



Original Article

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Biosimilarity Is a Structured Inference Problem Across Analytical, Functional, and Clinical Evidence

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ABSTRACT

Biosimilarity is commonly described as a totality-of-evidence judgment, but that phrase can obscure a central inferential problem: structural, functional, pharmacokinetic, pharmacodynamic, immunogenicity, and clinical evidence do not interrogate the same uncertainty with equal sensitivity. This Current Opinion argues that biosimilarity is better understood as structured reconciliation across evidence classes. Analytical characterization interrogates product attributes directly; functional assays test whether variation propagates into mechanism-relevant activity; pharmacokinetic and pharmacodynamic studies provide human-level bridges; and immunogenicity and clinical studies address selected residual consequences under defined conditions. Discordance should therefore be localized before escalation. An analytical difference should be interpreted through criticality, function, exposure or response, and clinical context rather than automatically neutralized by a distal endpoint. Conversely, clinical concordance cannot erase unresolved product-level uncertainty when the endpoint is poorly discriminatory. The article proposes an evidential-reconciliation framework in which evidence is weighted by proximity to the uncertainty, sensitivity, mechanistic relevance, independence, convergence, and boundary conditions. The framework is conceptual rather than prospectively validated.

Keywords: Biosimilars, Totality of evidence, Analytical similarity, Pharmacokinetics, Pharmacodynamics, Immunogenicity

INTRODUCTION

Biosimilar development uses comparative evidence to establish high similarity to a reference product without requiring molecular identity. The totality-of-evidence approach therefore begins with extensive analytical and functional comparison and adds further evidence according to remaining uncertainty [1]. Regulatory experience has progressively refined this logic toward product-specific development rather than a fixed sequence of mandatory study types [2].

That refinement matters because heterogeneous evidence can be flattened into a checklist. The European framework has evolved as analytical capability and biosimilar experience accumulated [3], while regulatory analyses have questioned the routine information gain of confirmatory efficacy trials when analytical similarity and clinical pharmacology are already persuasive for selected products [4]. This does not make clinical evidence dispensable; it changes the question from whether clinical data exist to whether a clinical experiment can discriminate the residual difference that matters.

The central problem is therefore structured inference. A data-driven analysis of approved adalimumab and bevacizumab biosimilars found varying quality-attribute concordance and limited ability of comparative efficacy

studies to resolve some quality concerns [5]. The article consequently treats evidence classes as complementary but non-equivalent and asks how concordance, discordance, sensitivity, and transfer boundaries should determine their weight. The resulting framework is proposed as an interpretive architecture, not as a validated regulatory algorithm.

Biosimilarity as a totality-of-evidence judgment

Totality of evidence is best understood as sequential uncertainty reduction rather than voting among datasets. Analytical and functional similarity form the scientific base of biosimilar development [1], while accumulated regulatory experience supports tailoring later requirements to questions that remain unresolved [2]. A later study is therefore useful to the extent that it can detect or exclude the specific difference still considered plausible.

This creates an asymmetry between rigor and information gain. A large efficacy trial may be rigorous yet insensitive to a subtle quality-attribute difference; a sensitive analytical signal may remain uninterpretable until mechanism-relevant function or human pharmacology shows whether it propagates. Arguments for streamlined development rest on this distinction, not on the proposition that clinical outcomes are unimportant [4]. The approved-monoclonal-antibody analysis similarly shows that quality discordance is not automatically resolved by the existence of comparative efficacy data [5].

The article therefore proposes that evidential weight should depend on proximity to the uncertainty, discriminatory sensitivity, mechanistic relevance, independence from other evidence, convergence, and explicit transfer boundaries. This weighting remains qualitative. It does not assign a universal score, threshold, or evidence hierarchy across unrelated biological products.

Structural and physicochemical similarity

Structural and physicochemical characterization is the most proximal evidence layer because it interrogates the product itself, but interpretation still requires criticality and method selection. Risk-based approaches emphasize rational selection and tiering of quality attributes and analytical tests according to potential clinical relevance rather than treating every measurable difference as equivalent [6]. Criticality remains product- and mechanism-dependent; it is not a universal numerical ranking.

Product-specific programs illustrate this logic. In the HLX03 adalimumab program, broad similarity was shown despite a lower high-mannose fraction relative to reference batches, requiring the glycan difference to be interpreted with functional evidence rather than in isolation [7]. The inference is bounded: this example does not establish that high-mannose variation is generally clinically irrelevant.

Orthogonal characterization can strengthen inference through convergence. SB12 was compared with eculizumab reference products using more than 40 analytical methods spanning structural, physicochemical, and biological properties [8]. BAT1806 was likewise evaluated against reference tocilizumab using extensive physicochemical and functional characterization [9]. These programs support cross-method convergence while also showing why assay panels cannot simply be transferred between products with different mechanisms.

Similarity is also a lifecycle proposition. Evaluation of 93 SB5 batches manufactured across 2013–2022 found monitored quality attributes remained controlled through manufacturing history and process changes [10]. Approval-time similarity therefore does not make manufacturing state irrelevant; continued control preserves assumptions on which comparability rests.

Functional assay evidence

Functional assays test whether structural or physicochemical variation changes a mechanism-relevant activity. In the HLX03 program, functional evidence helped contextualize an identified glycan difference instead of allowing the analytical signal either to dominate or to be dismissed [7]. SB12 and BAT1806 similarly coupled biological activity testing to structural characterization [8], with BAT1806 functional assessment tailored to tocilizumab biology [9].

Functional concordance is consequently strong evidence about the activity actually tested, not direct proof of every downstream clinical consequence. The proposed role of functional assays is diagnostic: reinforce convergent analytical evidence, interrogate a plausible consequence of discordance, or reveal that a chosen assay is insufficiently related to the unresolved mechanism. This is consistent with criticality-based test selection, in which evidential value depends on relevance rather than analytical availability [6].

Pharmacokinetic and pharmacodynamic comparability

Clinical pharmacology provides a direct human-level test of whether product differences propagate into exposure or biological response. Pharmacodynamic biomarkers can be particularly informative when they are biologically relevant, dose-sensitive, and capable of discriminating products within a feasible design [11]. A multistakeholder workshop similarly emphasized that broader PD use requires fit-for-purpose biomarkers, suitable assays, and sensitive study designs [12].

Experimental studies show why that fitness must be established before a biomarker is used inferentially. A randomized study in 72 healthy participants receiving different doses of mepolizumab or reslizumab characterized PD behavior in the IL-5 pathway [13]. A separate randomized study in 84 healthy participants evaluated interferon beta-1a products and response biomarkers including neopterin and Mx1 [14]. These experiments inform comparative-study design; neither establishes biosimilarity for an untested candidate.

PD should not be privileged merely because a signal is measurable. Critical analysis has emphasized that the scientific question must match what the biomarker can actually resolve [15]. Measurement precision and decision utility are therefore separate. PK provides a complementary bridge by testing human exposure under prespecified conditions. In a randomized HLX11 study, PK comparability was demonstrated against US-, EU-, and China-approved pertuzumab reference products in healthy male participants [16]. The inference remains bounded by the studied dose, population, and product.

Because PK and PD evidence can occupy different decision states, the comparison is clearer as a ledger of what is known, what remains uncertain, and what should trigger reassessment.

Table 1. Decision states for clinical-pharmacology evidence in biosimilarity inference

Decision	Governing condition	Human-level signal	Functional relevance carried forward	Permissible inference or action	Reassessment trigger
Exposure - concordant	Sensitive PK comparison is feasible	Prespecified PK comparability	Upstream analytical and functional evidence remains concordant	Exposure-related uncertainty is reduced within tested conditions	PK divergence, population-dependent disposition, or unresolved upstream discordance
Response - characterized	Relevant PD marker has a defined operating range	Dose-responsive biomarker behavior	Marker is linked to relevant pharmacology	Marker can support a sensitive comparative design	Weak dynamic range, unstable baseline, assay imprecision, or uncertain biological linkage
PK-PD convergent	Exposure and fit-for-purpose response address the same residual question	Concordant PK and PD	Mechanism-relevant function is consistent with human pharmacology	Proposed: residual uncertainty may be reduced without default escalation to a less sensitive distal endpoint	PK-PD discordance or an uncaptured clinically relevant mechanism
Biomarker-limited	A PD signal is measurable but poorly qualified	Quantifiable response of uncertain decision value	Functional bridge is incomplete	Do not treat measurability as evidentiary sufficiency	Failure of dose sensitivity, relevance, or reproducibility
Context-bounded	PK or PD comparability is established only under defined conditions	Valid result within the tested population, dose, and treatment state	Product-level evidence remains supportive	Carry the result forward only within its transfer boundary	New population, dose, sequence, or mechanism creates a new uncertainty

The relationship between product attributes, function, human pharmacology, and downstream consequences also requires a multilevel visual rather than a simple stepwise ladder.

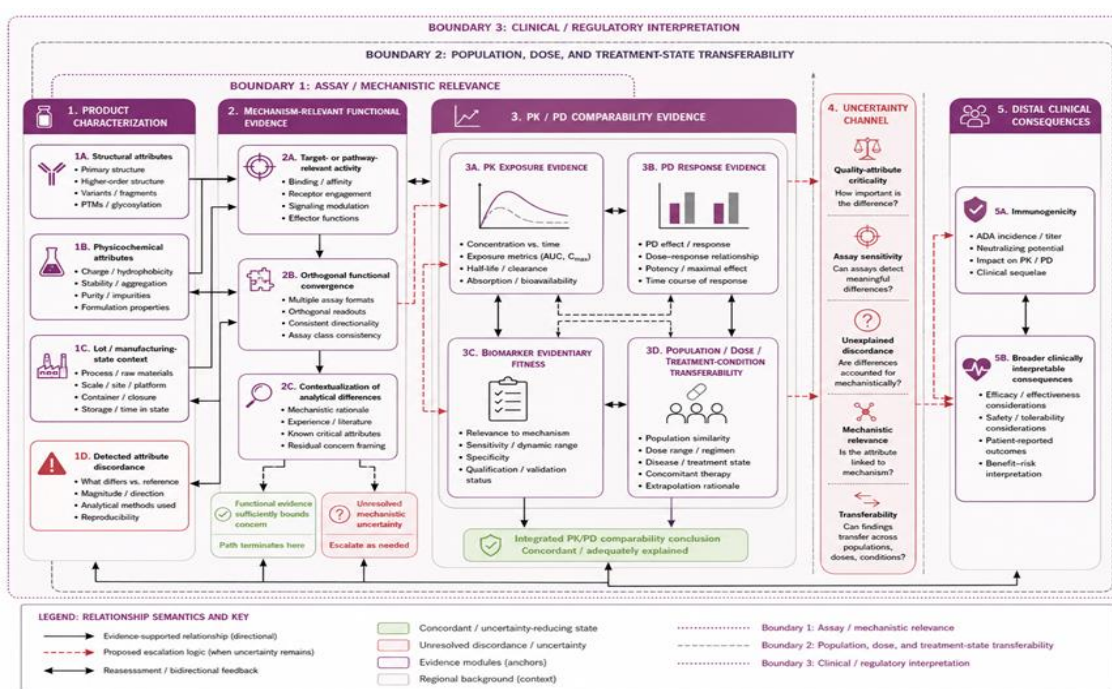


Figure 1. Propagation boundaries between detected product differences and clinically interpretable consequences

Immunogenicity

Immunogenicity exposes the limits of simple evidence ranking because observed antibody responses depend on product attributes, host biology, assay design, treatment context, and time. Reviews of biosimilars in rheumatic disease, psoriasis, and inflammatory bowel disease have generally reported comparable immunogenicity to reference products while documenting substantial heterogeneity in assays and observed antibody incidence [17]. Raw ADA percentages therefore cannot be treated as directly commensurable across programs.

An analysis of 22 US monoclonal-antibody biosimilar applications found broad consistency in immunogenicity assessment while also identifying variability and numerical differences that required contextual interpretation [18]. The relevant question is not merely whether ADA incidence differs, but whether a difference is persistent, assay-credible, associated with neutralizing activity, PK, safety, or efficacy, and plausible in light of product characteristics.

A retrospective analysis of 30 full-length monoclonal-antibody biosimilars found that the limited observed differences in high-molecular-weight aggregates were not associated with differences in ADA incidence [19]. This is useful null evidence, but it is bounded by the restricted range of aggregate differences in marketed products; it does not establish that aggregates can never influence immunogenicity. Mechanistic literature likewise identifies multiple product- and patient-related determinants of monoclonal-antibody immunogenicity [20], so biological plausibility should guide investigation without being mistaken for a measured clinical consequence. Comparative clinical evidence remains informative when it targets the remaining question. In the AVT02 adalimumab program in plaque psoriasis, efficacy, safety, and immunogenicity were comparable to originator adalimumab, including through the study's switching phase [21]. The finding supports that defined product and context, not interchangeability across all adalimumab products or treatment sequences.

The sequence from product concern to immune signal and then to possible clinical consequence is easier to audit when precursor state and interruption conditions remain visible.

Table 2. Sequence states linking immunogenicity signals to residual clinical meaning

Immunogeni city	Precursor condition	Transition trigger	Observable readout	Clinical linkage	Sequence interruption condition	Unresolved biosimilarity question
Attribute-concern	Product attribute has plausible	Analytical discordance is detected	Product-level difference without patient immune data	None established	Orthogonal or functional evidence	Does the attribute plausibly alter immune exposure or activation?

Immunogenicity	Precursor condition	Transition trigger	Observable readout	Clinical linkage	Sequence interruption condition	Unresolved biosimilarity question
	immune relevance				bounds the concern	
Assay-signal	Comparative treatment has occurred	ADA assay detects a numerical difference	Binding or neutralizing antibody signal	Not yet established	Timing, baseline status, assay sensitivity, or transient response explains the signal	Is the difference analytically credible and persistent?
Exposure-linked	ADA signal is credible	Antibody response coincides with altered disposition	ADA plus PK change	Potential pharmacological consequence	No consistent exposure effect across time or participants	Does immune recognition materially alter exposure under the studied regimen?
Consequence-linked	Immune and exposure findings remain concordant	Safety, efficacy, or clinically relevant response differs coherently	Multilevel clinical linkage	Consequence supported within tested context	Disease, adherence, treatment, or assay explanation remains plausible	Is the clinical difference attributable to product-related immunogenicity?
Bounded-null	Plausible risk factor is present	Downstream comparative evidence remains concordant	Null or non-divergent immune/clinical evidence	No measured consequence in evaluated range	Larger attribute changes, different hosts, or exposures fall outside the evidence	Proposed: how far should the null finding reduce residual uncertainty without overgeneralization?

Residual clinical uncertainty

Residual clinical uncertainty is not a fixed remainder that always requires a large efficacy trial. It is the unresolved consequence left after analytical, functional, and clinical-pharmacology evidence have been interpreted together. A systematic review and meta-analysis of cancer biosimilar trials identified 31 studies including 12,310 patients and found comparable outcomes across the evaluated programs [22]. These studies demonstrate clinical concordance, but their size alone does not establish how much additional discrimination they provided after preceding evidence or whether the same designs are necessary for unrelated products.

Switching evidence shows the same dependence on the question being asked. An earlier systematic review reported broadly reassuring findings while emphasizing limitations in study size, follow-up, and repeated-switch evidence [23]. Those limitations defined what could not yet be resolved; they were neither evidence of harm nor a license to dismiss uncertainty.

A later systematic review encompassing 178 switching studies found no major overall signal for loss of efficacy, safety, or immunogenicity after reference-to-biosimilar switching, while also documenting heterogeneity across randomized and observational designs and possible nocebo-related discontinuation in some settings [24]. Residual uncertainty can therefore arise from the product, study sensitivity, treatment sequence, patient expectation, disease context, or endpoint. A discordant quality attribute, a weak PD marker, an unexplained ADA signal, and post-switch discontinuation are not interchangeable reasons to request “more clinical data.” The inferential task is to localize the unresolved question before choosing the evidence capable of answering it.

Weighting concordant and discordant evidence

Concordance increases confidence only when the contributing evidence classes address meaningfully different uncertainties. Repeated measurements of the same underlying attribute do not carry the same inferential value as convergence across structure, function, human exposure, immune response, and clinically relevant outcomes. Discordance likewise requires localization: the first task is to determine which level disagrees and whether that level can plausibly propagate into a consequence.

Biosimilar-to-biosimilar switching makes this problem explicit. Separate biosimilars are each compared with a common reference product, but this does not constitute direct pairwise analytical demonstration between the two biosimilars [25]. A systematic review of biosimilar-to-biosimilar switching found reassuring effectiveness and safety findings, although all identified studies were observational [26]. Randomized multiple-switch evidence can address a narrower question more directly: repeated switching between PF-06410293 and reference adalimumab satisfied the study's prespecified PK comparability criteria without a meaningful safety or immunogenicity divergence [27].

Different evidence designs therefore resolve different residual questions. A French national cohort found no increased hospitalization risk for severe hypersensitivity after rituximab biosimilar initiation or switching compared with originator use [28]. Updated cross-switching evidence has also remained broadly reassuring as observational experience expanded [29]. These findings reduce defined uncertainties but do not make every switching sequence, product pair, indication, or endpoint evidentially equivalent.

The article therefore proposes weighting discordance by its location, mechanistic plausibility, sensitivity of the detecting method, downstream propagation, independence of corroborating evidence, and applicability boundary. A quality-attribute difference with preserved relevant function is a different state from a PK divergence, persistent ADA signal, or clinically coherent safety difference. **Table 3** separates these states without converting them into a numerical hierarchy.

Table 3. Constraint states for reconciling concordant and discordant biosimilarity evidence

Evidence	Enabling condition	Coupled constraint	PK or PD consequence	Immunogenicity or clinical linkage	Non-negotiable boundary	Structured-inference endpoint
Proximal discordance, downstream concordance	A product-level difference is reproducibly detected	Relevant functional interrogation is available	No propagated exposure or response difference detected	No coherent downstream signal	Tested assays and conditions only	Proposed: localize the difference before escalating evidence
Cross-level convergence	Independent evidence layers agree	Each layer must remain sufficiently sensitive	Human pharmacology is concordant where informative	Clinical or immune findings do not contradict the chain	Product, population, dose, and treatment-state limits remain	Proposed: confidence derives from convergence, not evidence count
Human-pharmacology discordance	Analytical and functional evidence is persuasive	PK or PD produces unexplained divergence	Exposure or response uncertainty remains	Clinical interpretation cannot safely bypass the divergence	Assay, population, and design causes require evaluation	Re-examine upstream assumptions and study conditions
Immune-signal discordance	ADA difference is analytically credible	Clinical meaning depends on persistence and consequence	PK may clarify altered disposition	Safety or efficacy linkage may or may not emerge	Cross-study ADA percentages are not interchangeable	Resolve whether immune discordance is consequential
Switching-specific residual uncertainty	Baseline biosimilarity is established	Treatment sequence introduces a distinct question	PK may be decisive in controlled multiple-switch designs	RWE can address selected safety or persistence questions	Evidence does not transfer automatically across product pairs	Match switching evidence to the exact transition being inferred

The switching literature also requires a visual separation between evidence strata and the gates that prevent inappropriate cross-scale transfer.

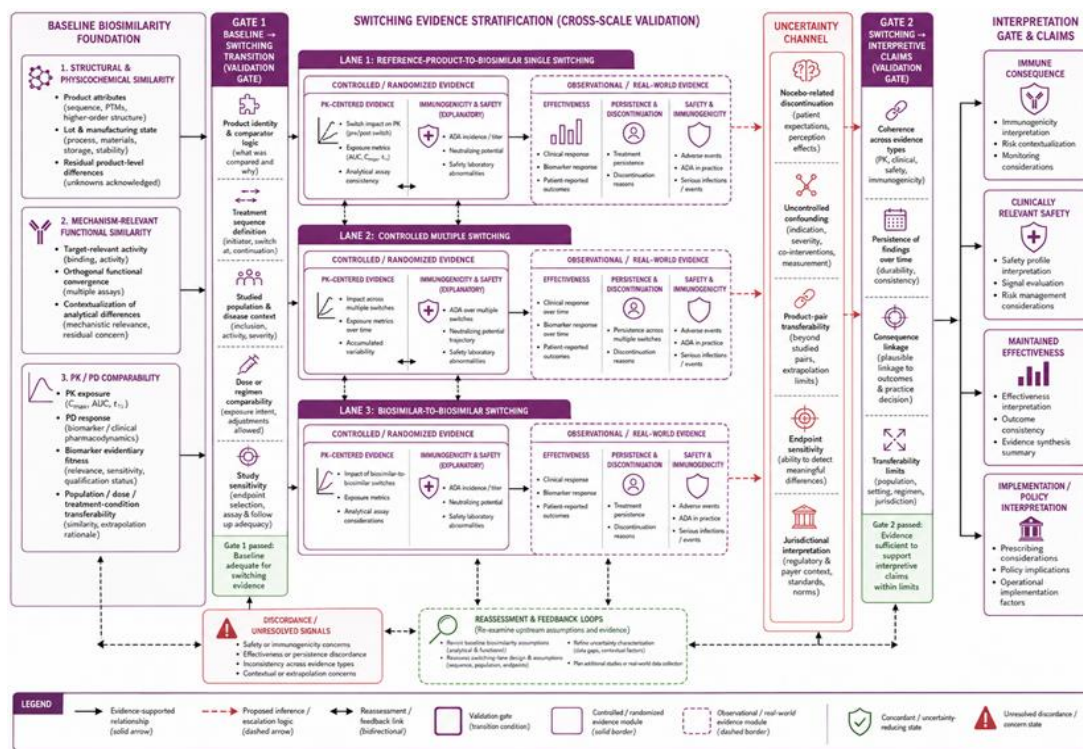


Figure 2. Validation gates governing transfer from product biosimilarity to switching-related inference

A structured evidential-reconciliation framework

The proposed framework begins by defining the unresolved question before selecting the evidence intended to answer it. Analytical criticality identifies where a product-level difference may matter; functional evidence tests biologically plausible propagation; PK or fit-for-purpose PD tests human-level propagation; and immunogenicity or clinical evidence is used when the remaining uncertainty concerns those downstream consequences. This reverses the tendency to equate later evidence with intrinsically stronger evidence.

A second principle is conditional convergence. Agreement across partially independent evidence classes can reduce uncertainty more than repeated concordance within one class, but convergence is meaningful only when the methods are sensitive to the relevant difference. Conversely, discordance should trigger investigation at the nearest informative level. The approved monoclonal-antibody analyses illustrate why a clinical efficacy endpoint may be poorly suited to resolve a quality concern [5], while immunogenicity evidence shows that analytical plausibility and observed clinical immune response can diverge [19].

The framework therefore has no universal score. Its proposed decision variables are uncertainty proximity, sensitivity, mechanistic relevance, evidential independence, convergence, and transfer boundary. Any application must preserve product, manufacturing state, assay, dose, population, disease, treatment sequence, and temporal context. Prospective validation would be required before these principles could be treated as a predictive decision rule.

Regulatory and development implications

Product-specific programs show how cross-level evidence can cohere without requiring every evidence class to carry identical weight. The natalizumab biosimilar program integrates analytical, functional, clinical-pharmacology, and clinical information in a neurological product context [30]. It is an informative example, not a universal development template.

Scientific inference must also be separated from policy acceptance. A systematic review of organizational position statements found heterogeneity in recommendations concerning biosimilar use [31]. Such variation reflects implementation and policy context and does not redefine the scientific demonstration of biosimilarity.

Prescriber perspectives similarly show that understanding of biosimilar evidence and clinical pharmacology can influence adoption [32]. The proposed reconciliation framework may therefore have explanatory value: it makes explicit why development can become more efficient when additional testing is tied to residual uncertainty. Regulatory refinement already supports tailored programs [2], and analyses questioning routine confirmatory

efficacy studies reinforce that direction [4]. However, streamlining should follow demonstrated resolution of the relevant uncertainty rather than a predetermined preference for fewer studies.

CONCLUSION

Biosimilarity is most coherently interpreted as structured reconciliation across evidence classes rather than accumulation of interchangeable proof. Analytical, functional, PK, PD, immunogenicity, clinical, and real-world evidence differ in what they can detect and what they can legitimately resolve. The proposed framework therefore localizes uncertainty, tests its propagation, weighs independent convergence, and preserves product, population, treatment, and methodological boundaries. Its purpose is disciplined interpretation, not numerical scoring or automatic regulatory decision-making. Future evaluation should test whether this structure improves the transparency and consistency of biosimilarity reasoning without obscuring genuine product-specific uncertainty.

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