publications in the rheumatology field [76] as well as in gastroenterology [77] support the view

that anti-TNF biosimilars create an opportunity for earlier initiation of biological therapy—an approach shown to be effective, efficient, and safe in the short, medium, and long term. Such paradigm shifts are expected to benefit tens of thousands of patients.

Other illustrative cases include the co-administration of bevacizumab and sorafenib in hepatocellular carcinoma [78]; the combined use of anti-TNF agents with vedolizumab or ustekinumab in inflammatory bowel disease [79, 80]; and the use of dual biologics targeting different therapeutic pathways in refractory spondyloarthritis [81, 82]. Moreover, a recent review on the future of bevacizumab highlighted the potential of new combinations with immunotherapy and the growing role of targeted therapies in late-stage clinical development [83]—advances that could undoubtedly be accelerated by broader biosimilar market penetration. A further example comes from the Vall d’Hebron Institute of Oncology in Spain, where the availability of bevacizumab biosimilars created a window of opportunity for patients. It enabled the conduct of a phase II clinical trial evaluating the efficacy of combination therapy with encorafenib, cetuximab, and bevacizumab in patients with metastatic colorectal cancer (CRC) harboring the BRAF-V600E mutation (BRAVE study). Such combination-based strategies may be essential for improving survival rates in CRC [84].

To accelerate the detection and implementation of paradigm shifts, the introduction of biosimilars should be accompanied by resources to support the establishment of patient registries. Health authorities, with industry support, could fund such initiatives. Algorithms applied to these large datasets (big data) would enable more rapid substantiation of real-world outcomes across therapeutic scenarios. The EMA itself has emphasized the importance of registries in generating knowledge from clinical practice evidence [85]. In a presentation to the European Parliament, the Chair of the Special Committee on Beating Cancer (BECA) [86] underscored that oncology care is indisputably optimized through data gathered from cancer registries and databases. Biosimilars will undoubtedly expand the evidence base and thereby help drive further evolution in therapeutic paradigms across multiple areas.

Overall, as discussed by Penninx et al. [87], biological medicines should be continuously optimized in clinical practice as evidence and experience accumulate. The entry of biosimilars may further facilitate this process by reducing treatment costs and broadening the use of biological therapies, thereby generating experience in larger patient populations and creating additional opportunities for treatment optimization.

3 Conclusions

Beyond their contribution to healthcare sustainability, biosimilars function as catalysts for innovation, with the potential to enhance clinical practice and improve patient outcomes. The expanding evidence base in Europe now permits a systematic evaluation of biosimilar-driven innovation. Although the connection between biosimilars and innovation has long been recognized, it has received limited analytical attention. This review proposes a structured classification of biosimilar-driven innovation, examines its sources and mechanisms, and substantiates their actual or potential clinical impact. The delineation into Pharmaceutical, Technological, and Therapeutic Innovation clarifies how biosimilar development, manufacturing, commercialization, and use translate into innovative outcomes that ultimately converge in therapeutic progress. Biosimilars also stimulate innovation in the regulatory arena. EMA-led debates [88, 89], which laid the groundwork for biosimilar regulatory science, are particularly noteworthy. Recent regulatory revisions point to a clear trend toward reducing the number of clinical studies required, in recognition of their limited additional contribution to demonstrating biosimilarity in many cases, even when intended to provide confirmatory evidence within the comparability exercise [90]. Regulatory approaches are also evolving with respect to pharmacodynamic biomarkers. FDA has emphasized their value as sensitive tools for demonstrating similarity in pharmacological response and, in appropriate circumstances, as an alternative to conventional comparative efficacy studies [91]. The latest EMA tailored clinical approach goes further by recognizing that, for well-characterized biologics with compelling structural and functional similarity, comparative human PD data may themselves be unnecessary. This evolution reflects a long-standing regulatory and scientific debate and is likely to further streamline biosimilar development while reinforcing the intrinsic value of the biosimilar pathway.

Overall, biosimilars deliver value that extends beyond cost-efficiency, opening new opportunities for healthcare systems and generating meaningful—though sometimes indirect or delayed—patient benefits. Realizing these benefits requires acknowledging their innovative potential and implementing incentives that support clinical uptake. In this regard, the European debate has stressed the need to ensure a sustainable biosimilar market and to encourage adoption within healthcare institutions. Proposed measures include supply-side interventions, such as pricing and procurement strategies designed to stimulate competition, ensure supply continuity, and maintain patient-centeredness, alongside demand-side initiatives directed at prescribers, pharmacists, and patients. Particularly

effective are gainsharing programs, which reinvest savings from biosimilar use into clinical services and reduce the opportunity costs associated with underuse. This rationale underpins the European Parliament's call for greater reliance on off-patent medicines [92], as well as a US FDA report affirming that competition and innovation—through the biosimilar–innovation nexus—are mutually reinforcing rather than opposing forces [93].

Although seemingly paradoxical, the analysis presented here demonstrates that replicating a reference biological medicine can itself embody substantive innovative value. Therefore, the contribution of biosimilars extends well beyond sustainability: they support incremental innovation and create conditions that enable more disruptive advances—both linked to improved healthcare delivery and, ultimately, better patient outcomes. We hope that this review will raise awareness among healthcare professionals that promoting the use of biosimilars in both treatment-naïve patients and those already receiving therapy contributes to healthcare sustainability and broader access to biological treatment. Importantly, however, their use also incentivizes scientific, technological and clinical advances that will ultimately benefit the patients of tomorrow.

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