

**BIOSIMILARS IN MODERN THERAPEUTICS: SCIENCE, REGULATION, AND THE
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ABSTRACT

The expiry of patents covering the first generation of recombinant biological medicines has opened the way for a distinct class of therapeutics known as biosimilars — biological products developed to be highly similar, though never identical, to an already-licensed reference biologic. Unlike small-molecule generic drugs, which can be reproduced as exact chemical copies, biosimilars are manufactured in living cells through processes that are inherently variable, so that perfect replication of the reference product is not achievable. This review draws together historical, regulatory, clinical, and economic literature, together with current regulatory and market data, to give an integrated picture of where the field now stands. It traces the conceptual distinction between biosimilars, generics, and originator biologics; examines the manufacturing and analytical challenges that make biosimilar development a fundamentally different exercise from generic drug development; and compares the regulatory pathways of the European Medicines Agency, the United States Food and Drug Administration, and the World Health Organization, including the substantial policy shifts of 2022–2025 toward routine interchangeability. The review also considers immunogenicity, extrapolation of indications, switching, and interchangeability, and the economic forces that have shaped biosimilar uptake in Europe and the United States, where generic and biosimilar medicines together generated an estimated 467 billion United States dollars in healthcare savings in 2024 alone. Evidence from erythropoietin, filgrastim, infliximab, etanercept, and adalimumab biosimilars illustrates general principles throughout. The review concludes that, while biosimilars carry genuine promise for expanding access to biological therapy and easing the financial burden on health systems, their responsible use depends on continued vigilance around manufacturing consistency, robust post-marketing surveillance, and clear communication between regulators, manufacturers, and clinicians.

KEYWORDS: biosimilars; biologics; biopharmaceuticals; regulatory science; immunogenicity; extrapolation; interchangeability; pharmacovigilance; healthcare economics.**1. INTRODUCTION**

Biological medicines — proteins manufactured using recombinant DNA technology, hybridoma techniques, and controlled gene expression — have transformed the treatment of conditions once considered untreatable, from anaemia and rheumatoid arthritis to certain cancers and inflammatory bowel disease (Nowicki, 2007; Sekhon & Saluja, 2011). Since the approval of recombinant human insulin in 1982, the biologics sector has grown into one of the fastest-expanding segments of the

pharmaceutical industry. Independent market analyses now place the global biosimilars market at somewhere between 12 billion and 41 billion United States dollars in 2024–2025, depending on methodology, with most forecasts projecting continued double-digit annual growth through the early 2030s (BCC Research, 2025; Precedence Research, 2025; Straits Research, 2025; Mordor Intelligence, 2025).

As patents on the earliest biologics — including epoetin alfa, filgrastim, interferons, and human growth hormone — began to expire in the mid-2000s, manufacturers other than the original innovators sought to bring similar, lower-cost versions of these products to market. Because biological molecules cannot be copied with the precision of a small chemical drug, regulators in Europe and elsewhere coined a new term for these products: biosimilars, known in the United States for some years as "follow-on biologics" (Roger, 2006; Nowicki, 2007). The European Union approved the first biosimilars, Omnitrope and Valtropin, in 2006, and by the time the United States Food and Drug Administration approved its first biosimilar, Zarxio, in 2015, the European experience already spanned nearly a decade (Nowicki, 2007; Kirchhoff *et al.*, 2017).

Growth since then has accelerated markedly. The FDA approved only five biosimilars in 2023 but 18–19 in 2024, a record year, with a further 18 approvals recorded across 2025 covering aflibercept, denosumab, insulin aspart, pertuzumab, tocilizumab, and ustekinumab biosimilars, among others (GaBI Online, 2026; Center for Biosimilars, 2025; Pharmaceutical Technology, 2025). By late 2025, cumulative FDA biosimilar approvals had reached the high 80s, with the most recent addition being an insulin aspart biosimilar approved in July 2026 (Drugs.com, 2026; Biosimilars Forum, 2025). This review brings together these historical and current strands of the biosimilar literature — spanning basic science, regulatory policy, pharmacovigilance, and health economics — to answer a deceptively simple question that recurs throughout the field: how similar is similar enough?

2. Biosimilars, Generics, and Originator Biologics: Conceptual Foundations

The central conceptual point running through nearly every paper on this subject is that a biosimilar is not a generic. A generic drug is a chemical and therapeutic equivalent of a small-molecule reference product;

because such molecules are typically fewer than 1,000 daltons in molecular weight and can be fully defined by a single chemical formula, an independent manufacturer can reproduce them exactly (Roger, 2006; Sekhon & Saluja, 2011). Approval of a generic therefore requires only proof of pharmaceutical equivalence and bioequivalence, usually established in a modest study of healthy volunteers (Crommelin *et al.*, 2005).

Biologics occupy an entirely different order of complexity. Filgrastim has a molecular weight of roughly 18,800 daltons, epoetin alfa around 30,400 daltons, rituximab around 145,000 daltons, and Factor VIII more than 264,000 daltons — one hundred to one thousand times larger than typical chemical drugs such as aspirin or simvastatin (Roger, 2006; Nowicki, 2007). Beyond their primary amino-acid sequence, biologics possess secondary, tertiary, and sometimes quaternary structure, stabilised by hydrogen and disulphide bonds, and many undergo post-translational modification such as glycosylation that can vary from batch to batch and from cell line to cell line (Roger, 2006; Sekhon & Saluja, 2011). Because these products are grown in living host cells rather than assembled through predictable organic chemistry, "the process is the product": even a subtle, seemingly inconsequential change in fermentation conditions, purification steps, or formulation can alter the clinical behaviour of the final molecule (Roger, 2006; Crommelin *et al.*, 2005).

For this reason, every regulatory authority that has issued biosimilar guidance — the European Medicines Agency, the United States Food and Drug Administration, and the World Health Organization — defines a biosimilar not as an identical copy but as a product that is "highly similar" to its reference biologic, with no clinically meaningful differences in safety, purity, and potency (Kirchhoff *et al.*, 2017; Carrascosa *et al.*, 2018). Table 1 summarises how the major regulatory definitions converge on this same principle while differing slightly in wording and emphasis.

Table 1: Regulatory Definitions of a Biosimilar

Body	Definition
EMA	A biological medicinal product that contains a version of the active substance of an already authorised reference medicinal product in the European Economic Area.
FDA	A biological product that is highly similar to a US-licensed reference product notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences in safety, purity, or potency.
WHO	A biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference product.

Source: adapted from Kirchhoff *et al.* (2017).

Sekhon and Saluja (2011) offer a useful complementary framework, contrasting biologics, biosimilars, and generics across manufacturing, clinical development, and

regulatory dimensions. Generics require only Phase I bioequivalence data and are subject to automatic pharmacy-level substitution; biosimilars, like their

reference biologics, require extensive Phase I–III trials, ongoing pharmacovigilance, and — historically, though this is now changing — no automatic substitution without physician involvement (Sekhon & Saluja, 2011; Nowicki, 2007).

3. The Manufacturing Challenge: Why Biosimilars Cannot Be Identical

The manufacture of a biosimilar begins years, sometimes decades, after the reference product was first developed, and the biosimilar manufacturer has no access to the innovator's proprietary cell line, expression vector, or purification protocol (Kirchhoff et al., 2017; Carrascosa et al., 2018). The developer must therefore reverse-engineer a production process from public information — patents, published literature, and regulatory assessment reports — and then confirm through extensive laboratory work that the resulting molecule matches the reference product's critical quality attributes (Kirchhoff et al., 2017).

Every stage of this process introduces an opportunity for variation. A different host cell line (bacterial, yeast, or mammalian) can alter glycosylation patterns; different fermentation vessels, culture media, temperature, and agitation conditions can change protein folding and aggregation; and different chromatographic purification steps can leave behind different residual impurities (Crommelin et al., 2005; Roger, 2006; Carrascosa et al., 2018). Nowicki (2007) notes that recombinant erythropoietins differ from one another in carbohydrate structure and sialic-acid content depending on the cell line used, while Roger (2006) observes that no two "master cell banks" are ever exactly alike.

These are not abstract concerns. Crommelin et al. (2005) describe an analysis of Brazilian biosimilar epoetins in which potency ranged from 68 to 119 per cent of the value stated on the label, and a later study of eleven biosimilar epoetins from eight manufacturers found *in vivo* bioactivity ranging from 71 to 226 per cent of specification, with isoform patterns varying even between batches from the same manufacturer. Roger (2006) reports similar findings using the EPREX reference standard, where activity in a mouse bioassay ranged from 71 to 226 per cent, and some samples contained up to 50 per cent more epoetin alfa than the label claimed. These historical findings, largely from products marketed outside the stringent EU, US, Canadian, or Australian regulatory frameworks, underscore why modern biosimilar guidelines insist on head-to-head analytical comparison rather than independent specification-setting.

Modern analytical science has become considerably more capable of detecting these differences. Kirchhoff et al. (2017) catalogue the techniques now routinely used to establish analytical similarity: mass spectrometry and peptide mapping to confirm primary sequence; circular dichroism, differential scanning calorimetry, and X-ray

crystallography to assess higher-order structure; chromatographic and electrophoretic methods to evaluate charge heterogeneity and aggregation; and cell-based bioassays, surface plasmon resonance, and enzyme-linked immunosorbent assays to confirm functional activity such as receptor binding and antibody-dependent cytotoxicity. The FDA formalises this into a three-tier statistical framework, in which critical quality attributes judged to have a high impact on safety or efficacy are subjected to a rigorous equivalence analysis, while those of lower impact are evaluated through quality-range comparison or simple graphical presentation (Kirchhoff et al., 2017).

4. Global Regulatory Frameworks

4.1 The European Union: A Pioneering Pathway

The European Union was the first jurisdiction in the world to establish a dedicated legal pathway for biosimilars, beginning with Directive 2001/83/EC and its 2004 amendment (Directive 2004/27/EC), which explicitly distinguished biosimilars from generic medicinal products (Roger, 2006; Nowicki, 2007). The European Medicines Agency subsequently issued an overarching biosimilars guideline together with product-class-specific annexes covering recombinant erythropoietin, somatropin, granulocyte colony-stimulating factor, human insulin, interferon alfa, and low-molecular-weight heparins (Nowicki, 2007; Sekhon & Saluja, 2011). The maturity of this pathway is reflected in the scale of approvals: by 2017 the EMA had authorised biosimilars across eleven product classes under thirty-one different trade names (Kirchhoff et al., 2017), and by September 2022 the agency reported having reviewed more than one hundred biosimilar candidate submissions and authorised 86 biosimilar medicines over fifteen years of experience (European Medicines Agency & Heads of Medicines Agencies, 2022).

A landmark policy shift occurred on 19 September 2022, when the EMA and the Heads of Medicines Agencies issued a joint statement confirming that, from a scientific standpoint, all biosimilars authorised in the European Union are interchangeable with their reference product or with an equivalent biosimilar of the same reference product (European Medicines Agency & Heads of Medicines Agencies, 2022; European Pharmaceutical Review, 2022). This statement, updated on 21 April 2023, was grounded in more than one million patient-treatment years of safety data and explicitly removed the need for additional systematic switching studies before a prescriber or health system can interchange products (GaBI Online, 2023a; Big Molecule Watch, 2022). Notably, the statement addresses scientific interchangeability rather than automatic pharmacy-level substitution, decisions about which remain the responsibility of individual member states (European Pharmaceutical Review, 2022).

4.2 The United States: A Later but Rapidly Converging Pathway

The United States lagged behind Europe by nearly a decade. The Biologics Price Competition and Innovation Act of 2009 created an abbreviated licensure pathway for biosimilars, granting twelve years of market exclusivity and four years of data exclusivity to reference biologics (Blackstone & Fuhr, 2013). As of mid-January 2013, the FDA had received only thirteen inquiries about potential biosimilar applications and had not yet approved a single product; the first US biosimilar, Zarxio, a filgrastim biosimilar, was not approved until 2015 (Blackstone & Fuhr, 2013; Kirchhoff et al., 2017).

Since then, growth has been rapid. By August 2024 the FDA had approved 59 biosimilars; 2024 alone brought 18–19 new approvals, including the first biosimilars of ustekinumab (Wezlana) and denosumab (Wyost and Jubbonti), and 2025 added a further 18 approvals across aflibercept, bevacizumab, denosumab, insulin aspart, omalizumab, pegfilgrastim, pertuzumab, ranibizumab, tocilizumab, and ustekinumab (Center for Biosimilars, 2024, 2025; GaBI Online, 2026). Cumulative FDA approvals had reached roughly 88 products by mid-2026 (Drugs.com, 2026).

A distinctive feature of US law has historically been the concept of interchangeability, a designation beyond biosimilarity that permits pharmacy-level substitution without prescriber intervention in states that allow it. To earn this status, sponsors were originally required to submit data from a dedicated switching study involving at least two alternating exposures between the biosimilar and reference product (Carrascosa et al., 2018). This requirement has since been substantially relaxed. A meta-analysis by FDA scientists, published in 2023 and covering 5,252 patients who switched between a biosimilar and its reference product, found essentially no difference in the risk of death, serious adverse events, treatment discontinuation, or immunogenicity between switched and non-switched patients (Herndon et al., 2023; U.S. Food and Drug Administration, 2023). On the strength of this and similar evidence, the FDA issued updated draft guidance in June 2024 stating that dedicated switching studies are generally no longer necessary to support an interchangeability designation, and by September 2024 the agency had already deemed several biosimilars interchangeable without such studies (Center for Biosimilars, 2024; The Rheumatologist, 2024; Paragon Institute, 2025). In October 2025 the FDA extended this logic further, proposing in draft guidance that comparative efficacy trials with clinical endpoints may not be necessary at all to establish biosimilarity, relying instead on analytical and pharmacokinetic comparison (Jones Day, 2025). The agency has also recommended to Congress that the legal distinction between "biosimilar" and "interchangeable biosimilar" be eliminated altogether, arguing that it creates a false perception that interchangeable products are safer than

ordinary biosimilars (AgencyIQ, 2024; GaBI Online, 2025).

4.3 The World Health Organization and Global Harmonisation

The World Health Organization published its first general guiding principles for biosimilar evaluation in 2009 with the explicit aim of harmonising national frameworks; countries including Canada, Brazil, South Africa, Japan, and South Korea have drawn on these principles in constructing their own guidelines (Kirchhoff et al., 2017). The WHO Expert Committee on Biological Standardization adopted a substantially revised version of these guidelines at its seventy-fifth meeting in April 2022, broadening their scope from "similar biotherapeutic products" to the wider category of "biosimilars," and, notably, permitting the use of a non-locally sourced reference product as a comparator where the originating jurisdiction has comparable scientific and regulatory standards (Kang et al., 2023; World Health Organization, 2022; Wadhwa et al., 2022). This last change is particularly significant for smaller regulatory authorities, including those in the Middle East and North Africa, which have historically depended on WHO guidance to structure their own biosimilar pathways (Kurki et al., 2022; PMC, 2024).

Even so, Kirchhoff et al. (2017) emphasise that global harmonisation remains incomplete: countries differ in their requirements for the selection of reference products, the amount of in-vivo non-clinical data required, and the criteria for extrapolating a biosimilar's approval across multiple indications. Outside these frameworks, so-called "non-comparable biotherapeutic products" or "intended copies" have entered some markets, particularly in Latin America, without following an internationally recognised biosimilarity pathway; Carrascosa et al. (2018) caution that such products cannot properly be called biosimilars.

5. From Analytical Bench to Bedside: The Similarity-Assessment Ladder

A defining feature of biosimilar development, in contrast to originator biologic development, is that clinical trials are not designed to re-establish safety and efficacy from scratch. Instead, the entire development programme is structured as a stepwise, "totality of the evidence" exercise intended to resolve any residual uncertainty left over after analytical comparison (Kirchhoff et al., 2017; Carrascosa et al., 2018).

The first and most heavily weighted step is analytical and functional characterisation, comparing primary sequence, higher-order structure, glycosylation, charge variants, and bioactivity between multiple lots of the biosimilar and the reference product (Kirchhoff et al., 2017). Where residual uncertainty remains, non-clinical in-vivo studies may be required, though regulatory opinion has moved steadily away from routine animal testing given its ethical costs and limited predictive value for immunogenicity in humans (Kirchhoff et al., 2017).

Finally, comparative clinical pharmacokinetic and pharmacodynamic studies, and, where necessary, an equivalence trial in a clinically sensitive patient population, have traditionally been used to confirm that no clinically meaningful differences exist — though, as described above, the FDA's October 2025 draft guidance signals movement away from requiring even this final clinical step in most cases (Jones Day, 2025). Kirchhoff *et al.* (2017) summarise the underlying logic succinctly: clinical studies are "a blunt instrument" in biosimilar development, while analytical evaluation is the more sensitive tool for detecting meaningful differences.

This logic also underpins the principle of extrapolation, whereby a biosimilar studied clinically in only one or two indications of the reference product may be approved for all of the reference product's other licensed indications, provided the mechanism of action is shared across those indications and no unique safety concerns are anticipated (Carrascosa *et al.*, 2018; Kirchhoff *et al.*, 2017). Several infliximab biosimilars, for example, were studied clinically only in rheumatoid arthritis and ankylosing spondylitis yet were approved for psoriasis, Crohn's disease, and ulcerative colitis on the strength of extrapolated data (Carrascosa *et al.*, 2018). Physician comfort with extrapolation has historically been mixed — in one US survey, only 12.3 per cent of specialists said they would be comfortable using a biosimilar across all approved indications without indication-specific data (Carrascosa *et al.*, 2018) — underscoring a persistent gap between regulatory science and clinical confidence that ongoing education efforts continue to address.

6. Immunogenicity and Pharmacovigilance

If there is a single safety issue that unites the biosimilar literature, it is immunogenicity — the capacity of a therapeutic protein to provoke an antibody response, ranging from clinically silent to severe or life-threatening (Nowicki, 2007; Crommelin *et al.*, 2005; Sekhon & Saluja, 2011). The paradigm case, referenced throughout this literature, is the outbreak of antibody-mediated pure red cell aplasia associated with Eprex (epoetin alfa) in the early 2000s. A change in formulation — replacing human serum albumin with polysorbate 80 as a stabiliser, combined with the use of uncoated rubber stoppers in pre-filled syringes — allowed organic compounds to leach from the stoppers, acting as adjuvants that triggered neutralising antibody formation against native erythropoietin in patients treated subcutaneously (Nowicki, 2007; Roger, 2006; Crommelin *et al.*, 2005). Patients who developed pure red cell aplasia became profoundly anaemic and transfusion-dependent; the episode occurred more than ten years after epoetin's original approval and was traced to what was, on paper, a minor manufacturing change (Nowicki, 2007).

The Eprex case illustrates two enduring lessons. First, analytical and non-clinical tools cannot reliably predict clinical immunogenicity in isolation; as Roger (2006) puts it, "one protein can be different from another in

ways that cannot be detected in the laboratory, but are seen only by the body's exquisitely sensitive immune system." Second, because immunogenic reactions are often rare, pre-approval clinical trials are typically underpowered to detect them, making robust post-marketing pharmacovigilance indispensable rather than optional (Crommelin *et al.*, 2005; Sekhon & Saluja, 2011).

More recent, larger-scale evidence has been reassuring. Beyond the FDA's 2023 meta-analysis described above, a 2022 systematic review by Cohen and colleagues examining switching between different biosimilars of the same reference product — rather than simply between originator and biosimilar — likewise found no signal of increased immunogenicity or loss of efficacy, a finding subsequently reinforced by additional real-world studies published in 2024 (Cohen *et al.*, 2022; Cohen & Bodenmueller, 2024; American Journal of Managed Care, 2024). Nonetheless, both the EMA and the FDA continue to require risk-management and pharmacovigilance plans as a condition of biosimilar approval, with particular attention to long-term immunogenicity monitoring and clear product traceability, since biosimilars sharing an international non-proprietary name with their reference product can otherwise complicate the attribution of adverse-event reports to the correct manufacturer (Nowicki, 2007; Roger, 2006; Carrascosa *et al.*, 2018).

7. Switching and Interchangeability in Clinical Practice

As biosimilars have matured, the clinical question has shifted from "can this product be approved" to "can this patient safely be moved onto it." Carrascosa *et al.* (2018) provide an extensive synthesis of early switching evidence, drawing on infliximab, etanercept, and adalimumab biosimilar trials, and this evidence base has since grown considerably larger and more reassuring.

For infliximab, the NOR-SWITCH trial — a randomised, blinded, non-inferiority study spanning multiple indications including psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, and ulcerative colitis — found comparable rates of treatment-emergent adverse events and anti-drug antibodies between patients who switched to the CT-P13 biosimilar and those who remained on the originator (Carrascosa *et al.*, 2018). Similar findings emerged from open-label extensions of the PLANETRA and PLANETAS trials and from large real-world registries such as the Danish DANBIO and DERMBIO cohorts, which found no significant increase in discontinuation risk after a non-medical switch from originator infliximab or etanercept to their respective biosimilars (Carrascosa *et al.*, 2018).

The EQUALITY study of the etanercept biosimilar GP2015 used a multiple-switch design in which patients alternated between originator and biosimilar etanercept up to three times over thirty weeks; repeated switching

produced no detectable loss of efficacy, no increase in adverse events, and no anti-drug antibody positivity in either arm (Carrascosa et al., 2018). This body of single- and multiple-switch evidence has since been extended by pooled analyses: the 2023 FDA-led meta-analysis of 5,252 switched patients found a risk difference of essentially zero for death, serious adverse events, and treatment discontinuation across all switch types studied (Herndon et al., 2023). A parallel line of research has examined switching between different biosimilars of the same reference product — an increasingly common scenario now that products such as adalimumab have ten or more approved biosimilars on the US market — and has likewise found switching to be well tolerated, without loss of clinical, functional, or inflammatory remission (Cohen et al., 2022; Cohen & Bodenmueller, 2024).

This accumulated evidence underpinned the regulatory shifts described in Section 4: the EMA and Heads of Medicines Agencies concluded in 2022 that all EU-authorized biosimilars can be regarded as interchangeable from a scientific standpoint (European Medicines Agency & Heads of Medicines Agencies, 2022), while the FDA's 2024 and 2025 guidance updates progressively removed the requirement for dedicated switching studies and comparative efficacy trials (Center for Biosimilars, 2024; Jones Day, 2025). Even so, Carrascosa et al. (2018) caution against over-generalising switching findings from one biosimilar to another biosimilar of a different molecule, since immunogenic potential may differ by product, and most switching studies to date have still been conducted in rheumatic disease populations rather than in dermatological or other extrapolated indications specifically.

8. The Economics of Biosimilars

The economic case for biosimilars begins with a stark cost disparity: Blackstone and Fuhr (2013) report an average daily cost of biologic therapy in the United States of roughly 45 US dollars, compared with about 2 US dollars for small-molecule drugs. Because a large share of the best-selling pharmaceutical products worldwide are now biologics, and because tens of billions of dollars of biologic sales have lost or will soon lose patent protection, the commercial stakes surrounding biosimilar entry remain considerable (Blackstone & Fuhr, 2013; Pharmaceutical Technology, 2025).

Yet, as Blackstone and Fuhr (2013) demonstrate at length, the economics of biosimilar entry bear little resemblance to the economics of small-molecule generic entry. Developing a biosimilar has historically cost an estimated 100–250 million US dollars and taken seven to eight years, compared with roughly 1–4 million US dollars and a much shorter timeline for a conventional generic. Manufacturing expertise, cold-chain distribution, immunogenicity testing, and the need to recruit patients into comparative clinical trials all raise

the barriers to entry well above those faced by generic manufacturers (Blackstone & Fuhr, 2013). The FDA's recent moves to remove comparative efficacy trial requirements are explicitly intended to narrow this cost gap and accelerate market entry (Jones Day, 2025).

In the European Union, where biosimilars have been available since 2007, prices have typically been fifteen to thirty per cent lower than the reference product — a smaller discount than the eighty to ninety per cent reductions typically seen once several small-molecule generics enter a market (Blackstone & Fuhr, 2013; Carrascosa et al., 2018). In the United States, however, biosimilar savings have grown rapidly as the market has matured. According to the Association for Accessible Medicines and the IQVIA Institute, biosimilar medicines alone generated 12.4 billion US dollars in savings in 2023, rising to 20.2 billion US dollars in 2024, with cumulative biosimilar savings since the 2015 launch of Zarxio reaching 56.2 billion US dollars by the end of 2024 (Association for Accessible Medicines & IQVIA Institute, 2024, 2025). Generic and biosimilar medicines combined delivered an estimated 445 billion US dollars in system-wide savings in 2023 and 467 billion US dollars in 2024, out of total savings exceeding 3.4 trillion US dollars over the preceding decade (Association for Accessible Medicines & IQVIA Institute, 2025). A separate IQVIA forecast projects that cumulative US biosimilar spending could reach 129 billion US dollars between 2023 and 2027, generating as much as 180 billion US dollars in savings over the same period as additional blockbuster biologics face competition (IQVIA Institute, 2023; Oncology Practice Management, 2023).

Even modest per-unit discounts can translate into meaningful system-level savings given the scale of biologic spending. Carrascosa et al. (2018) cite a budget-impact analysis estimating that switching rheumatoid arthritis patients across France, Germany, Italy, and the United Kingdom from originator to biosimilar infliximab could generate savings exceeding 433 million euros over five years. Blackstone and Fuhr (2013) similarly argue that large, well-established pharmaceutical companies with existing manufacturing and marketing infrastructure — rather than small new entrants — are best positioned to dominate the biosimilar market, a prediction broadly consistent with the roster of approved biosimilar manufacturers, including Sandoz, Amgen, Celltrion, Samsung Bioepis, and Pfizer, that continues to dominate approvals today (Kirchhoff et al., 2017; Pharmaceutical Technology, 2025).

9. Biosimilars in Clinical Practice: Nephrology and Dermatology as Case Studies

Nephrology was the first specialty to confront the practical realities of biosimilar substitution, given the early expiry of epoetin alfa patents and the centrality of erythropoiesis-stimulating agents to the management of renal anaemia. Roger (2006) and Nowicki (2007) both

frame nephrology as a bellwether for the rest of medicine: the pure red cell aplasia episode described above occurred in dialysis patients, and the resulting emphasis on rigorous post-marketing surveillance, careful formulation control, and cautious substitution policy became the template followed by other therapeutic areas.

Dermatology offers a more recent and, in some ways, more encouraging case study. Carrascosa *et al.* (2018) document how anti-tumour necrosis factor biosimilars of adalimumab, etanercept, and infliximab entered psoriasis care largely through extrapolation from rheumatological trials, and how accumulating switching data — from randomised trials such as EGALITY and NOR-SWITCH to real-world registries such as DERMBIO — have generally reassured clinicians about the safety of transition. National dermatology societies nonetheless differ in how far they are willing to go: some explicitly favour biosimilars studied directly in psoriasis populations over those approved solely by extrapolation, while others emphasise that the prescribing physician must always retain the final say over any switch (Carrascosa *et al.*, 2018).

Across both fields, the role of nurses and pharmacists remains central. Sekhon and Saluja (2011) argue that because biosimilars are not interchangeable with their reference products in the same sense as small-molecule generics — at least in the traditional US legal sense, even as the scientific distinction narrows — nurses administering these agents and pharmacists dispensing them must be specifically educated about the differences, and meticulous record-keeping of exactly which product a patient received remains essential for meaningful pharmacovigilance. Crommelin *et al.* (2005) translate this concern into a practical tool, proposing a detailed checklist for hospital pharmacists covering quality, clinical efficacy, safety, and value considerations before a biosimilar is adopted into formulary use.

10. Remaining Challenges and Future Directions

Several unresolved issues recur across the literature reviewed here. The first is nomenclature: the WHO and national regulators have not reached full consensus on whether biosimilars should carry a distinguishing suffix or an entirely separate international non-proprietary name, a decision with direct consequences for pharmacovigilance traceability, although the FDA's 2023 labelling guidance moved toward a unifying "biosimilarity statement" rather than a separate interchangeability statement (Hogan Lovells, 2023; Nowicki, 2007; Roger, 2006).

The second is the pace and structure of competitive entry. Blackstone and Fuhr (2013) note that, unlike the Hatch-Waxman framework for small-molecule generics, the first biosimilar entrant in the United States receives no period of exclusivity analogous to the 180-day exclusivity granted to first generic challengers, which

may blunt the incentive for early entry. The Association for Accessible Medicines' 2024 savings report similarly warns that despite biosimilars accounting for roughly a third of the addressable market against brand biologics, sustained uptake faces structural challenges from pharmacy benefit manager formulary practices, particularly for high-profile molecules such as adalimumab (Association for Accessible Medicines & IQVIA Institute, 2024).

The third is the durability of manufacturing consistency over the product life cycle. Kirchhoff *et al.* (2017) emphasise that biosimilar developers must not only match the reference product at launch but sustain that similarity across every subsequent production run, even as manufacturing technology, and sometimes production facilities, evolve over time.

Finally, the regulatory landscape itself is now evolving rapidly. The near-simultaneous 2022 EMA-HMA interchangeability statement, the 2022 WHO guideline revision, and the FDA's 2024–2025 draft guidances removing switching-study and comparative-efficacy requirements collectively represent the most significant liberalisation of biosimilar regulatory science since the field began (European Medicines Agency & Heads of Medicines Agencies, 2022; Kang *et al.*, 2023; Jones Day, 2025). Whether clinical practice, payer policy, and patient trust converge as quickly as regulatory science has moved remains, as Carrascosa *et al.* (2018) and Kirchhoff *et al.* (2017) both observe, an open and consequential question.

11. CONCLUSION

Biosimilars occupy a genuinely distinct category in pharmaceutical science — close enough to their reference biologics to share a fundamental mechanism of action and clinical purpose, yet distinct enough in molecular detail that they can never be assumed identical in the way a small-molecule generic can. This duality explains almost everything distinctive about how biosimilars are made, regulated, monitored, and used in practice: the historical reliance on comparative rather than de-novo clinical trials, the emphasis on analytical characterisation over clinical testing, the persistence of immunogenicity as the central safety concern, and the comparatively modest price discounts observed relative to conventional generics.

The evidence reviewed here, spanning nearly two decades of European experience and a shorter but rapidly maturing body of US data, is on balance reassuring: well-regulated biosimilars approved through the EMA, FDA, or WHO-aligned pathways have not demonstrated systematic safety or efficacy shortfalls relative to their reference products, and large pooled analyses of switching across infliximab, etanercept, adalimumab, and other biosimilars have shown no meaningful loss of efficacy or increase in immunogenicity. This accumulated confidence is now visible directly in policy:

the EMA and Heads of Medicines Agencies declared EU-approved biosimilars scientifically interchangeable in 2022, and the FDA has since 2024 been dismantling the separate interchangeability pathway it once required, with proposals in 2025 to remove comparative efficacy trials from biosimilar development altogether. At the same time, the historical episodes of variable potency among unregulated "biosimilar" epoetins, and the Eprex pure red cell aplasia outbreak among fully regulated products, remain reminders that vigilance cannot be relaxed simply because a product carries regulatory approval. As more complex molecules move through the biosimilar pipeline and the regulatory bar for entry continues to fall, the responsibility for translating good regulatory science into good clinical practice will increasingly rest with informed prescribers, pharmacists, and patients working from an accurate, shared understanding of what a biosimilar is, and is not.

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