RESEARCH PAPER

From Molecule to Market: A Comprehensive Review of Biosimilar Manufacturing, Regulatory Evolution, and Global Access Strategies

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ABSTRACT
Chronic and severe conditions have drastically changed with biopharmaceuticals, but their high prices still limit accessibility for many people globally. As a possible alternative to traditional pharmaceuticals, biosimilars — which are almost but not exactly identical to already marketed reference biologics — offer therapeutic benefits that could reduce overall costs to the healthcare system. This paper includes an extensive, evidence-based review of the scientific, regulatory and commercial processes involved in developing biosimilars; uses current literature; references authorities' guidelines from around the world, as well as clinical data from 2015 through 2026; and highlights various aspects of biomanufacturing processes (cell line development through purification) as well as the importance of implementing Quality by Design (QbD) principles to assure CQAs are consistent. In addition, the global regulatory environment has evolved over time, with a major shift at the U.S. FDA and EMA in 2025–2026 favouring characterising products at the molecular level via high-res analytic methods rather than conducting extensive head-to-head clinical trials to reduce development costs associated with producing biosimilars, potentially between USD100 million and USD300 million per product. A real-life example of developing adalimumab biosimilars demonstrates how you can use the totality of evidence approach to evaluate data from Phase I and Phase III studies. It has been concluded that there is now an increasing convergence between simplified regulations for approval and improvements in biopharmaceutical technology, which is resulting in a worldwide biologics market that is equitable, sustainable, and compliant.

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1. INTRODUCTION

The global pharmaceutical sector is undergoing a significant change in structure away from small-molecule "blockbuster" pharmaceuticals towards more complex biopharmaceuticals. Biologics, such as monoclonal antibodies (mAbs) like infliximab, adalimumab and trastuzumab, are large glycoproteins that exhibit structural variability (heterogeneity) and are produced from living cells within both prokaryotic (bacteria) and eukaryotic (yeast, mammalian CHO) systems. Biologics differ from chemically synthesized drugs, which have defined and reproducible molecular structures due to their chemical synthesis process, because biologics can be produced using different cellular equipment or at different manufacturing sites that can lead to greater structural or chemical variability of the biologic product during manufacture. [1]

The importance of both the clinical and commercial aspects of biologics can be seen through the economic impact of these products: In 2022 biopharmaceuticals made up about 1/3 of total worldwide sales in pharmaceuticals, representing around $383 billion dollars on an annual basis with expected annual increases around 9% until 2032. While there are numerous clinical benefits to using biologics for the treatment of conditions across all fields (oncology, immunology, endocrinology, and neurology), the costs associated with the use of biologics present major barriers/access challenges in many developing nations and when considering out-of-pocket spending for healthcare in relation to income levels.

Regulatory and commercial strategies known as "biosimilars" are designed to close the access gap between generic drugs and the biologics used by patients. Per the FDA and EMA, biosimilar products are defined as being "highly similar" to reference products, including an approved reference product (RP) for which there are no clinically significant differences in regards to safety, purity or potency. Unlike generics that contain small molecules,

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"highly similar" does not mean that a biosimilar is an exact match to its RP. There can be no two curbs to the same extent because proteins' naturally occurring biological diversity means that different proprietary production methods will have been used to make the RP and subsequent curbs. Developers of biosimilars are required to demonstrate biosimilarity through a thorough review of all data sources including analytical, functional, preclinical, and clinical. [2]

The biosimilars industry's economic opportunity is enormous as market forecasts project biosimilars' potential will yield up to $383 billion in total savings to the U.S. healthcare industry within five years (2023-2027) primarily due to direct deficit reduction benefits from lower prices for products sold under the new brand name (i.e., via pricing pressure on original brand manufacturer's pricing).[4] However, significant scientific, regulatory, commercial, and legal challenges must be addressed before widespread adoption of biosimilars occurs. This literature will report on each of the above areas, providing an integrated review and an up-to- date, confirmatory (evidence-based) typology of the existing biosimilars marketplace as it exists at the end of this reporting period.

2. THE BIOPHARMACEUTICAL PARADIGM: BIOLOGICS VERSUS BIOSIMILARS

A basic yet often overlooked distinction in the field of pharmaceuticals is between biosimilars and small molecule generics. It has major implications for development strategies, regulatory requirements, and clinical practices. Both Generics and Biosimilars are used for providing cost reductions over branded products; however, equating them creates significant oversimplification resulting in expensive strategic missteps. [5]

Generic drugs that are smaller than a molecule are made from chemicals and are manufactured to be structurally identical to their reference product(s). Small-molecule generics can be fully characterized using analytical techniques. Generic drugs are licensed based on demonstrating that they are bioequivalent to the reference product through pharmacokinetic testing. Biosimilars, on the other hand, are large and complex proteins that are produced from biological processes that have an inherent element of variability. These proteins are structurally complex and include many components, such as primary amino acid structure, three-dimensional conformation, glycosylation (a posttranslational modification), and higher-order confidentiality of the protein's structure cannot be replicated because the proprietary cell lines and manufacturing processes used by the innovator are not available to biosimilar developers. [6]

As a result, biosimilar developers must independently establish their own manufacturing process and demonstrate comparability to the reference product through extensive analytical, functional, and clinical testing a process that typically spans 8–10 years and costs USD 100–300 million. Table 1 presents a comparative summary of the key differences between small-molecule generics and biosimilars across structure, development complexity, regulatory requirements, and market considerations.

Table 1: Comparative Analysis of Small-Molecule Generics and Biosimilars

Parameter	Small-Molecule Generics	Biosimilars
Molecular Size	Small (~300–500 Da)	Large (150,000+ Da for mAbs)
Manufacturing	Chemical synthesis	Living cell-based bioproduction
Structural Identity	Chemically identical to reference	Highly similar but not identical
Development Time	3–5 years	8–10 years
Development Cost	USD 1–5 million	USD 100–300 million
Regulatory Pathway	Abbreviated NDA (ANDA); bioequivalence studies	Abbreviated BLA; totality-of-evidence comparability exercise
Clinical Requirement	PK bioequivalence only	PK, PD, safety, efficacy, immunogenicity studies
Batch Variability	Minimal; defined by specification	Inherent biological variability; managed through QbD
Interchangeability	Automatic substitution permitted	Requires specific "interchangeability" designation (U.S.)

Biosimilars are classified by molecular type, including monoclonal antibodies (mAbs), cytokines, recombinant hormones, and fusion proteins. Monoclonal antibodies represent the largest and most commercially significant biosimilar category, particularly in therapeutic areas such as oncology, rheumatology, gastroenterology, and dermatology. By late 2019, the EMA had approved 55 biosimilars and received 65 marketing authorization

applications, while the FDA had authorized 26 biosimilars. Since then these numbers have increased significantly as a maturing global biosimilar ecosystem has developed. [7]

3. GLOBAL REGULATORY FRAMEWORK: EVOLUTION AND CURRENT STATUS

The regulatory assessment of biosimilars is based on "the totality of the evidence," a methodical, hierarchical comparability exercise that utilizes a detailed analytical characterization and then proceeds through functional and nonclinical studies and clinical trials. The amount of evidence required at each subsequent level of the comparability evaluation may be reduced if there is enough evidence from previous levels that demonstrate the biosimilars are similar; this allows for an accelerated and scientific rationale for the development of biosimilars. [9]

3.1 Chronological Development of Regulatory Pathways

In 2005, the European Medicines Agency (EMA) became the first agency to set the standards for the development and approval of biosimilars through its first Guidance Document and approved the first biosimilar product ever, Omnitrope (somatropin), in 2006. This model established a scientific and regulatory framework for subsequent global biogeneric/biologic regulations. In 2010, the enactment of the Affordable Care Act included the Biologics Price Competition and Innovation Act (BPCI Act), which created an abbreviated pathway for FDA approval of biosimilars in the USA. Zarxio (filgrastim-sndz) was the first biosimilar approved in the USA in 2015. In 2009, the World Health Organization (WHO) provided a framework by establishing guidelines for Similar Biotherapeutic Products (SBPs) that could be adapted by all national regulatory authorities around the world. [9]

The approval timeline has an industry maturation pattern. The EMA was more cautious and methodical in approving products first (2006-2013) and established scientific precedent with these. Once the FDA had an established pathway for approval, it began to approve at a faster pace than the EMA in the period from 2015 to present. The FDA's faster rate of approval can be attributed to both the regulatory experience they gained from working with the EMA as well as an increase in scientific confidence in using the totality of the evidence method for making approval decisions. [10]

3.2 The 2025–2026 Regulatory Pivot: Analytical Characterization Over Large Clinical Trials

A defining moment occurred with worldwide regulation of biosimilars during the new timeframe of 2025 to 2026 as two organizations, the FDA & EMA, began to implement similar philosophies concerning development of biosimilars; that is analytical-first.

The first important component of this change was in 2026 when the FDA updated its previous draft guidance with what was considered to be the most expansive change in policy since passage of The Biologics Price Competition and Innovation Act ("BPCIA"). The biggest change involved removal of the head-to-head clinical bridging study requirement that had previously required developers to utilize only U.S.-licensed reference products. Following release of the new draft guidance, clinical data derived from non-U.S.-licensed reference products can be used as a basis for approval of a biosimilar if rigorous scientific justification and analytical bridge has been established for the comparisons. Examples of how these changes will impact the following areas include:

- **Reduction of Redundant Bridging Studies:** Previously, three-arm pharmacokinetic/pharmacodynamics (PK/PD) studies were required to determine the equivalence of the biosimilar to the U.S. reference and foreign reference product; however, these studies will not universally be required anymore, which will decrease the time to develop these new products by an estimated 12–18 months.
- **Considerable Reduction in Cost:** By removing these studies, it is expected that there will be a decrease of up to 50% of the costs related to the PK development of these products, which will provide capital cost avoidance of approximately USD 20 million for each one of these development projects.
- **Increased Market Competition:** As the U.S. reference product requirement will be eliminated, international biopharmaceutical companies will have a lower barrier to entry to the U.S. marketplace, thus increasing the amount of competitive pressure and possibly accelerating the price reductions. [11][12][13]

Independently, in April 2025, the EMA announced a similar and complementary regulatory evolution a deliberate de-emphasis of large-scale comparative efficacy trials for well-characterized biosimilar molecules, replacing them with high-resolution analytical characterization and targeted PK studies. The EMA's position is grounded in the recognition that advances in analytical technology have reached a level of precision at which structure-function relationships can be established with sufficient confidence to make large clinical efficacy trials scientifically redundant for well-characterized molecules. [14]

Table 2 compares the key regulatory metrics for FDA biosimilar development in the pre-2024 era versus the current framework, illustrating the scope of this transition.

Table 2: Evolution of FDA Biosimilar Regulatory Metrics—Pre-2024 vs. Current (2025–2026) Framework

Metric	Pre-2024 Requirements	Current Framework (2025–2026)
Reference Product Source	U.S.-licensed RP required for all clinical studies	Non-U.S. RP acceptable with analytical bridge
PK/PD Bridging Studies	Three-arm study mandatory	Waivable with strong analytical package
Phase III Efficacy Trials	Typically required for all indications	Reduced or waived for well-characterized molecules
Primary Evidence Focus	Clinical trial data	High-resolution analytical characterization + PK data
Estimated Cost Impact	USD 100–300 million/program	Potential 30–50% cost reduction
Time to Approval	10–12 years from initiation	Targeted reduction to 7–9 years

4. BIOMANUFACTURING: UPSTREAM AND DOWNSTREAM PROCESSING

Biopharmaceutical manufacturing is a highly complex, multi-stage process that critically distinguishes biosimilar development from conventional generic drug development. Biosimilar production mirrors the biopharmaceutical development pathway but incorporates additional analytical and comparability steps at each stage. Unlike innovator biologics—which begin with novel protein discovery biosimilar development begins with the reverse engineering of an existing reference product, requiring the developer to independently reconstruct a manufacturing process capable of producing a structurally and functionally comparable protein. Figure 1 provides a schematic overview of the stepwise biosimilar manufacturing process.

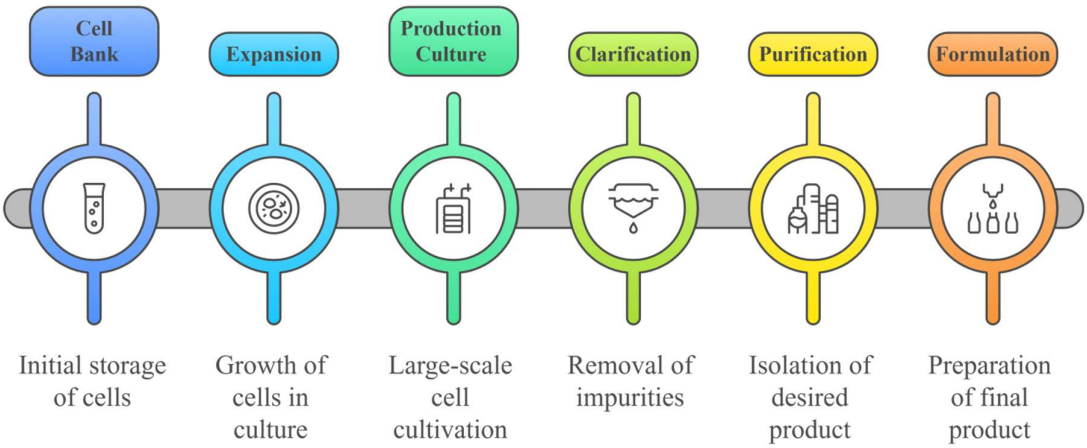

Figure 1: Schematic overview of the biosimilar manufacturing process, illustrating the key upstream and downstream stages from cell-line development through final drug product formulation.

4.1 Upstream Processing: Cell-Line Development and Protein Expression

The term "upstream" refers to all activities involved with the identification, creation and growing of a host cell line that will be used to make your target protein. The first decision you will have to make when getting ready to start an upstream phase is which expression system will be used. For both mAbs and complex glycoproteins, CHO (Chinese Hamster Ovary) cells are by far the most common expression platform because they have the ability to carry out human-like post-translational modifications, especially glycosylation. For much simpler proteins, they may be expressed in either Escherichia coli or Saccharomyces cerevisiae. It is important to understand that, as the developer of a biosimilar, developing your own proprietary cell line is necessary since the innovator is not going to give you access to their cell line. [7]

Oligosaccharide chains are attached to specific parts of the protein by an enzymatic mechanism called Glycosylation. This process is of the utmost importance when developing a biosimilar. The glycan profiles of biologics have a significant impact on half-life, receptor binding, effector

function (antibody-dependent cellular cytotoxicity, ADCC), and immunogenicity of the product.

To achieve a glycosylation profile that is within acceptable ranges compared to the reference product, very specific cell culture conditions including pH, dissolved oxygen levels, temperature, nutrient feeding strategy, and osmolarity must be strictly controlled. Minor deviations in any of these parameters may produce changes in critical quality attributes (CQAs) that are virtually undetectable without sophisticated analytical techniques or may have unintended consequences in clinical results. [15]

In order to ensure consistent protein expression, large volume bioreactors (approximately 1000-20,000 L for commercial production) have been equipped with closed loop process control systems to provide strict environmental parameters. The development of robust process analytical technology (PAT) to monitor bioreactor performance and enable real-time controls is a key part of the QbD approach for upstream processing.

4.2 Downstream Processing: Purification and Formulation

Downstream processing encompasses the sequential purification and formulation steps required to transform the crude cell culture harvest into a pure, stable, and clinically acceptable drug product.

Purification: Following cell harvest, the target protein must be separated from a complex mixture of host cell proteins, host cell DNA, viral particles, and process-related impurities. A typical downstream purification train for a mAb includes: Protein A affinity chromatography (primary capture step); virus inactivation (low-pH hold); ion exchange chromatography (cation and anion exchange for impurity removal); virus filtration; and ultrafiltration/diafiltration (buffer exchange and concentration). The specific sequence and operational parameters of these steps are optimized to achieve the required purity, yield, and molecular profile while ensuring that the purification process does not introduce new impurities or alter the structural integrity of the protein.

Formulation: The final drug product created from the purified protein bulk is either a liquid for intravenous or subcutaneous dosing, or a lyophilized powder that will be dissolved prior to administration. Formulation development aims to improve the quality and longevity of the final drug product by protecting the protein from various degradation processes, including aggregation, deamidation, oxidation, and denaturation. Stabilizers, including sugars, polyols, surfactants, and amino acids, are used during formulation development. There is also a strong current trend in innovative formulations in the market, specifically focused on creating high-concentration, buffer-free subcutaneous formulations that utilize the inherent self-buffering properties of the protein to provide reduced doses for patients, increased comfort during injection, and improved long-term stability of the finished drug product. [16]

5. CHALLENGES IN BIOSIMILAR DEVELOPMENT AND MANUFACTURING

5.1 Manufacturing Complexity and Quality Control Challenges

Regulatory agencies must provide proof through a variety of means that biosimilars are comparable to a reference product. These comparisons are quite different than those provided for small-molecule drugs because creating and demonstrating evidence of the biologically derived product's similarity must meet many different scientific and operational standards; these are the basis of all regulatory submissions for biosimilars. The FDA also defines biosimilars as "highly similar," with no meaningful clinical difference concerning safety, purity, and potency. To help manufacturers create a CQAs control system during the product development process, utilizing QbD, including the use of systematic risk assessment, defining a design space, and utilizing process analytical technology, will help identify and control appropriate CQAs for the biologically derived product and will assist in meeting the various requirements set forth by the FDAs in the biosimilar manufacturing regulatory submissions. [17][18]

There are several major manufacturing challenges associated with biosimilar biomanufacturing, including:

- **Interdependence of Process and Product**: In biogenerics, the way the product is made is just as important as the actual product itself; therefore, any change to any one of the way(s) in which a biomanufactured product is produced, such as (but not limited to) cell line passage number, bioreactor culture system conditions, chromatography resin lot, and formulation excipient grade will cause a significant change in how that product meets its CQAs (i.e. glycan profile, charge variant distribution, propensity for aggregation, potential immunogenicity) and as such, the characteristics of the manufacturing process necessitates the development and implementation of an extensive process validation program as well as continued monitoring of the manufacturing process, throughout the life of the product. [24]
- **Critical Nature of Cold Chain**: Biosimilar biomanufactured products are biological proteins that are sensitive to various environmental influences (such as temperature excursions from the proper storage temperature, mechanical stress and/or exposure to light). Therefore, it is sometimes very difficult and/or expensive (operational complexity) to maintain an unbroken cold chain (usually 2–8 degrees Celsius) from the point of manufacture through distribution to the point of patient use, especially given worldwide distribution networks, as well as healthcare environments with limited resources. [24]
- **Infrastructure and Skilled Labor Availability**: Commercial-scale biomanufacturing is capital intensive due to the required investment in specialized

manufacturing facilities, bioreactors, chromatography systems, quality control laboratories and specialized scientific personnel. Due to these costs, biosimilar biomanufacturers in lower-income countries have a substantial barrier to entry into the market. [24]

5.2 Reference Biologic Product (RBP) Sourcing Challenges

Head-to-head analytical comparison of the reference biologic product [RBP] to the biosimilar has substantial logistical and financial challenges, especially with respect to the procurement of sufficient quantities of the RBP across numerous geographical locations and many production lots. A few of the unique challenges associated with the procurement of sufficient amounts of the reference product are:

- **Multi-Lot Procurement Requirements:** Regulatory requirements for biosimilars state that the development of a successful product must involve the characterization and sourcing from multiple lots (generally 3-10 batches) of the RBP in order to address the natural variability exhibited between lots of a reference product and to establish a meaningful contractual range of comparability. Additionally, obtaining sufficient RBP from representative batches, which may be sourced from various geographies (including the U.S., Europe, and the remainder of the World), can create a significant barrier to development.
- **Volume and Cost:** As RBP for use in both comprehensive analytical characterizations of biosimilars and in comparative clinical studies will generally require large quantities of RBP, acquisition of RBP from a commercial source at market price will represent a significant development expense, particularly for biologics with a high market value such as adalimumab (Humira) which, on average, costs greater than USD 10,000 per dose.
- **Innovator Countermeasures:** Innovator companies could utilize a "buy and hold" strategy by purchasing large quantities of their own product lots through pharmacy channels in order to intentionally limit the availability of specific lot numbers to biosimilar developers and thereby increase the variability of the reference lot pool with potential impact to the subsequent biosimilar product.
- **Market Access Restrictions:** In some emerging markets where biologic products are distributed exclusively through government channels (e.g., Russia, certain Middle Eastern countries), there is no access to RBPs, resulting in the inability of domestic biosimilar developers to develop a biosimilar product based on the RBP.

5.3 Analytical and Functional Characterization

The most essential building block of biosimilar or biobetter development is the extensive physicochemical and functional characterization of the biosimilar in comparison to the reference product, which is the most in-depth scientific, labor-intensive component of biosimilar development. This evaluation of similarity must take place through a hierarchically laid-out series of attributes for both physicochemical and functional properties.

Structural Characterization:

1) **Primary structure –** Verified by peptide mapping/mass spectrometry to confirm amino acid sequence.
2) **Higher-order structure –** Verified through circular dichroism, Fourier transform infrared spectroscopy, and hydrogen-deuterium exchange mass spectrometry to provide an equivalent secondary and tertiary structure.
3) **Post-translational modifications –** Verified through glycan profiling, oxidation, and deamidation, as well as verification of clipping of C-terminal lysine residues.
4) **Size and charge heterogeneity –** Verified through size exclusion chromatography, cation exchange chromatography, and capillary electrophoresis.[21]

FUNCTIONAL CHARACTERIZATION

Functional comparability studies confirm whether or not the biosimilar has the same mechanism of action and equal biological potency compared to the reference product with respect to all approved indications. To do this, a number of functional assays must be completed, including binding assays (e.g., surface plasmon resonance, ELISA), effector function (e.g., ADCC, complement-dependent cytotoxicity), and receptor binding (e.g., Fc gamma receptors and FcRn). [22]

Figures 2 and 3 show the framework and the spectrum of functional and biological attributes that comprise the evaluation of the quality of the biosimilar during the evaluation process, respectively.

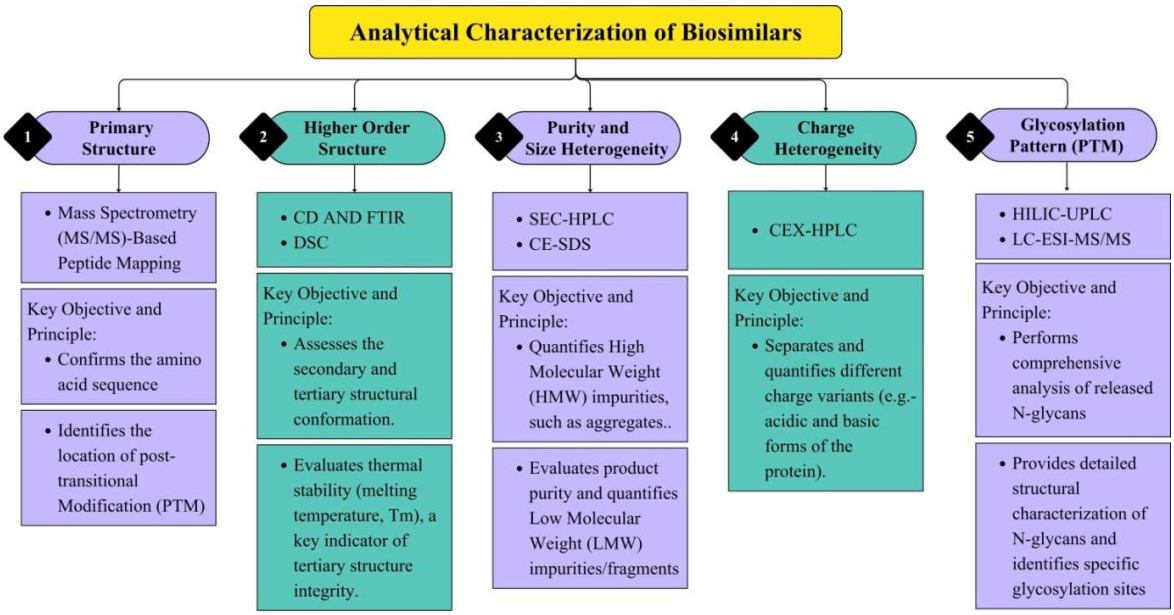

Figure 2: Hierarchical framework for biosimilar quality evaluation, illustrating the identification and control of critical quality attributes (CQAs) and their relationship to clinical outcomes.

Functional Attribute	Specific Analytical Methods	Key Objective and Principle
Target Binding / Primary MOA	Non-cell-based ligand binding assays	Compares the affinity, specificity, and kinetic rates of the biosimilar to its therapeutic target
Functional Potency	Cell-based assays	Measures the overall functional potency and biological response to ensure equivalence
Fc-Effector Functions	Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) assay	Compares the ability of the antibody to induce target cell death

Figure 3: Spectrum of functional and biological attributes assessed during biosimilar comparability exercises, including target binding, effector functions, and mechanism-of-action confirmation.

5.4 Non-Clinical and Clinical Evaluation

5.4.1 Non-Clinical Evaluation

The non-clinical development package for a biosimilar is deliberately streamlined and targeted. Its primary purpose is to resolve any residual uncertainty regarding similarity that has not been definitively addressed by the extensive analytical and functional comparability data. Non-clinical studies are not intended to re-establish the safety and efficacy profile of the reference molecule which is already well-characterized from years of clinical use—but rather to confirm that the biosimilar's pharmacological and safety characteristics are consistent with those of the reference product. [18]

Pharmacodynamic (PD) Studies: In vitro PD studies confirm similar MOA and biological effect magnitude using relevant cell-based or receptor-binding assay platforms. Where in vitro studies are insufficient to resolve outstanding questions, comparative animal studies may be conducted, although their predictive value for human immunogenicity is acknowledged to be limited. [10]

Toxicology Studies: Repeat-dose comparative toxicology studies in a relevant animal species are conducted on a case-by-case basis, primarily when analytical data suggest differences in impurity profiles or structural attributes that may affect tolerability. They are not a default requirement for all biosimilar programs. [18][19]

Immunogenicity Risk Assessment: Non-clinical studies contribute to immunogenicity risk assessment through evaluation of product-related attributes known to influence anti-drug antibody (ADA) formation particularly protein aggregation and impurity levels. High-quality analytical data on these attributes serve as surrogate predictors of immunogenicity risk prior to clinical evaluation. [19]

5.4.2 Clinical Evaluation

Clinical development of a biosimilar is designed to confirm the absence of clinically meaningful differences between the biosimilar and the reference product, rather than to re-establish its clinical activity. The design of clinical trials must balance statistical power, ethical considerations, and scientific sensitivity:

- **Population Selection:** Clinical trials use highly sensitive patient populations typically those with conditions such as rheumatoid arthritis (RA) or plaque psoriasis (PsO) for mAbs where even small pharmacological differences are detectable within reasonable study sizes and durations.
- **Equivalence Margins:** Trials are designed as equivalence studies with pre-specified margins, requiring the biosimilar to demonstrate neither inferiority nor superiority to the reference biologic within the defined bounds.
- **Immunogenicity Assessment:** Comprehensive evaluation of ADA formation rates, neutralizing antibody incidence, and ADA impact on PK and efficacy is a mandatory component of clinical programs, given that even subtle structural differences in post-translational modifications can influence immunogenic potential.
- **Indication Extrapolation:** Once biosimilarity is established in a single sensitive indication, regulatory authorities may grant approval for all indications held by the reference product a practice known as indication extrapolation provided the MOA is shared and the totality of evidence supports extrapolation. [10]

5.5 Regulatory Challenges

5.5.1 The Bio-Better Paradigm and Competitive Landscape

Bio-betters represent a distinct and growing category of biological products that have introduced a new competitive dynamic into the biosimilar market. Unlike biosimilars, which are designed to demonstrate analytical and clinical equivalence to a reference product, bio-betters are engineered versions of existing biologics designed to demonstrate superiority in one or more clinical attributes. Common bio-better strategies include:

- **Expanded Functionality:** Changes made to either the fc region or the variable domain to increase target binding, potency, and/or half-life (eg. Fc-engineered antibodies with enhanced fcRn binding capabilities and thus extend serum half-life).
- **Minimised Immunogenicity:** Use of protein engineering/deimmunisation techniques for decreasing T-cell epitope number and decreasing probability of ADA development.
- **Improved Delivery Profiles:** Availability of high concentration subcutaneous formulations for self-administration, or use of extended-release systems that decrease the frequency of dosing and increase patient compliance.

Investing in developing a bio-better involves a substantially larger capital outlay than what would be incurred in developing biosimilars, as biosimilars can be approved via an abbreviated review process while bio-betters must go through a full innovator biologic review process. On the other hand, due to the enhanced clinical characteristics, bio-betters are eligible for premium pricing and can occupy an independent market space, creating a significant competitive challenge to biosimilars that compete on the basis of cost and not on the ability to differentiate their clinical performance.

5.5.2 Global Interchangeability Standards

The interchangeability definition, which allows for automatic pharmacy-level substitution of a biosimilar for its reference biologic without requiring physician intervention, is among the most significant clinical and commercial regulatory distinctions among jurisdictions:

- **U.S. FDA Framework:** The FDA has a special designation of "interchangeable" that requires more data on switching back and forth between a biosimilar

and its reference biologic, showing that patients switching from the biosimilar product back to the reference product is no greater than if they had remained on the reference product only. As such, there are only a few interchangeability designations due to the additional data required, making it difficult for pharmacies to automatically substitute biosimilars in the United States.

- **EMA and WHO Frameworks:** In the EU and in countries that follow WHO guidelines, interchangeability decisions are regulated by each country or can be made by the prescribing physician. Therefore, there is no standard for interchangeability; thus, the interchangeability landscape varies across the EU member states and the other adopting countries.
- **Clinical & Commercial Implications:** These regulatory differences will result in a fragmented global market such that the same biosimilar product in one country may be able to be substituted without any approval from the prescribing physician and in another country the same product will require the prescribing physician's approval. The above-mentioned regulatory differences will cause complications for developing global launch strategies, pricing models, and for creating pharmacovigilance programs for international biosimilar developers.

5.5.3 Indication Extrapolation and Clinical Hesitancy

The standard for extrapolating indications for medications, while scientifically sound and economically relevant, still contributes to a reluctance to prescribe among physicians who specialize in treating patients with complex and chronic biologic therapies (e.g., rheumatology, gastroenterology, and oncology). These specialists often worry that the current “highly similar” standard may not adequately consider the effect of small differences between products’ PTM (physiologically active therapeutic molecules) profiles on the different response rates of their patients based on a unique patient population. In response to this, regulatory agencies are implementing more robust pharmacovigilance requirements to address this concern, including safety studies of marketed products after approval and utilizing real-world evidence (RWE) to establish long-term safety data across all approved indications. [10]

5.5.4 Intellectual Property and the Patent Thicket

Beyond scientific and regulatory barriers, the biosimilar approval process is frequently delayed by complex intellectual property challenges. Innovator companies routinely employ "patent thicket" strategies the deliberate accumulation of overlapping patent filings covering the reference biologic's molecular structure, manufacturing process, formulation, device, and dosing regimen to extend de facto market exclusivity well beyond the primary patent expiry. In the United States, the BPCI Act's "patent dance" provisions establish a complex, multi-round disclosure and litigation process through which biosimilar applicants and reference product sponsors must negotiate and litigate patent infringement claims before market entry. This process can add 2–4 years of delay and tens of millions of dollars in legal costs to a biosimilar development program. [26]

5.6 Naming, Labeling, and Pharmacovigilance

The absence of global harmonization in biosimilar nomenclature and labeling creates meaningful challenges for post-marketing safety surveillance and pharmacovigilance. Accurate identification of the specific biological product whether the reference biologic or a particular biosimilar is essential for the attribution of adverse events in pharmacovigilance databases. Current divergences include:

- **FDA Naming Convention and Logic**: A nonproprietary name, including the core Inactive Ingredient Identifiers (INNs) plus a four-character suffix that has no meaning, must be provided by the US FDA for all biologics, including biosimilars (for example, infliximab-dyyb, adalimumab-atto). In theory, the unique suffix would allow the identification of each individual product and its associated adverse events. However, there has been a concern that the additional suffixes will confuse prescribers and complicate the substitution of one biologic for another at the dispensing stage of pharmacy.
- **EMA/WHO Naming Logic**: The EMA and WHO trace medicines based on an INN system, not requiring any additional suffixes; traceability is accomplished through the INN, brand name, and batch number. Thus, with regard to prescribing, this relatively simpler naming approach provides less granularity to allow for product level traceability of spontaneous adverse events.
- **Patent Thickets and Legal Issues Relating to the Naming and Labeling of Biologics:** The patent thicket of biologics and the resulting multiple patents covering the same biologic as discussed in Section 5.5.4 are adding an additional legal hurdle to the issues of lucidity and clarity regarding the naming and labeling of biologics, as patent restrictions can have an effect on the manner in which the biologic has been marketed and how that will be reflected on the label when manufactured. [26]

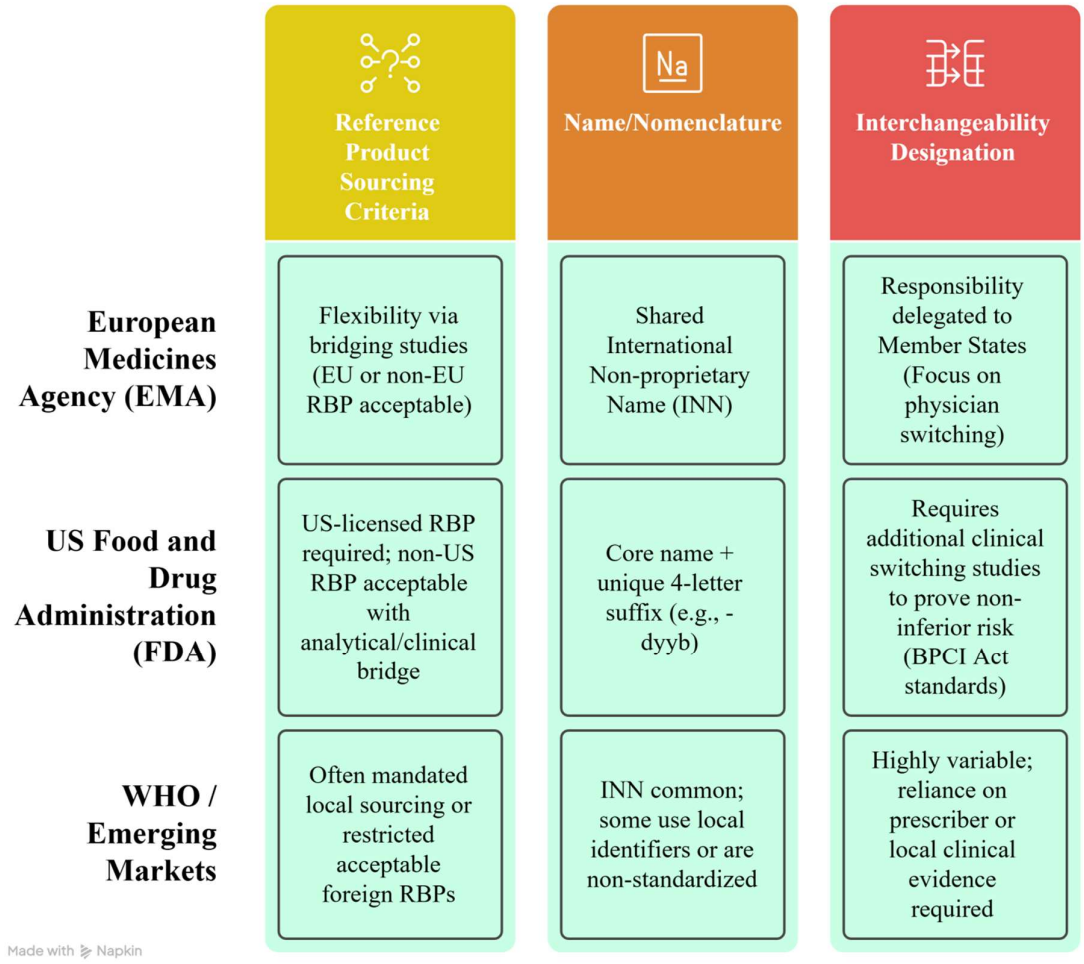

Figure 4: Regional comparison of biosimilar regulatory requirements, illustrating differences in naming conventions, interchangeability standards, and reference biologic product sourcing requirements across the U.S. FDA, EMA, and WHO frameworks.

5.7 Commercial Barriers and Market Adoption

The translation of regulatory approval into commercial market share is far from automatic for biosimilars. Multiple demand-side barriers operate simultaneously to slow uptake:

- **Physician & Patient Hesitancy**: Although so many factors have been reviewed by regulatory teams for significance, not many prescribers accept biosimilars due to concerns regarding immunogenicity, complexity in prescribing from different formularies, and all patients' responses to switching medications they know to be effective. Shifting these hesitations requires sustainable medical education, publication of data regarding switching studies transparently, & perform patient retention programs proactively.
- **Brand Loyalty / Support from Originator Companies**: Innovator companies build switching barriers based on established brand relationships, patient support programs, co-pay assistance cards, & hospital contracts and therefore create barriers-for-new-market-entry of all biosimilars from an innovator's established drug. These brand-market strategies for innovator companies may carry greater weight than pricing differences alone; especially within markets where the health care system protects patients from having to worry about price differences due to [commercial, government, insurance, managed care] payment models.
- **Economic Comparison of Price Competition vs. Cost Recovery for Research and Development**: For example, biosimilar products typically enter markets as low as 15-35% less than that of the reference (origination) product's list price. This will benefit payers immediately in that they save dollars through the continued use of their reference (origination) product at a lower price compared to their (actual) usual cost of reference (origination) product due to decreased competition from other biosimilar competitors. The introduction of additional biosimilar competitors will subject the biosimilar pricing system to an increasing amount of downward pricing pressure;

yet developers can only provide lower priced/biosimilar products while recovering their development costs ($100 million to $300 million), which is an economic differentiating factor between the cost structure for biosimilar vs. small molecule generic types of products that are developed at much lower costs than biosimilars'.

6. FUTURE PROSPECTS FOR THE BIOSIMILAR INDUSTRY

The market for biosimilars is undergoing a major transition as a result of many different factors including patent expiration, advancement of technology, and changes in regulations. These various trends are uniting and signalling major growth in the future of this type of market.

Reduction in Costs and Healthcare Economics: When patents on high-value biologics such as checkpoint antibodies used for oncology treatment and IL-17/IL-23 inhibitors, used for treating immune diseases, expire, this creates new opportunities for biosimilar development. Competition from multiple biosimilar products will result in a significant decrease in the cost of treatment: projected at 30-60% cost savings. This gives healthcare systems the opportunity to redirect of substantial budgets to innovative therapies and under-served disease areas.

Increased Access to Patients and Improved Health Equity: The availability of biosimilars at significantly lower costs may lead to improved access to) treatment for patients with complex chronic diseases in developing countries (low- and middle-income countries). These patients have historically had limited access to the high-priced originator biologics. In addition, when more biosimilars become available, there will be more manufacturers to provide essential biologic medicines, providing supply chain security.

Streamlined Regulatory Pathways: The changes in regulatory policy planned for the FDA and EMA in 2025/2026 will lead to a significant decrease in relative cost and time to develop a biosimilar product. This will allow for greater developer economic feasibility of developing new biosimilar products and attract new companies to the bilateral biosimilar marketplace from developing biopharma ecosystems, such as India, South Korea and Brazil.

Innovative Technologies Within Biomanufacturing: Advanced Technologies Such as Continuous Manufacturing Platforms, Single-Use Bioreactor Systems, Advanced Process Analytical Technology (PAT), And Process Optimization Using AI Are Altering The Economics Of And Consistency Within The Creation Of Biosimilars. The Use Of Digital Twins Whereby Computational Models Are Created To Replicate Manufacturing Processes In Real Time Allow For Virtual Process Improvements And Predictive Quality Control, Therefore Reducing Experimental Costs, And In Turn, The Number Of Batch Failures.

Wearable Devices That Allow Patients To Monitor Their Health And Medication Adherence As Well As Monitor Treatment Outcomes In Post Marketing Studies Using Biosimilars Are Also Being Investigated.

Artificial Intelligence (AI) and Machine Learning (ML): Used in various steps along the biosimilar development process, from predictions of protein and glycan structure to the interpretation of analytical data, from the optimization of clinical trials, to the identification of pharmacovigilance signals found in the real world. The inclusion of these tools into the regulations of submissions will provide additional support for comparative evidence in regulatory evaluations, thus enabling faster approval processes.

7. CASE STUDY: ADALIMUMAB BIOSIMILAR DEVELOPMENT PROGRAMS

Adalimumab is an entirely human Monoclonal Antibody (mAb) which works as an anti-tumor necrosis factor (TNF)-α agent that is used to treat many different inflammatory diseases, such as rheumatoid arthritis (RA), Crohn's disease, and psoriatic arthritis. Adalimumab is by far the number one selling biopharmaceutical worldwide; therefore, the majority of biosimilar products have been developed based on adalimumab. Between 1998 and 2024, FDA and EMA have approved about ten different potentially interchangeable biosimilar products based on adalimumab. With respect to their clinical development programs, all of the biosimilar agents have taken a rigorous approach to the totality of evidence approach, using it to guide the design of their Phase I and Phase III clinical trials.

7.1 Phase I Clinical Pharmacokinetic Studies

Phase I studies for adalimumab biosimilars are designed to demonstrate pharmacokinetic (PK) equivalence between the biosimilar candidate and the reference biologic. They are typically conducted in healthy volunteers to minimize biological variability that might obscure PK differences.

The strategic design feature of these studies is the use of a three-arm parallel or crossover design, comparing the biosimilar simultaneously against both the U.S.- and EU-licensed versions of Humira®. This "bridging" strategy generates the analytical and clinical linkage necessary to support regulatory submissions in both jurisdictions within a single study, thereby avoiding duplicative PK programs. Table 3 presents a representative overview of Phase I clinical trial data for major adalimumab biosimilar programs.

Table 3: Overview of Phase I Clinical Pharmacokinetic Trials for Adalimumab Biosimilars

Biosimilar (INN Suffix)	Sponsor	Study Design	N (Randomized)	PK Endpoints	Equivalence Demonstrated
adalimumab-atto (Amjevita)	Amgen	3-arm, single-dose, crossover; SC 40 mg PFS	~350	AUC0-inf, Cmax	Yes; all 90% CIs within 80–125%
adalimumab-adbm (Cyltezo)	Boehringer Ingelheim	3-arm, single-dose; SC 40 mg PFS	~306	AUC0-inf, Cmax	Yes; all 90% CIs within 80–125%
adalimumab-bwwd (Hadlima)	Samsung Bioepis	3-arm, parallel; SC 40 mg PFS	~321	AUC0-inf, Cmax	Yes; all 90% CIs within 80–125%
adalimumab-fkjp (Hulio)	Mylan/Fujifilm Kyowa Kirin	3-arm, single-dose; SC 40 mg PFS	~336	AUC0-inf, Cmax	Yes; all 90% CIs within 80–125%

Abbreviations: AUC0-inf = Area Under the Concentration-Time Curve from time zero to infinity; Cmax = Maximum plasma concentration; PFS = Pre-filled syringe; SC = Subcutaneous; PK = Pharmacokinetic; N = Total randomized participants; INN = International Nonproprietary Name; CI = Confidence Interval.

7.2 Phase III Confirmatory Efficacy and Safety Evaluation

Phase III studies confirm the absence of clinically meaningful differences in therapeutic efficacy and safety between the biosimilar candidate and the reference biologic. The most commonly used study populations for adalimumab biosimilar Phase III trials are patients with moderate-to-severe RA (primary sensitivity population for anti-TNF agents) and moderate-to-severe plaque psoriasis, both of which provide a clinically sensitive and objectively measurable response framework. Primary endpoints typically include the ACR20 response criterion at week 24 for RA and the PASI 75 response at week 16 for PsO. Pre-specified equivalence margins are defined a priori, and the study is considered to demonstrate equivalence if the two-sided 90% confidence interval for the treatment difference falls entirely within the margin. Table 4 presents a representative summary of Phase III clinical trial outcomes for key adalimumab biosimilar programs.

Table 4: Overview of Phase III Clinical Efficacy and Safety Trials for Adalimumab Biosimilars

Biosimilar	Indication	N (Randomized)	Primary Endpoint	Equivalence Margin	Outcome
adalimumab-atto	RA	~526	ACR20 at Week 24	±15%	Equivalence demonstrated; CI within margin
adalimumab-adbm	PsO	~888	PASI 75 at Week 16	-15%/+15%	Equivalence demonstrated; CI within margin
adalimumab-bwwd	RA	~560	ACR20 at Week 24	±15%	Equivalence demonstrated; CI within margin
adalimumab-fkjp	RA	~649	ACR20 at Week 24	±15%	Equivalence demonstrated; CI within margin

Abbreviations: RA = Rheumatoid Arthritis; PsO = Plaque Psoriasis; ACR20 = American College of Rheumatology 20% improvement criterion; PASI 75 = Psoriasis Area and Severity Index 75% reduction; N = Total randomized participants; CI = Confidence Interval.

Biosimilar products for adalimumab were established as having been clinically equivalent to the reference medicine Humira® across all completed Phase III studies evaluated for this pharmacovigilance assessment; therefore supporting that there is no clinically significant difference, based on clinical data and other forms of data, in efficacy or safety (adverse events and immunogenicity) between the two products (e.g., biosimilars & reference) of interest and represent the clinical portion of the entire body of information that supports the biosimilars to be

therapeutically comparable(same drug/different source) to the reference products.

8. CONCLUSION

A significant shift in the worldwide biosimilar market is currently occurring due to changes in science, regulation, and commerce globally. As patents for major biologic medications expire and regulatory policies become increasingly analytical in nature (with landmark regulatory policy changes expected between 2025-2026 by both the FDA and EMA), there is an improving ability for the development of major biosimilar medications to occur due to developments in biomanufacturing technology and advancements in artificial intelligence.

The review outlines that the development of biosimilars is a scientifically complex task that is fundamentally different from the development of generic small molecules. The foundation upon which biosimilarity is established is the totality of evidence (TOE) framework, which is based on a comprehensive analytical characterization, supported by comparative nonclinical and clinical studies and established through an accumulation of literature and regulatory history, provides adequate basis for establishing biosimilars are equivalent. The establishment of biosimilars based primarily upon high-resolution analytical characterizations represents an evolution of maturity and evidence-based regulatory science; and will over time reduce development costs while maintaining appropriate patient safety standards.

There are many challenges still to solve. Several things can impede the complete realization of biosimilar's potential as a cost-saving measure such as large patent trees, barriers to procurement of reference biologics, physician and patient resistance, differing global naming conventions and labelling standards and the dynamics of the commercial market. To forward movement on these challenges, there will need to be unified action on behalf of regulatory agencies, health insurance companies and payers, prescribing physicians, patient advocacy groups, and biosimilar manufacturers.

Ultimately, biosimilars are the base of a clinically validated, economically transformative and socially relevant class of therapeutic drugs. As intellectual property obstacles disappear, more efficient regulatory passage occurs and technological advances take place, biosimilars will have an even larger impact on ensuring global financial sustainability in health care and expanding access to life-saving biological medication for patients with chronic or life-threatening diseases in all parts of the world.

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