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Why Analytical Similarity Cannot Be Reduced to a Single Number: A Hierarchical Evidence Model for Biosimilar Comparability

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ABSTRACT

Analytical similarity is foundational to biosimilar development, yet modern comparability programs generate heterogeneous evidence that cannot be represented adequately by one composite score. This article proposes an original hierarchical evidence model that preserves attribute identity across structural, physicochemical, functional, clinical-consequence, residual-uncertainty, and decision-response layers. The model rejects context-free compensation because extensive agreement among low-criticality attributes could conceal an unresolved difference in a clinically important characteristic. Critical quality attributes are therefore interpreted according to product-specific mechanism, assay confidence, reference-product variability, and plausible consequence for pharmacokinetics, pharmacodynamics, immunogenicity, safety, or efficacy. Residual uncertainty is defined as the decision-relevant question that remains after available evidence has been integrated, not as the number of studies still unperformed. Additional evidence is selected according to that question: targeted analytical reassessment, mechanism-relevant functional testing, sensitive pharmacokinetic or pharmacodynamic evaluation, focused immunogenicity investigation, or comparative clinical evidence when clinically meaningful uncertainty cannot be resolved more directly. Retrospective validation would require blinded reconstruction of comparability cases, explicit treatment of missing information, inter-rater assessment, falsification cases, lifecycle lot evaluation, and calibration against independent outcomes, followed by prospective testing. The contribution is a proposed non-empirical architecture rather than a validated scoring system, regulatory standard, clinical recommendation, or deployment-ready tool. Its principal boundaries arise from incomplete mechanism knowledge, assay limitations, reference-product drift, product-class differences, and jurisdiction-specific interchangeability decisions.

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

Biopharmaceutical comparability is intrinsically multidimensional because a biological product cannot be defined by one identity test or performance endpoint. Biosimilarity concerns comparison with an authorized reference product, whereas analytical similarity describes the structural, physicochemical, and functional evidence generated within that comparison. Comparability also applies to manufacturing changes and lifecycle management. Critical quality attributes may affect identity, purity, biological activity, exposure, immunogenicity, safety, or efficacy. Indication extrapolation and interchangeability are related downstream questions, but neither is synonymous with analytical similarity.

The prevailing biosimilar framework is based on a stepwise totality of evidence. Analytical comparison provides the scientific foundation, while the need for later evidence depends on the questions left unresolved by structural, functional, pharmacokinetic, clinical, and immunogenicity information. Interchangeability remains a distinct decision concept whose legal and evidentiary meaning varies by jurisdiction [1–3].

The central difficulty is not lack of data. Contemporary programs may characterize sequence, higher-order structure, glycosylation, charge variants, aggregation, particles, process impurities, binding, potency, effector functions, degradation behavior, and lot variability. The problem arises when this evidence is collapsed into an undifferentiated conclusion that obscures which attributes agree, which differ, how reliable each measurement is, and whether any difference is mechanistically or clinically consequential.

This article presents an original, non-empirical hierarchical evidence model for biosimilar comparability. It does not replace statistical analysis, regulatory judgment, or clinical evaluation. Its purpose is to organize how attribute-level evidence moves from analytical observation to functional interpretation, clinical-consequence appraisal, residual-uncertainty assessment, and proportionate evidence escalation.

Why scalar similarity scores are scientifically inadequate

A scalar score becomes scientifically inadequate when heterogeneous findings are compressed into a context-free number. Statistical comparisons of means, ranges, variability, or distributions answer different questions and depend on lot selection and assay properties. Quality attributes differ in criticality, and orthogonal platforms interrogate distinct molecular properties with different uncertainty structures. These features prevent defensible reduction to one compensatory index [4–6].

The core weakness is numerical compensation. Strong similarity across numerous low-consequence attributes could offset one unresolved difference in a high-criticality attribute. Yet a sequence variant affecting target binding, a potentially immunostimulatory impurity, and a minor physicochemical shift cannot be treated as interchangeable units merely because they can be normalized onto a common scale [5].

A scalar also hides direction and distribution. Two products may receive the same aggregate value even when one shows small, coherent shifts across low-criticality attributes and another shows broad agreement interrupted by one mechanism-relevant discordance. Method count is similarly misleading when assays share sample preparation, calibration, or common blind spots [4].

The proposed alternative is a noncompensatory hierarchy. Numerical summaries may be used within attribute-specific analyses, but each material observation remains linked to its method, reference-lot context, uncertainty, functional implications, and unresolved question. This structure does not imply that every detectable difference is clinically important; it prevents the evidentiary path from disappearing inside a single number.

Hierarchy of critical quality attributes

Analytical detectability is not equivalent to clinical criticality. Attributes become critical through plausible relationships with molecular integrity, biological activity, exposure, immune response, safety, or efficacy. Evidence of drift in antibody-dependent cellular cytotoxicity-related characteristics of reference trastuzumab illustrates why interpretation must also accommodate lifecycle variability [7]. Drift does not make an attribute unimportant, nor does it automatically justify a comparable biosimilar change.

The first level contains structural and physicochemical attributes, including sequence, disulfide connectivity, higher-order conformation, glycans, charge and size variants, particles, and impurities. Nuclear magnetic resonance assessment of higher-order structure demonstrates that conformational evidence adds information that cannot be recovered from primary sequence alone [8]. No single method, however, establishes complete structural similarity.

The second level concerns functional consequence. C-terminal lysine clipping illustrates that a detectable molecular variant may have limited influence on selected Fc-receptor interactions under tested conditions [9]. This supports separating analytical observation, functional effect, and clinical consequence rather than assigning importance from analytical magnitude alone.

The third level is contextual consequence. Criticality may change with molecular class, mechanism, dose, route, patient population, indication, or immune susceptibility. The proposed hierarchy is therefore not a universal ranking. It is an auditable rationale explaining why an attribute matters in a defined product and decision context.

Proposed hierarchical evidence model

The proposed model contains five linked layers: analytical observation, mechanism-relevant function, clinical-consequence appraisal, residual-uncertainty integration, and decision response. Each attribute begins as a traceable observation associated with a method, lot context, and uncertainty. It progresses only through relationships supported by evidence or bounded mechanistic reasoning.

Figure 1 presents the original conceptual synthesis for hierarchical biosimilar comparability evidence model, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

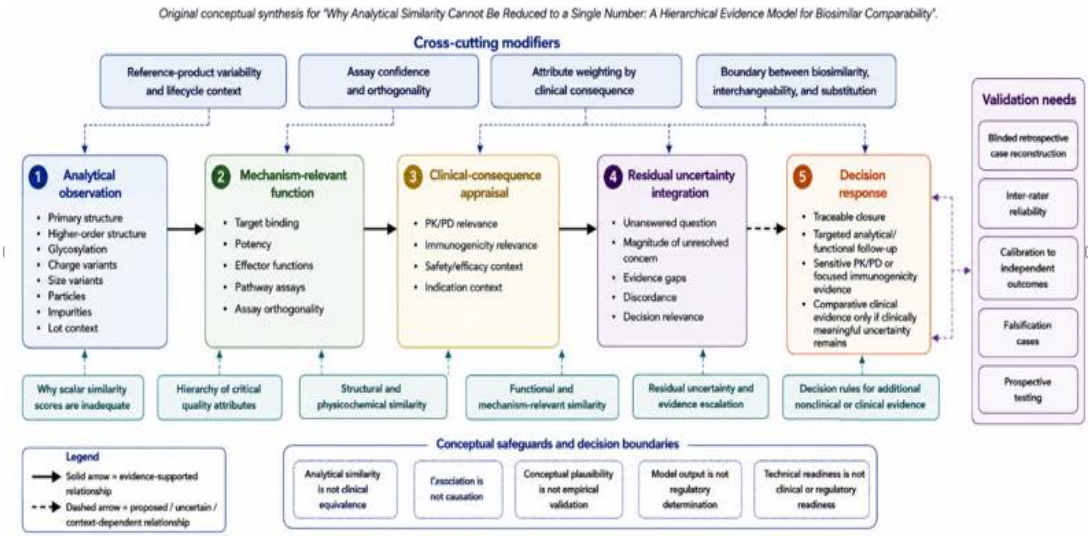

Figure 1. Hierarchical Biosimilar Comparability Evidence Model

The model preserves the totality-of-evidence principle while making its internal logic explicit. Regulatory analyses and product-level cases support tailoring later evidence to the residual uncertainty remaining after robust analytical and functional comparison [10–12].

Residual uncertainty is the clinically or pharmaceutically relevant question that remains unresolved after evidence has been assessed for quality, concordance, and mechanistic sufficiency. It is not the number of tests that have not yet been performed. A large program may retain substantial uncertainty if one high-criticality difference remains unexplained.

A noncompensatory gate separates the layers. High-criticality discordance cannot be cancelled by favorable lower-tier evidence. Passing a gate does not require literal identity; it requires a documented rationale showing that observed variation is analytically credible, contextually interpreted, and unlikely to leave a clinically meaningful question unanswered.

Decision responses are traceable closure, targeted follow-up, or evidence escalation. These are proposed categories rather than validated regulatory outcomes and require empirical evaluation across product classes and lifecycle contexts.

Structural and physicochemical similarity

Structural and physicochemical similarity forms the foundational layer. Orthogonal characterization of trastuzumab biosimilar CT-P6 demonstrates how evidence can be distributed across primary structure, higher-order structure, purity, variants, and physicochemical properties rather than collapsed into one result [13].

The evidence object should retain lot-level and method-level structure. Characterization of rituximab biosimilar CT-P10 shows the importance of multidimensional comparison across lots and methods [14]. Reference variability provides context, but it is not an unrestricted acceptance region.

Localized differences should remain visible. Assessment of adalimumab biosimilar SB5 illustrates how small differences can be interpreted against reference variability, assay capability, and biological relevance [15]. The model proposes carrying reproducible, plausibly consequential differences forward to functional testing.

Structural similarity is necessary but not independently sufficient for clinical equivalence, indication extrapolation, immunogenicity conclusions, or interchangeability. Its role is to identify, characterize, and bound molecular uncertainty.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in why analytical similarity cannot be reduced to a single number.

Table 1. Definitions, components, relationships, and intended uses in Why Analytical Similarity Cannot Be Reduced to a Single Number

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Structural profile	Global summaries hide domain-specific findings	Sequence, conformation, glycans, variants, particles, impurities	Preserve evidence by attribute and method	Molecular traceability	Orthogonal lot evidence [13]	Correlated assays mistaken for independent evidence	Analytical breadth is not clinical equivalence
Reference distribution	A fixed comparator ignores lifecycle variability	Lot and temporal context	Interpret observations within structured variability	Distinguishes drift from discordance	Lot-wise evidence [14]	Broad ranges used as automatic acceptance criteria	Reference variability does not justify uncontrolled change
Localized difference	Binary labels conceal discordance	Direction, magnitude, reproducibility	Carry plausible differences forward	Prevents premature closure	Attribute-specific analysis [15]	Over- or underinterpretation	Detectability is not consequence
Critical quality attribute	Equal weighting ignores unequal importance	Mechanism, exposure, immune and clinical relevance	Prioritize by plausible consequence	Focuses decision attention	Product-specific rationale [5]	Conventional rather than causal ranking	No universal numerical weight
Noncompensatory gate — proposed	Favorable low-tier evidence masks critical uncertainty	Criticality and assay confidence	High-criticality discordance remains active	Protects transparency	Prespecified qualitative rules	Inconsistent assessor judgments	Not a validated regulatory threshold
Residual uncertainty — proposed	Test volume is confused with sufficiency	Missing evidence and discordance	Define the unanswered decision-relevant question	Directs escalation	Cross-layer integration [10]	Vague or overstated concern	Not a calibrated probability

Functional and mechanism-relevant similarity

Functional similarity evaluates whether compared products behave consistently in assays linked to known or plausible mechanisms. Analytical and functional assessment of ABP 215 illustrates how target binding, potency, and biological activity can complement structural evidence [16].

Structural and functional evidence are linked but not interchangeable. A rituximab comparability case demonstrates the value of joint interpretation while preserving the distinct contribution of each domain [17].

Orthogonal functional evidence may reduce uncertainty when assays interrogate genuinely different mechanisms. Assessment of BVZ-BC illustrates broad concordance across structural and biological-activity domains while retaining localized findings for interpretation [18].

The model therefore requires a mechanism-coverage statement identifying what each assay addresses, what remains untested, and how closely the assay relates to the relevant pharmaceutical consequence. Functional similarity supports causal plausibility but does not independently establish patient-level equivalence.

Attribute weighting by clinical consequence

Weighting should begin with a causal pathway from attribute to function, exposure, immune response, safety, or efficacy. Glycosylation demonstrates why fixed universal weights are inappropriate: the consequence of a glycan difference depends on product architecture, mechanism, exposure, and indication [19].

Stress studies can reveal latent structure–function sensitivity. Forced degradation of modified antibodies shows how controlled perturbation may identify vulnerabilities not apparent under routine conditions [20]. Such evidence remains supportive and product-specific.

Process impurities show why low abundance does not equal low criticality. Experimental evidence linking a heat-shock-protein impurity to immunogenic potential supports separating concentration, hazard, exposure, and demonstrated clinical risk [21].

The proposed weighting process is qualitative and auditable. High criticality means uncertainty cannot be dismissed through compensation; it does not prove harm. Low criticality means limited plausible consequence under defined conditions; it does not mean permanent irrelevance.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for why analytical similarity cannot be reduced to a single number.

Table 2. Testable propositions, evidence requirements, and validation criteria for Why Analytical Similarity Cannot Be Reduced to a Single Number

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Analytical observation	Preserve attribute-level evidence	Method output enters structured records	Supplies structural findings	Conclusions can be reconstructed from lot data	Premature aggregation	Analytical scientists	Conceptual stage only
Functional interrogation	Test structure–function hypotheses	Findings direct mechanism-relevant assays	Returns functional evidence	Assays answer the specified question [16]	Mechanistic redundancy	Bioassay experts	Not complete clinical evidence
Clinical-consequence appraisal	Bound plausible impact	Functional evidence informs consequence hypotheses	Determines criticality	Rationale identifies a plausible pathway [19]	Association treated as causation	Multidisciplinary review	No patient-level prediction
Noncompensatory gate — proposed	Preserve critical discordance	Unresolved differences remain active	Controls closure or escalation	Consistent blinded classification	Excessive or inconsistent escalation	Independent adjudication	No approved cut-point
Residual-uncertainty integration — proposed	Define the unanswered question	Lower-layer gaps become an uncertainty statement	Determines additional evidence	Inter-rater reproducibility	Vague concern	Independent assessors	Requires calibration
Retrospective validation — proposed	Test reproducibility and falsifiability	Historical cases enter a locked model	Evaluates the architecture	Blinding, falsification, and missing-data robustness	Outcome leakage	Independent validation team	Not deployment validation

Residual uncertainty and evidence escalation

Comparative efficacy trials may add limited discriminatory information when analytical, functional, and pharmacokinetic evidence has already resolved the relevant question [22]. Their value depends on endpoint sensitivity, population variability, and the mechanism of the remaining difference.

Escalation should be matched to uncertainty. A structural ambiguity may require a better analytical method; a functional concern may require a more sensitive assay; an exposure concern may require pharmacokinetic or pharmacodynamic evaluation. Tailored clinical-development approaches support this question-specific principle [23].

Immunogenicity, switching, indication extrapolation, and interchangeability require distinct boundaries. Analytical similarity is foundational, but safety, immune response, and switching decisions remain context-dependent [24].

The model classifies uncertainty by source, plausible consequence, and resolvability. These categories are proposed and should not be interpreted as approved regulatory classifications.

Decision rules for additional nonclinical or clinical evidence

The first rule is to select the most sensitive evidence capable of answering the unresolved question. A suitable pharmacodynamic biomarker may be more informative than a broad efficacy endpoint when it directly reflects the product's biological response [25].

The second rule is to optimize study conditions for discriminatory sensitivity. Model-based dose selection for pegfilgrastim pharmacokinetic and pharmacodynamic similarity studies illustrates how quantitative pharmacology can identify more informative conditions [26].

The third rule is to avoid routine escalation. Nonclinical or comparative clinical evidence is justified only when clinically meaningful uncertainty cannot be resolved more directly through analytical, functional, or clinical-pharmacology approaches.

The fourth rule is to document responsibility. The trigger, competing explanations, selected study, expected information gain, and closure criteria should be recorded transparently.

Table 3 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for failure modes, boundary conditions, governance needs, and implementation priorities for why analytical similarity cannot be reduced to a single number.

Table 3. Failure modes, boundary conditions, governance needs, and implementation priorities for Why Analytical Similarity Cannot Be Reduced to a Single Number

Decision scenario or design trade-off	Trigger or context	Competing objective	Evidence threshold	Uncertainty treatment	Corrective or escalation action	Expected implication	What cannot be concluded
High-criticality discordance	Reproducible consequential difference	Rapid closure versus false reassurance	Credible analytical and mechanistic concern	Keep uncertainty active	Targeted functional study	Prevents masking	Does not prove inferiority
Difference within reference range	Result lies within pooled variability	Flexibility versus traceability	Lot and temporal context	Separate drift from divergence	Additional lot analysis	Improves lifecycle interpretation	Range membership is not automatic acceptance
Structural difference without functional evidence	Plausible biological relevance	Economy versus mechanism coverage	Testable structure–function hypothesis	State the untested function	Add a sensitive assay	Converts concern into a testable question	Structure alone is not clinical consequence
Low-level impurity	Plausible immune activity	Manufacturing practicality versus risk control	Mechanistic hazard evidence	Separate hazard from incidence	Focused impurity assessment	Protects criticality reasoning	Does not quantify patient risk
Exposure uncertainty	Mature analytical package	Minimize studies versus answer a PK/PD question	Defined exposure concern	Retain uncertainty at the PK/PD layer	Sensitive PK/PD study [25]	Targets the unresolved question	Does not establish every clinical outcome
Comparative efficacy proposal	Uncertainty remains	Convention versus information value	No more sensitive alternative	Document incremental value	Clinical study when justified	Aligns evidence with need	The framework does not prohibit trials
Interchangeability claim	Biosimilarity evidence is extended beyond scope	Simplicity versus legal precision	Jurisdiction-specific criteria	Separate decision categories	Governance review	Prevents conflation	Analytical similarity does not authorize substitution

Validation through retrospective comparability cases

Published biosimilarity assessments vary in the extent and detail with which attributes, methods, lots, and discordances are reported [27]. Missing information must therefore be classified as absent, unreported, or unavailable rather than assumed similar.

Retrospective validation should include product-development cases, manufacturing-change exercises, post-approval lots, and both concordant and discordant examples. Post-approval characterization of biosimilar and reference monoclonal antibodies provides a suitable lifecycle domain [28].

Assessors should work with locked definitions and without knowledge of regulatory or development outcomes. They would reconstruct attributes, criticality rationales, assay confidence, residual uncertainty, and escalation decisions. Inter-rater reliability, calibration, and falsification should then be evaluated.

Retrospective agreement is only preliminary. Prospective validation requires registered cases, predefined governance, independent adjudication, and testing of whether the framework improves transparency and study selection without missing consequential differences.

Limitations and implementation priorities

Clinical switching evidence cannot serve as a universal gold standard for analytical comparability because findings remain product-, population-, indication-, and design-dependent [29]. Absence of a detected clinical difference does not establish molecular identity.

Figure 2 presents the original conceptual synthesis for escalation pathway based on residual uncertainty and clinical relevance, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

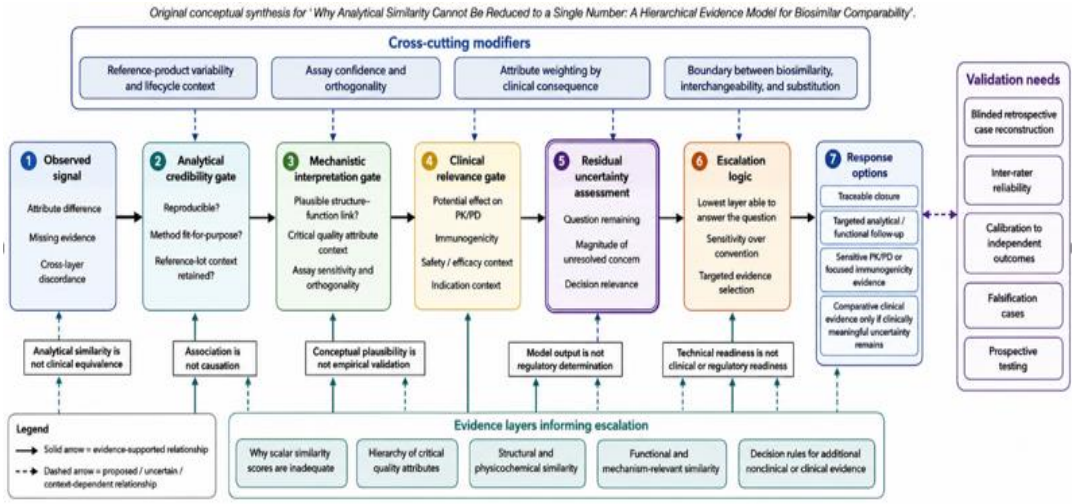

Figure 2. Escalation Pathway Based on Residual Uncertainty and Clinical Relevance

Implementation requires governance that separates biosimilarity, interchangeability, substitution, switching, and lifecycle comparability. Debate around interchangeability confirms that analytical similarity cannot be converted automatically into a universal substitution decision [30].

Further limitations include incomplete mechanism knowledge, assay sensitivity, reference-product evolution, reporting bias, and product-class transportability. The framework may create false reassurance if important mechanisms are omitted or unnecessary escalation if uncertainty is defined too broadly.

Priorities include standardized attribute-level data, transparent assay-dependency maps, prospective case registration, independent adjudication, documented expert overrides, and product-class recalibration. These are requirements for future evaluation, not evidence of implementation readiness.

CONCLUSION

Analytical similarity cannot be reduced responsibly to one number because biosimilar comparability depends on heterogeneous attributes, unequal consequences, method-specific uncertainty, reference-product variability, mechanism-relevant function, and decision context. The proposed hierarchical model preserves these dimensions through linked evidence layers and noncompensatory gates. Its escalation logic directs additional evidence toward

the specific question that remains unresolved. The framework is an original conceptual synthesis, not a validated score, regulatory standard, clinical recommendation, or universal development pathway. Its value must be tested through blinded retrospective cases, inter-rater analysis, falsification, lifecycle evaluation, and prospective validation.

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