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Review Article

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Biopharmaceuticals and Biosimilars from Molecule to Market: An Integrative Review of Comparability, Immunogenicity, Interchangeability, and Access

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ABSTRACT

Biopharmaceuticals have transformed treatment across oncology, immunology, and other therapeutic fields, but their molecular heterogeneity, manufacturing dependence, immunogenic potential, and cost complicate development and access. Biosimilars seek to expand competition without reproducing an originator's proprietary manufacturing process or exact molecular microheterogeneity. This integrative review examines how evidence from manufacturing knowledge, analytical and functional comparability, comparative pharmacokinetics, residual clinical investigation, immunogenicity assessment, switching studies, pharmacovigilance, and market implementation contributes to biosimilar evaluation. Heterogeneous evidence was compared according to the question it can resolve, its sensitivity, relevance to decision-making, and remaining uncertainty. Analytical and functional comparison carries the greatest discriminatory burden, whereas pharmacokinetic, pharmacodynamic, clinical, and immunogenicity evidence should address defined residual questions rather than repeat information already provided by more sensitive methods. Nevertheless, strong comparability evidence does not automatically establish interchangeability, substitution policy, market uptake, or patient access. Remaining tensions concern the clinical meaning of small quality-attribute differences, circumstances in which confirmatory efficacy studies may be reduced, generalizability of multiple-switch evidence, sufficiency of streamlined immunogenicity assessment, traceability limitations, and sustainability of price-based competition. A molecule-to-market interpretation therefore requires linked but non-interchangeable scientific, clinical, surveillance, and implementation domains. Biosimilar evaluation is best understood as a bounded totality-of-evidence process in which each evidence type has a distinct inferential role and downstream use remains context-dependent.

Key words: *Biosimilar, Biopharmaceuticals, Biosimilars, Comparability, Analytical similarity, Immunogenicity*
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INTRODUCTION

Biopharmaceuticals commonly exist as populations of related molecular variants shaped by cellular expression, purification, formulation, storage, and handling. A biosimilar is therefore not expected to reproduce every molecular feature of its reference product. The central question is whether observed differences remain scientifically acceptable and whether the comparative evidence excludes clinically meaningful differences in quality, safety, and efficacy [1].

The totality-of-evidence model distributes the evidentiary burden across complementary domains. Structural and physicochemical studies identify molecular differences; functional assays examine mechanism-relevant activity;

comparative pharmacokinetics and pharmacodynamic biomarkers assess in-vivo behavior; and clinical or immunogenicity studies address remaining uncertainty. Confidence should arise from coherence across these layers rather than from one test or trial [2].

Biosimilarity, switching, substitution, and interchangeability are related but distinct. Biosimilarity is a comparative scientific determination, switching is a treatment transition, and substitution concerns replacement under jurisdiction-specific rules. Interchangeability may have a formal regulatory meaning in some jurisdictions and a broader clinical meaning elsewhere. Scientific switching evidence does not independently determine legal substitution authority [3].

The contemporary question is therefore not simply whether biosimilars can be developed, but how evidence requirements should evolve while retaining sensitivity to product-specific risk. This review integrates manufacturing, analytical, clinical, immunogenicity, surveillance, and market evidence to clarify what each domain can establish, where conclusions converge or conflict, and why scientific comparability does not automatically produce access [4].

Integrative-review scope and evidence-identification approach

An integrative-review design was used because no single evidence type can explain the pathway from molecule to market. Manufacturing studies address sources of variability; analytical and functional studies characterize product similarity; pharmacokinetic and clinical studies evaluate in-vivo behavior; pharmacovigilance studies address postauthorization attribution; and implementation research examines uptake, competition, and access.

Evidence identification combined terms related to manufacturing change, lifecycle comparability, critical quality attributes, analytical similarity, comparative pharmacokinetics, pharmacodynamic biomarkers, immunogenicity, indication extrapolation, switching, interchangeability, traceability, pricing, uptake, and access. Sources were retained when they supported a defined claim, uncertainty, table element, figure relationship, or cross-domain interpretation.

Extraction focused on the question each source could resolve. Analytical studies were examined by attribute, assay, functional linkage, and limitation. Clinical studies were compared by population, design sensitivity, endpoint, treatment sequence, and generalizability. Immunogenicity evidence was interpreted through exposure, assay design, antibody persistence, neutralizing activity, and clinical consequence.

Synthesis first preserved findings within their original product and methodological context, then compared convergence, conflict, and complementarity across domains. Residual uncertainty was classified as measurement, clinical-relevance, generalizability, causal-attribution, jurisdictional, or implementation uncertainty. The method organizes heterogeneous evidence without treating unlike study designs as quantitatively commensurable.

Molecular complexity and manufacturing dependence

Biopharmaceutical production links process conditions to the molecular population administered. Cell line, culture conditions, raw materials, purification, formulation, storage, and transportation may influence glycosylation, charge variants, aggregation, fragmentation, higher-order structure, and activity. Process dependence does not require process identity, nor does every process difference imply a clinically important product difference [5].

Manufacturing dependence is not unique to biosimilars. Reference products may undergo site transfer, scale change, equipment replacement, process optimization, or formulation modification. Controlled attribute variation can coexist with consistent performance when an appropriate comparability exercise demonstrates continued product control. Historical acceptance of one change, however, cannot prove that another change is benign [6].

The importance of a detected difference depends on biological relevance. A glycan, charge, or aggregate difference may be unimportant, reflect expected variability, or influence potency, disposition, immunogenicity, or effector function. Trastuzumab analyses linking Fc-related variation with antibody-dependent cellular cytotoxicity measurements illustrate the need to connect attributes with relevant functions [7].

Manufacturing changes and comparability assessments are routine across monoclonal-antibody and Fc-fusion-product lifecycles [8]. Lifecycle comparability and biosimilar development both require attribute identification, sensitive measurement, functional interpretation, and escalation when uncertainty remains. Their information bases differ, however, because originator manufacturers may possess proprietary process histories unavailable to biosimilar developers.

Analytical and functional comparability

Analytical similarity is the structured comparison of product characteristics that may affect activity, pharmacokinetics, safety, immunogenicity, or clinical performance. It should not be reduced to a binary result from one assay or universal statistical threshold. Attributes differ in relevance, expected variability, and assay precision; statistical methods must therefore remain attribute-sensitive and scientifically justified [9].

Product-specific programs show how evidence is assembled across structural, physicochemical, purity, binding, potency, and cell-based assessments. Evaluation of CT-P6 illustrates how convergence among independent methods can support a coherent comparability conclusion [10]. Similarity in one domain cannot erase an unexplained difference elsewhere, while detection alone does not establish clinical importance.

Orthogonal platforms strengthen comparison because chromatography, electrophoresis, spectroscopy, mass spectrometry, particle analysis, binding assays, and functional tests have different sensitivities and failure modes. Agreement across platforms reduces reliance on one method, but method selection should remain question-specific rather than becoming indiscriminate duplication [11].

Multi-attribute methods may improve efficiency by measuring several molecular characteristics within one platform, as demonstrated for adalimumab products [12]. Their outputs still require transparent attribute-level interpretation. Process knowledge, attribute characterization, and mechanism-relevant function are complementary [5, 7, 10]. Analytical similarity can substantially narrow uncertainty but cannot independently establish every pharmacokinetic, immune, switching, substitution, or access outcome.

Comparative pharmacokinetics and residual clinical evidence

Clinical development should address uncertainty remaining after analytical and functional comparison. Comparative pharmacokinetic studies are often sensitive because they integrate in-vivo disposition without relying on efficacy endpoints strongly influenced by disease variability, placebo response, or concomitant treatment. A study is valuable when it resolves a defined uncertainty rather than merely reproducing a conventional development stage [13].

Pharmacometric methods can improve dose selection, sampling schedules, population choice, covariate assessment, and interpretation of exposure measures. Their value depends on model adequacy, assay reliability, and valid assumptions. Modelling cannot rescue an insensitive design, but it can identify conditions under which potential product differences are more detectable [14].

Confirmatory efficacy trials may be necessary when a clinically meaningful uncertainty remains, but their endpoints may be less sensitive than analytical or pharmacokinetic measures. Routine use may therefore add cost and patient exposure without improving discrimination. Omission is justified only when preceding evidence has already addressed the relevant product-specific question [15].

Pharmacodynamic biomarkers may offer a more sensitive bridge when they are mechanistically linked, analytically reliable, and supported by an interpretable exposure–response relationship. Randomized evaluation of interleukin-5 antagonists demonstrates this potential [16]. Such evidence remains mechanism-specific and cannot be generalized to products lacking a suitable biomarker.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for evidence domains and integration framework for biopharmaceuticals and biosimilars from molecule to market.

Table 1. Evidence domains and integration framework for Biopharmaceuticals and Biosimilars from Molecule to Market

Evidence domain or review construct	Review question	Eligible evidence type	Key extraction fields	Appraisal or relevance criterion	Synthesis role	Main limitation	Interpretation boundary
Manufacturing control	How may process conditions affect the product?	Manufacturing and lifecycle analyses	Change, attribute, control strategy	Demonstrated process–attribute relationship	Defines potential variability [5]	Proprietary knowledge may be incomplete	Process difference is not clinical difference
Attribute–function linkage	Does a difference affect	Analytical-functional studies	Attribute, assay, mechanism	Functional relevance and sensitivity	Links structure with activity [7]	Product specificity	Detectability is not clinical importance

	biological activity?						
Analytical comparability	Are relevant attributes sufficiently similar?	Statistical and orthogonal analyses	Variability, criticality, assay performance	Prespecified scientific justification	Central discriminatory layer [9]	No panel detects every difference	No universal threshold proves biosimilarity
Multi-attribute analysis	Can several attributes be measured efficiently?	High-resolution platform studies	Attribute definition, performance	Transparent attribute interpretation	Emerging efficiency tool [12]	Composite outputs may obscure differences	Not a clinical predictor
Comparative PK or PD	Is in-vivo behavior comparable?	PK, pharmacometric, and biomarker studies	Population, dose, exposure, response	Design sensitivity	Resolves in-vivo uncertainty [14]	Model and biomarker assumptions	Does not establish every clinical outcome
Residual clinical evidence	Is another clinical study needed?	Targeted clinical studies	Remaining question, endpoint, population	Incremental discriminatory value	Proposed decision construct informed by [13]	Product-specific judgment	Study reduction is conditional

Note: The residual-evidence construct and synthesis-role descriptions are original integrative interpretations, not validated regulatory algorithms.

Immunogenicity assessment and uncertainty

Immunogenicity is commonly assessed through treatment-emergent antidrug antibodies and, where relevant, neutralizing activity. It is influenced by molecular attributes, aggregates, impurities, formulation, route, dose, duration, disease, immune status, concomitant therapy, prior exposure, and assay design. Reported antibody incidence is therefore not a product-only characteristic [17].

For biosimilars, immunogenicity assessment is comparative rather than an attempt to prove absence of immune responses. Analytical and functional evidence identify product-related factors that might alter risk, while pharmacokinetic, clinical, and postauthorization evidence may reveal altered exposure, loss of response, hypersensitivity, or uncommon events. These domains must be interpreted together [18].

Switching studies are generally reassuring, but their strength varies by product, switch direction, follow-up, assay method, background therapy, and statistical power. A systematic review found no consistent increase in immunogenicity attributable to switching while identifying heterogeneous designs and limited evidence for some repeated-switch scenarios [19].

For selected products, extensive analytical similarity and comparative single-dose pharmacokinetics may sufficiently reduce comparative immunogenicity uncertainty. An ustekinumab case study supports this possibility within a defined context [20]. The conclusion remains emerging because rare, delayed, or chronic-exposure responses may not be captured.

Figure 1 presents the original conceptual synthesis for totality-of-evidence pathway for biopharmaceuticals and biosimilars, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

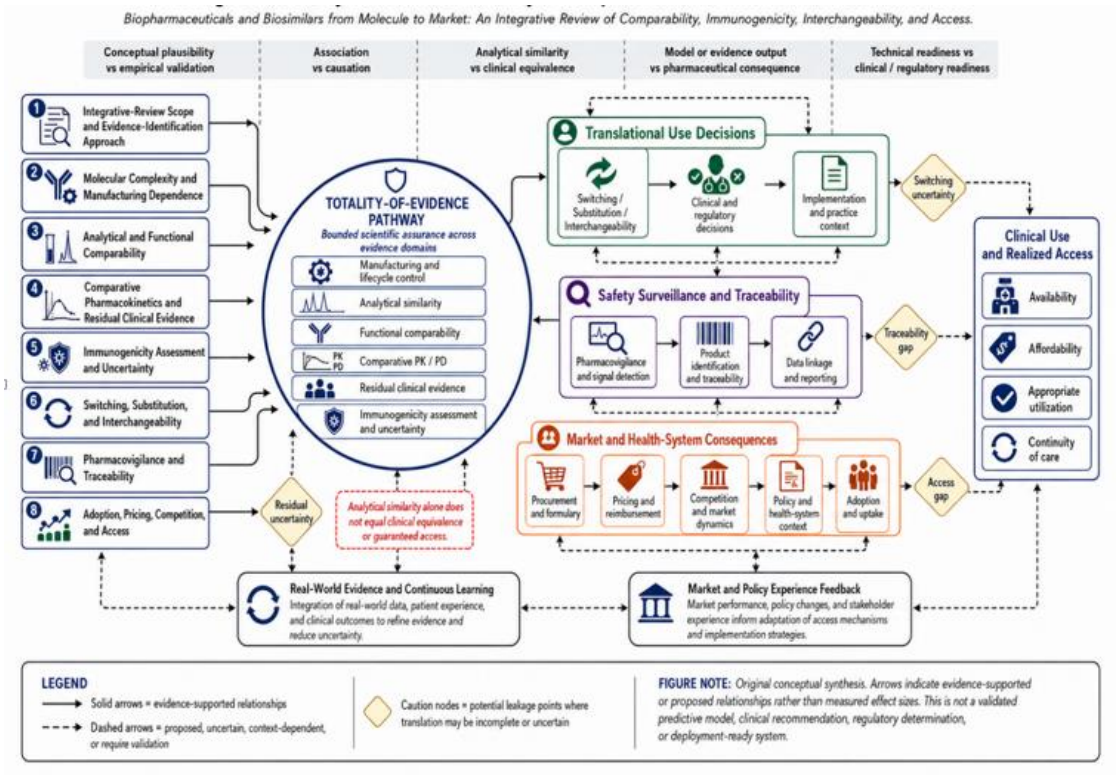

Figure 1. Totality-of-Evidence Pathway for Biopharmaceuticals and Biosimilars

The figure is an original conceptual synthesis developed for "Biopharmaceuticals and Biosimilars from Molecule to Market: An Integrative Review of Comparability, Immunogenicity, Interchangeability, and Access." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

Switching, substitution, and interchangeability

Switching evidence should be interpreted according to the product, indication, sequence, and study design. In NOR-SWITCH, patients receiving originator infliximab continued treatment or switched to CT-P13. The pooled noninferiority result supports the conclusion that a defined single switch did not produce a clinically meaningful loss of efficacy under the studied conditions [21].

The open-label extension added longer follow-up and further experience after transition. Its findings remained consistent with no important new efficacy, safety, or immunogenicity concern [22]. Extension evidence adds duration but is more vulnerable to expectation effects, selective retention, and other biases than a blinded randomized phase.

Multiple-switch studies address whether repeated transitions alter outcomes. In EGALITY, repeated switching between originator etanercept and GP2015 did not materially change efficacy, safety, or immunogenicity during the studied period [23]. A separate trial of GP2017 and reference adalimumab similarly found no detected clinically meaningful effect of multiple switching in psoriasis [24].

Across systematic synthesis, randomized single-switch evidence, and a multiple-switch trial, switching has generally not produced detected clinically meaningful loss of efficacy or new safety or immunogenicity concerns within studied settings [19, 21, 23]. This conclusion does not make switching, substitution, and interchangeability synonymous or establish universal support for automatic substitution.

Pharmacovigilance and traceability

Postauthorization surveillance requires the ability to identify which product and, where relevant, which batch a patient received. Brand-level identification is especially important when related biological products share an international nonproprietary name. Without adequate attribution, a safety report may be assignable only to a broad substance class [25].

European adverse-reaction reports have not always contained sufficient product-level identification. Reports may omit the brand or provide only the active-substance name [26]. These deficiencies do not demonstrate a safety difference, but they weaken investigation of whether an observed pattern is product-specific.

The UK BIO-TRAC study showed that information can be lost between procurement, dispensing, clinical documentation, and electronic adverse-reaction reporting, with batch information particularly vulnerable [27]. Traceability is therefore a system property involving records, coding standards, reporting interfaces, and professional practice.

Effective pharmacovigilance requires consistent brand recording, batch capture where relevant, interoperable systems, denominator data, and methods capable of distinguishing signals from reporting artefacts. Traceability supports attribution but cannot establish causality. Spontaneous reports may generate hypotheses that require analytical, clinical, epidemiological, or manufacturing investigation.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for cross-domain convergence, conflict, and complementarity in biopharmaceuticals and biosimilars from molecule to market.

Table 2. Cross-domain convergence, conflict, and complementarity in Biopharmaceuticals and Biosimilars from Molecule to Market

Method, platform, or evidence category	Representative application	Reported strength	Validation context	Generalization concern	Contradictory evidence	Evidence gap	Review interpretation
Manufacturing comparability	Process or site change	Links process change to attributes [6]	Product-specific lifecycle	Originator history may be unavailable	Process difference may be mistaken for product difference	Limited public process detail	Process knowledge and product testing are complementary
Attribute–function assessment	Fc attributes and ADCC	Provides mechanistic linkage [7]	Trastuzumab-specific	Relevance differs by product	Detectable differences may lack clinical consequence	Limited direct CQA–outcome links	Functional relevance should be tested
Orthogonal analytics	Structural and functional comparison	Reduces single-method blind spots [11]	Method-specific validation	No panel captures every difference	Methods may appear discordant	Integration of high-dimensional outputs	Convergence is stronger than isolated similarity
Comparative PK	Sensitive exposure comparison	Resolves disposition uncertainty [14]	Prespecified design	Population and model dependence	Similar PK may coexist with other uncertainty	Biomarker limitations	PK does not establish all outcomes
Switching trials	Defined treatment transitions	Directly tests a sequence [21]	Product and indication specific	Limited transfer to untested sequences	No consistent opposing signal	Broader multiple-switch evidence	Reassurance is context-bound
Traceability	Product-specific attribution	Supports signal assignment [25]	Documentation systems	Systems differ across settings	Records may contain data absent from reports [27]	Interoperable exposure capture	Necessary for attribution, not causality

Note: The review-interpretation column is original critical synthesis and does not assign evidence grades or regulatory status.

Adoption, pricing, competition, and access

Authorization creates an opportunity for competition but does not ensure uptake. European systems have used tenders, prescribing targets, gain-sharing, education, price regulation, reimbursement incentives, and substitution policies in different combinations [28]. The same policy may perform differently according to market size, clinical organization, contracting, professional trust, and supplier number.

Cross-country evidence confirms that biosimilar diffusion varies across products and national markets. Time since entry, originator position, therapeutic setting, procurement structure, and policy design may influence market

share [29]. Because these studies are observational, associations between policy and uptake should not automatically be interpreted as causal.

Analysis of tumour necrosis factor inhibitor markets also shows that price, market share, and utilization do not move uniformly after entry [30]. Lower prices may create savings or permit treatment expansion, but outcomes depend on how savings are allocated, whether prescribing barriers change, and whether products remain continuously available.

Access should therefore include availability, affordability, appropriate utilization, organizational reach, continuity of supply, and sustainability of competition. A market may achieve substantial discounts without expanding treatment, or may expand utilization while increasing supplier concentration. Scientific comparability is necessary for market participation but insufficient for realized access.

Integration of scientific, clinical, and implementation evidence

Accumulated analytical capability and clinical experience support refinement of biosimilar development while retaining product-specific assessment [31]. This does not lower the scientific standard. It shifts attention from routine repetition toward selecting the evidence most sensitive to the remaining uncertainty.

Implementation introduces different determinants. Prescriber confidence, patient understanding, communication about switching, institutional governance, incentives, and clarity of responsibility influence whether an authorized biosimilar is used [32]. These factors do not alter molecular comparability, but they may shape acceptance, adherence, treatment expectations, and reporting.

Economic evaluation also requires more than direct price comparison. Biosimilar value may include savings, dynamic competition, treatment expansion, budget reallocation, supply resilience, and effects on future entry. Existing assessment approaches do not consistently capture these system-level or time-dependent consequences [33].

Market response, stakeholder implementation, and value assessment explain why scientific comparability does not translate uniformly into uptake or health-system value [30, 32, 33]. Integration succeeds when sensitive comparison supports confidence and implementation converts confidence into appropriate use. It fails when strong evidence coexists with poor communication, weak traceability, fragmented incentives, or unstable competition.

Table 3 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for residual uncertainty, implementation implications, and decision boundaries.

Table 3. Residual uncertainty, implementation implications, and decision boundaries

Cross-study pattern or configuration	Context or boundary condition	Mechanism or explanatory factor	Observed or reported outcome	Rival explanation	Certainty or rigour concern	Implication	Research priority
Small analytical differences with comparable function	No demonstrated functional relevance	Attribute may not affect activity	Functional convergence may reduce concern [10]	Assay may miss a pathway	Clinical relevance remains indirect	Investigate rather than automatically escalate	Strengthen attribute–function linkage
Strong analytics with limited clinical evidence	Sensitive analytical and PK evidence	Efficacy endpoint may be less discriminatory	Streamlining may be plausible [15]	Trial could reveal an unexpected effect	Product-specific judgment	Additional studies should answer defined questions	Clarify residual-evidence criteria
Comparable PK with immune uncertainty	Short or selected exposure	Similar disposition reduces concern	Case-specific inference may support comparable risk [20]	Rare responses may be missed	Limited external validation	Preserve product-specific justification	Test additional product classes
Reassuring multiple switching	Defined product and sequence	Comparability is maintained through transitions	No important difference detected [24]	Duration or expectation effects	Limited generalizability	Do not infer universal substitution	Expand diverse multiple-switch studies

Incomplete safety attribution	Brand or batch missing	Exposure identity is lost	Signal assessment is weakened [26]	Reporting behaviour may explain patterns	Spontaneous reports cannot prove causality	Improve interoperable capture	Evaluate traceability interventions
Uneven adoption despite strong evidence	Implementation support varies	Communication and incentives shape use	Uptake remains variable [32]	Contracting or supply may dominate	Context-specific evidence	Authorization is insufficient for use	Compare implementation strategies
Lower prices without demonstrated access	Savings not linked to treatment expansion	Budget effects may not reach patients	Value remains uncertain [33]	Access changes may be unmeasured	Limited longitudinal data	Measure availability, use, and continuity	Develop access indicators

Note: Configurations, rival explanations, and priorities are original integrative synthesis rather than validated causal models or policy instructions.

Unresolved controversies and future priorities

A major unresolved question is how far development can be tailored without reducing confidence. A tailored approach would omit studies that add little discriminatory information while retaining investigations required by molecular complexity, mechanism, assay limitations, or unresolved clinical risk. Current regulatory-science discussion supports scientific justification rather than a universal minimal package [34].

Interchangeability remains contested because the term combines scientific, clinical, regulatory, and legal meanings. Reassessment of formal requirements reflects increasing confidence in analytical science and accumulated switching experience, particularly in the United States [35]. Biosimilarity or safe switching, however, does not independently determine substitution authority or notification requirements.

Short-term price pressure may also conflict with sustainable competition. Policies maximizing immediate discounts may reduce incentives for continued supply, market entry, or manufacturing investment. Commentary on endangered biosimilar markets suggests that balancing payer savings and supplier participation may be necessary [36]. This remains a plausible interpretation rather than a quantified causal law.

Figure 2 presents the original conceptual synthesis for translation from comparability evidence to access and clinical use, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

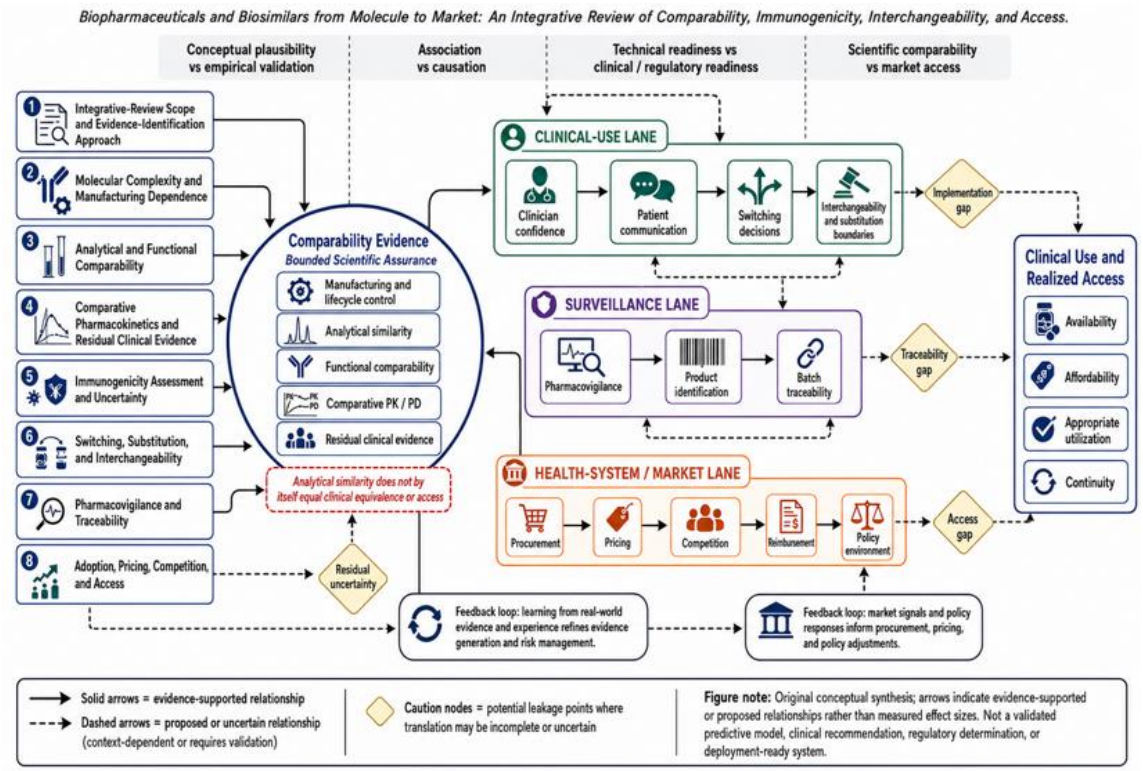

Figure 2. Translation from Comparability Evidence to Access and Clinical Use

The figure is an original conceptual synthesis developed for "Biopharmaceuticals and Biosimilars from Molecule to Market: An Integrative Review of Comparability, Immunogenicity, Interchangeability, and Access." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

A third controversy concerns whether intense short-term price pressure can undermine long-term competition. Policies that maximize immediate discounts may reduce commercial incentives for continued supply, new entry, manufacturing investment, or maintenance of multiple competitors. Commentary on endangered biosimilar markets suggests that balancing payer savings, supplier participation, and sustainable competition may be necessary for long-term benefit [36]. The proposition is plausible but should not be treated as a quantified causal law; market exit and supply vulnerability may also reflect production costs, procurement design, market size, portfolio strategy, or regulatory burden.

Research priorities should address the weakest links between evidence domains. Streamlined immunogenicity reasoning requires evaluation beyond isolated product cases [20]. Multiple-switch conclusions require broader products, devices, sequences, populations, and follow-up [24]. Traceability interventions should be tested for their ability to preserve brand and batch data through real clinical and reporting workflows [27]. Access research should connect pricing and market share with treatment initiation, continuity, equity, supply resilience, and long-term competition [30]. These priorities concern validation and transferability rather than expansion of claims from already reassuring evidence.

Review limitations

The integrative approach was designed to connect heterogeneous evidence rather than estimate a pooled treatment effect. It does not claim the exhaustiveness expected of a systematic review. Selection emphasized cross-domain relevance and may therefore underrepresent narrower findings or alternative interpretive traditions.

The evidence base varies in product class, assay platform, disease, endpoint, switching sequence, follow-up, jurisdiction, and market structure. Orthogonal analytical methods differ in capability [11], switching studies differ in design [19], and policy environments differ substantially [28]. Conclusions must remain tied to the contexts in which evidence was generated.

Regulatory-science and stakeholder publications provide essential interpretation but may reflect institutional roles and jurisdiction-specific terminology. European interchangeability concepts are not automatically transferable elsewhere [3], evidence refinement remains product-specific [31], and contemporary reform discussions are not universally settled scientific or legal positions [35].

Implementation and market evidence is largely observational. Uptake may be associated with procurement or incentives, but cross-country analysis cannot fully isolate causality [29]. Reporting and publication biases may favor successful analytical programs, reassuring switching studies, or markets with accessible data. Streamlined development proposals require broader external evaluation.

CONCLUSION

Biopharmaceutical and biosimilar evaluation is a connected but non-collapsible pathway from manufacturing and molecular characterization to clinical use, surveillance, competition, and access. Analytical and functional comparability provide the most sensitive foundation, while pharmacokinetic, pharmacodynamic, clinical, and immunogenicity evidence should resolve defined residual questions. Switching evidence is generally reassuring within studied products and sequences but does not automatically determine substitution or interchangeability. Pharmacovigilance requires reliable traceability, and authorization or lower prices do not alone establish equitable or sustainable access. Each evidence domain therefore has a distinct role, downstream conclusions remain context-dependent, and the proposed pathways should be treated as organizing syntheses rather than validated clinical, regulatory, or policy rules.

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