



Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Next-Generation Biosimilars Need Lifecycle Comparability Rather Than One-Time Similarity Judgments

Ravi Kumar^{1*}, Neha Sharma¹, Aniket Deshmukh², Sanjay Kulkarni³, Arjun Nair⁴

¹Department of Biosimilar Lifecycle Comparability, Faculty of Pharmacy, Indian Agricultural Research Institute, New Delhi, India.

²Department of Continuous Similarity Assessment, Faculty of Pharmacy, IIT Bombay, Mumbai, India.

³Department of Product Evolution and Quality, Faculty of Pharmaceutical Sciences, Savitribai Phule Pune University, Pune, India.

⁴Department of Biosimilar Development, Faculty of Pharmacy, IIT Kharagpur, Kharagpur, India.

*Email: ravi.kumar@iari.res.in

ABSTRACT

Biosimilarity is established at a defined point in product development, whereas both reference products and biosimilars continue to evolve after approval through manufacturing changes, site transfers, process optimization, formulation updates, and routine lot-to-lot variation. This creates a temporal problem that is poorly described by a one-time similarity judgment. Yet measurable change should not be equated with clinically meaningful drift: contemporary lifecycle evidence includes both documented time-dependent shifts in selected reference-product attributes and examples of long-term biosimilar quality stability. We argue that next-generation biosimilar oversight should therefore treat comparability as a longitudinal evidentiary problem. The proposed approach preserves the original biosimilarity bridge while following independently controlled reference-product and biosimilar trajectories. Analytical surveillance should first determine whether an observed signal is credible, then ask whether it affects mechanism-relevant function, pharmacokinetics, immunogenicity risk, or clinical performance. Clinical reassessment should be triggered by unresolved biologically plausible uncertainty rather than by change alone. This lifecycle framing is intended to improve interpretability and regulatory traceability, not to require routine re-demonstration of biosimilarity.

Keywords: Biosimilars, Comparability, Lifecycle management, Analytical surveillance, Product drift, Immunogenicity

Received: 02 July 2026; **Revised:** 19 September 2026; **Accepted:** 22 September 2026

INTRODUCTION

Biosimilars are approved through an evidence architecture that places comparative analytical and functional characterization at its scientific core. Reviews of successful monoclonal-antibody biosimilar programmes show recurring use of orthogonal physicochemical and functional methods to interrogate product quality attributes at a granularity that conventional clinical endpoints often cannot match [1]. That architecture is powerful, but its conventional representation is temporally compressed: a biosimilar is compared with an authorized reference product during development, and the resulting similarity conclusion is then carried forward as both products continue their own regulated manufacturing histories.

The word “drift” can obscure rather than clarify this problem. A recent regulatory-science analysis argues that well-controlled biologics and biosimilars do not progressively diverge simply because they are manufactured independently; current good manufacturing practice, validated control strategies, and serial comparability are

intended to prevent uncontrolled product evolution [2]. That counterargument is essential. Lifecycle comparability should not be built on an assumption that biosimilars inevitably move away from their reference products. The more defensible question is whether the evidentiary bridge established at approval remains interpretable when either product undergoes manufacturing or quality-state changes over time.

Post-change comparability already provides part of the answer. Patient-centric comparability frameworks emphasize scaling evidence to the potential clinical relevance of a manufacturing change rather than applying a fixed data package [3]. We extend that logic to biosimilars. The central proposal of this Current Opinion is a dynamic comparability framework that keeps the original biosimilarity determination intact, treats the reference product and biosimilar as independently controlled post-approval trajectories, and introduces explicit escalation only when longitudinal evidence generates unresolved mechanistic or clinical uncertainty.

The static biosimilarity model

The conventional biosimilarity model is not scientifically simplistic. It is a layered inference in which analytical similarity, functional similarity, pharmacokinetics, pharmacodynamics where informative, immunogenicity, and clinical evidence have different roles. The natalizumab biosimilar programme illustrates this totality-of-evidence logic: the conclusion does not arise from a single assay or endpoint but from concordance across levels whose relative evidentiary weight depends on product biology [4]. What is static is therefore not the science, but the time index of the principal comparison.

This distinction matters because biosimilarity does not require identity in every measurable attribute. In the comparative assessment of BAT1806/BIIB800 and reference tocilizumab, extensive structural and functional testing supported high similarity while minor differences were observed in less critical attributes [5]. Such findings demonstrate why a lifecycle model cannot treat any later analytical difference as evidence that similarity has been lost. The meaning of a difference depends on the attribute, its relationship to mechanism of action, assay performance, and whether functional consequences are detectable.

Orthogonality is equally important. ABP 710 was compared with US- and EU-sourced infliximab using complementary structural, physicochemical, purity, post-translational-modification, and functional methods [6]. A longitudinal framework should preserve this principle: repeated measurement is useful only if the measurement system remains capable of distinguishing true product-state change from analytical noise, method change, or benign variability. Thus, the approval-time biosimilarity conclusion should be understood as a well-supported bridge between two defined product states, not as a claim that future states must remain analytically frozen.

Product evolution after approval

Biological products change after approval because their manufacturing systems are living technical systems. Changes may involve process scale, equipment, sites, raw materials, purification, formulation, container-closure systems, or analytical methods. A survey of 85 monoclonal antibodies and 10 Fc-fusion proteins approved by the US Food and Drug Administration found that analytical comparability was used across manufacturing changes, whereas the need for nonclinical or clinical support varied with the nature of the change [7]. This is the key lifecycle principle: change is expected, but its evidentiary consequence is conditional.

Longitudinal biosimilar data show that product evolution does not imply progressive loss of control. SB5, an adalimumab biosimilar, maintained consistent purity, charge-variant distribution, tumor-necrosis-factor binding, and neutralization across 93 batches manufactured from 2013 to 2022, despite manufacturing-site and formulation changes during that period [8]. This provides a direct counterexample to the idea that independently manufactured biosimilars should be presumed to drift simply because time passes.

Longitudinal interpretation also depends on measurement continuity. World Health Organization international reference standards can support harmonized potency and bioactivity measurement across a product lifecycle, particularly when internal standards, assays, or laboratories change [9]. These standards do not replace product-specific comparability, but they illustrate a broader requirement: before a temporal difference is assigned to the product, the analytical system used to observe it must itself be anchored.

The lifecycle cases are therefore not interchangeable. A manufacturing change with stable critical attributes is different from an analytical shift confined to a low-relevance attribute, and both differ from a reproducible change linked to a mechanism-relevant functional assay. The distinctions below separate these states so that product evolution is not used as a synonym for loss of comparability.

Table 1. Product-State Changes That Require Different Lifecycle Comparability Interpretations

Source state and scale		Transfer conditions	Qualification endpoint
product-evolution state / Immunogenicity relevance	Clinical linkage / Comparability interpretation	Residual uncertainty / Lifecycle trigger	Decision consequence / Lifecycle endpoint
Proposed product-evolution state: Stable critical quality profile after manufacturing change Immunogenicity relevance: No new signal solely from the change	Clinical linkage: Existing clinical bridge remains applicable Comparability interpretation: Controlled evolution	Residual uncertainty: Assay continuity and unmeasured attributes Lifecycle trigger: Verified process or site change	Decision consequence: Continue routine control Lifecycle endpoint: Comparability confidence maintained
Proposed product-evolution state: Reproducible change confined to an attribute without plausible mechanism linkage Immunogenicity relevance: Low unless new evidence changes criticality	Clinical linkage: No automatic clinical inference Comparability interpretation: Analytical difference without demonstrated functional consequence	Residual uncertainty: Whether the attribute is truly noncritical Lifecycle trigger: Persistent temporal trend	Decision consequence: Targeted analytical follow-up Lifecycle endpoint: Maintain bridge with documented rationale
Proposed product-evolution state: Change in a mechanism-relevant attribute without functional shift Immunogenicity relevance: Potential but unresolved	Clinical linkage: Clinical consequence not established Comparability interpretation: Signal requiring functional adjudication	Residual uncertainty: Assay sensitivity and redundancy Lifecycle trigger: Confirmed critical-attribute movement	Decision consequence: Intensify function-focused testing Lifecycle endpoint: Resolve before clinical escalation
Proposed product-evolution state: Concordant analytical and mechanism-relevant functional change Immunogenicity relevance: Plausibly increased	Clinical linkage: Clinical relevance remains unproven Comparability interpretation: Comparability uncertainty increased	Residual uncertainty: Pharmacokinetic, immune and exposure-response consequences Lifecycle trigger: Reproducible cross-assay concordance	Decision consequence: Escalate evidence proportionately Lifecycle endpoint: Re-establish decision confidence
Proposed product-evolution state: Apparent product change accompanied by assay or reference-standard discontinuity Immunogenicity relevance: Indeterminate	Clinical linkage: Not interpretable Comparability interpretation: Product inference premature	Residual uncertainty: Measurement-system stability Lifecycle trigger: Method, laboratory or standard change	Decision consequence: Repair or bridge measurement system Lifecycle endpoint: Establish analytical continuity first

Manufacturing changes

Comparability after a manufacturing change is not unique to biosimilars. The same scientific problem exists whenever a biological product is produced before and after a process modification: the manufacturer must show that the relevant pre-change and post-change product states remain sufficiently comparable for the existing clinical knowledge to remain applicable. Global comparability analyses therefore support a shared scientific foundation for originators and biosimilars, even though jurisdictional procedures and evidence expectations are not fully harmonized [10].

The practical consequence is that lifecycle evidence should be proportional to the question created by the change. In a 2025 assessment of intravenous and subcutaneous RGB-19 products against corresponding tocilizumab reference presentations, 44 analytical and functional methods supported high similarity, with minor physicochemical differences not translating into meaningful effects in the critical functions examined [11]. Similarly, RGB-14 denosumab products were compared with Prolia and Xgeva reference products using a broad 38-method analytical and functional programme that supported high similarity [12]. These examples do not

establish that presentation or manufacturing changes are clinically irrelevant. They show instead that product-state differences can be interrogated at the level where they arise before clinical consequences are assumed.

A lifecycle approach should therefore resist two symmetrical errors. The first is to regard any manufacturing change as a reason to reopen the entire biosimilarity determination. The second is to assume that compliance with a change-control procedure makes every subsequent analytical signal uninformative. The scientifically useful middle position is serial, risk-based comparability: preserve the prior clinical bridge when the post-change evidence supports it, but retain a mechanism for escalating new discordant evidence.

Reference-product drift

The reference product is not a permanently fixed analytical target. One of the clearest examples comes from longitudinal characterization of Herceptin lots. Sequential changes in afucosylated and high-mannose glycans were accompanied by corresponding changes in FcγRIIIa binding and antibody-dependent cellular cytotoxicity, showing that selected reference-product quality attributes and mechanism-relevant functions can move over calendar time [13]. Importantly, this evidence demonstrates analytical and functional change; it does not by itself demonstrate deterioration in clinical efficacy or safety.

Reference evolution can matter even when clinical performance remains acceptable because the comparator distribution used during biosimilar development can change. Biological characterization of SB3 and trastuzumab reference lots showed that shifts in reference-product characteristics affected the similarity-assessment context, including the ranges against which biosimilar attributes were interpreted [14]. A biosimilar developed against one temporal window of reference lots may therefore face a later reference state that is not analytically identical to the earlier window, despite both reference states remaining acceptable products.

This observation must be balanced by newer cross-product evidence. A 2025 Japanese study comparing multiple post-approval lots of infliximab, trastuzumab, rituximab, bevacizumab, and etanercept reference products and biosimilars found product-specific ranges and temporal trends in some attributes, but reported no clear lot drift overall [15]. That null finding is central to the terminology used here. “Variability,” “trend,” “attribute shift,” and “drift” should not be treated as synonyms. A lifecycle framework should reserve stronger interpretations for signals that are reproducible, analytically credible, and connected to functional or clinical relevance.

The resulting reference-product trajectory is therefore neither frozen nor presumed unstable. It is a sequence of controlled product states. Historical biosimilarity remains meaningful because it was established against an authorized reference state; subsequent surveillance becomes informative when it identifies a change that could alter the biological assumptions supporting that bridge.

Biosimilar drift

The same discipline is required for the biosimilar trajectory. A measurable difference emerging after approval should first be treated as an analytical observation, not as evidence of clinical divergence. In a structure–activity investigation of BAT1806/BIIB800 and reference tocilizumab, differences involving glycation, glycosylation, charge variants, oxidation, and deamidation were interrogated for functional consequences. Within the tested assays and conditions, the observed differences did not produce relevant effects on the critical biological functions examined [16]. This is precisely the type of evidence needed to prevent analytical sensitivity from becoming interpretive overreach.

Attribute criticality also changes how statistical differences should be read. The CT-P6 trastuzumab biosimilar programme used risk-tiered statistical approaches so that highly critical attributes received more stringent similarity analysis than attributes of lower clinical relevance [17]. Although statistical frameworks have evolved, the underlying principle remains valuable for lifecycle surveillance: a uniform threshold across all measured attributes would ignore differences in biological importance, assay precision, natural variability, and mechanism linkage.

The stronger concern is not “biosimilar drift” as an assumed property of independent manufacture, but unresolved discordance across evidence levels. A temporal change that remains within the validated control strategy and lacks functional consequence is not equivalent to a reproducible shift in a mechanism-relevant function. Conversely, a clinical complaint or pharmacovigilance signal without analytical concordance should not be back-labelled as product drift until formulation, device, disease, treatment sequence, and contextual explanations have been considered. The framework proposed here therefore treats the reference product and biosimilar as parallel controlled trajectories rather than as two lines that must remain numerically superimposable at every future time point.

The distinctions become clearest when biosimilar temporal signals are arranged according to the evidence needed to interpret them rather than according to whether a measurement simply moved.

Table 2. Biosimilar Temporal Signals Separated by Their Evidentiary Consequence

State and entry conditions	Evidence through time	Transition and reassessment	
biosimilar-drift state / Immunogenicity relevance / Comparability interpretation	Clinical linkage / Lifecycle trigger	Residual uncertainty / Decision consequence	Lifecycle endpoint
Proposed biosimilar-drift state: Controlled lot-to-lot variation within the established quality state Immunogenicity relevance: No new implication Comparability interpretation: Expected product variability	Clinical linkage: Existing bridge retained Lifecycle trigger: Serial-lot monitoring	Residual uncertainty: Routine residual uncertainty Decision consequence: Continue surveillance	Confidence maintained
Proposed biosimilar-drift state: Persistent analytical trend without mechanism-relevant functional change Immunogenicity relevance: Usually unresolved rather than adverse Comparability interpretation: Temporal signal, not demonstrated drift	Clinical linkage: No direct clinical inference Lifecycle trigger: Reproducible multi-lot movement	Residual uncertainty: Long-term direction and assay stability Decision consequence: Confirm trend and criticality	Documented bounded variation or further escalation
Proposed biosimilar-drift state: Mechanism-relevant attribute change with stable functional assays Immunogenicity relevance: Potential theoretical relevance Comparability interpretation: Analytical concern under adjudication	Clinical linkage: Not demonstrated Lifecycle trigger: Critical-attribute movement	Residual uncertainty: Assay sensitivity and compensating attributes Decision consequence: Expand orthogonal functional testing	Functional uncertainty resolved
Proposed biosimilar-drift state: Concordant change across critical attribute and function Immunogenicity relevance: Plausible Comparability interpretation: Evidence of biologically meaningful product-state change	Clinical linkage: Requires targeted pharmacokinetic, immunogenicity or clinical reasoning Lifecycle trigger: Cross-level concordance	Residual uncertainty: Translation to patients Decision consequence: Escalate proportionately	Restore comparability confidence or revise control
Proposed biosimilar-drift state: Clinical or immunogenicity signal without analytical concordance Immunogenicity relevance: Possible but source uncertain Comparability interpretation: Product drift not established	Clinical linkage: Directly observed at patient level Lifecycle trigger: Credible postmarket signal	Residual uncertainty: Product versus contextual causation Decision consequence: Investigate competing explanations and product evidence	Causal attribution remains evidence-dependent

A reconciliation lattice is needed because the decisive question is not whether a biosimilar changes, but whether independent evidence streams converge on a biologically consequential state.

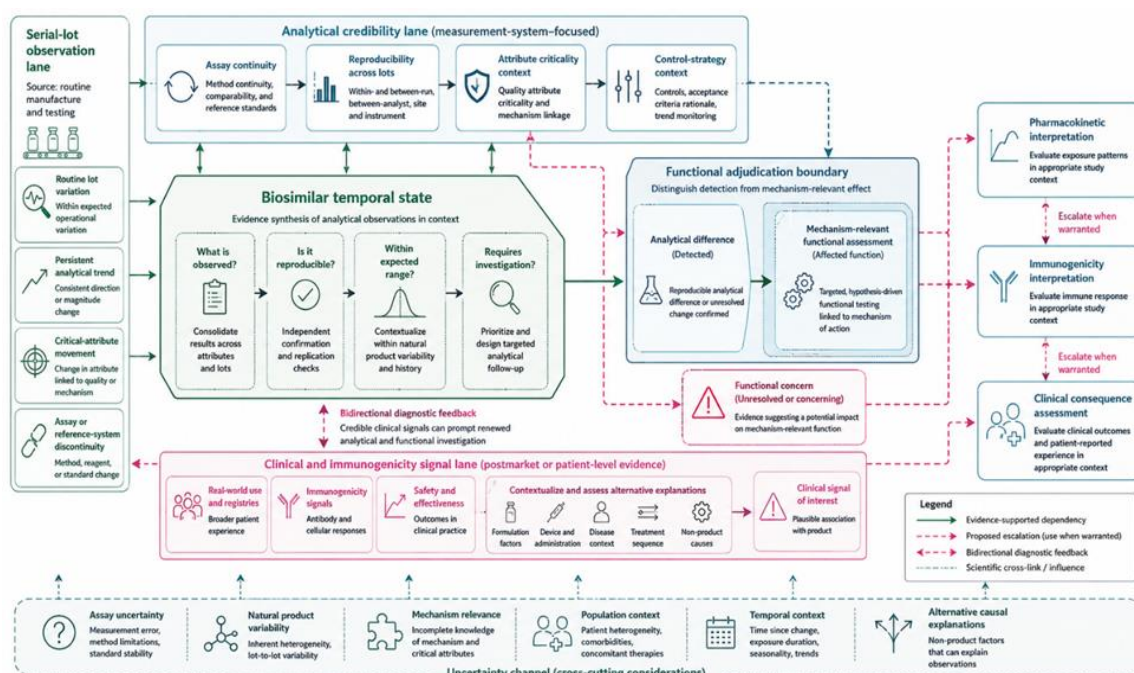


Figure 1. When a Temporal Biosimilar Signal Becomes a Comparability Concern

Analytical surveillance across time

Longitudinal surveillance is only useful when a temporal comparison is scientifically valid. The first requirement is measurement continuity. Analytical platforms, laboratories, internal standards, reagents, and data-processing practices may themselves change over a product lifecycle. World Health Organization international reference standards illustrate how external anchors can support continuity for selected potency and bioactivity measurements [9]. The surveillance question must therefore begin with whether the observation is comparable across time before asking whether the product has changed.

The second requirement is classification without premature causality. The Herceptin experience shows that coherent temporal movement across a quality attribute and mechanism-relevant function can occur [13]. The Japanese multi-product analysis, however, shows that trends and range differences can also appear without clear evidence of lot drift [15]. A surveillance system should therefore distinguish ordinary variability, persistent trend, mechanism-relevant change, and unresolved discordance. These categories are proposed interpretive states, not validated universal regulatory categories, and they should not be tied to fabricated numerical thresholds.

The third requirement is escalation across levels rather than direct translation. Structure–activity work demonstrates that measurable physicochemical differences may fail to alter relevant functional assays [16], while risk-tiered analytical approaches show why criticality should influence how differences are judged [17]. Longitudinal surveillance should consequently operate as a series of falsification gates. A suspected product-state change must survive checks on measurement validity, reproducibility, attribute relevance, and functional consequence before pharmacokinetic, immunogenicity, or clinical reassessment is inferred to be necessary.

This architecture also permits feedback. A credible postmarket clinical signal may justify renewed analytical investigation even when routine product testing has not identified a trend. Conversely, an isolated analytical signal with no functional consequence should not be amplified into a clinical concern merely because it is statistically detectable. The purpose of time-aware surveillance is therefore not to create more opportunities to declare failure; it is to localize uncertainty and identify the smallest evidence package capable of resolving it.

The lifecycle logic is summarized visually as parallel temporal bands rather than a single deteriorating trajectory.

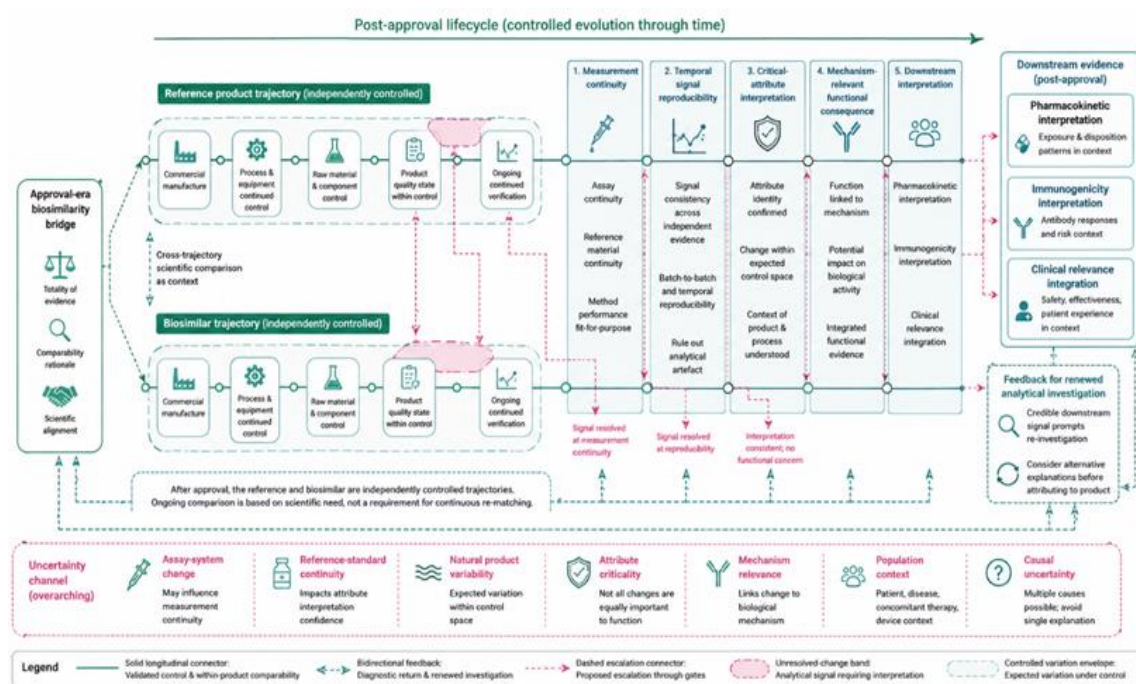


Figure 2. Time-Aware Analytical Surveillance Distinguishes Controlled Evolution from Unresolved Comparability Change

Clinical and immunogenicity reassessment

A lifecycle framework should not default to repeated comparative efficacy studies whenever an analytical change appears. An ustekinumab case analysis found that analytical characterization combined with single-dose pharmacokinetics reproduced the comparative immunogenicity conclusion reached by comparative efficacy studies in the programmes examined [18]. This supports risk-triggered escalation, not universal removal of clinical evidence: the relevant question is whether analytical, functional, pharmacokinetic, and immunogenicity uncertainty has already been resolved for the product and change under consideration.

Patient-level evidence remains important because clinical experience can expose questions that product analytics alone cannot explain. In the prospective YU-MATTER study, satisfaction after transition to CT-P17 was generally maintained or improved, while tolerability differed with prior formulation experience [19]. Large real-world analyses of trastuzumab likewise found no major difference in the examined safety or recurrence outcomes between originator and biosimilar use, although observational confounding and pharmacovigilance limitations remain [20]. Adalimumab experience outside the United States is similarly broadly reassuring while showing that education, policy, device, and patient expectations influence switching experience [21].

Multiple-switch evidence reinforces that distinction. Updated evidence across 31 observational studies and 6081 patients did not identify new safety concerns with biosimilar-to-biosimilar switching [22]. An earlier systematic review of 23 studies and 3657 patients reached a similarly reassuring conclusion but emphasized the observational nature of the evidence [23]. Broader reference-to-biosimilar reviews found no major systematic efficacy, safety, or immunogenicity penalty while identifying open-label discontinuation and contextual effects [24]. A large earlier literature review was also predominantly reassuring [25]. Clinical reassessment should therefore respond to a credible unresolved signal, not to the mere passage of time.

Lifecycle evidence integration

No evidence layer should be allowed to stand in for another. Product history establishes what changed; analytical surveillance establishes whether a difference is credible; functional assays test mechanism relevance; pharmacokinetic and immunogenicity evidence interrogate human biological consequences; clinical and pharmacovigilance evidence address outcomes. Earlier systematic work found broadly similar switching outcomes while still identifying gaps in long-term follow-up and multiple-switch evidence [26]. The lesson is not that residual uncertainty invalidates biosimilarity, but that uncertainty should remain visible and should shrink or expand as evidence accumulates.

The proposed integration rule is therefore asymmetric: reassuring upstream evidence can prevent unnecessary escalation, whereas concordant concerns across independent levels increase the justification for downstream

reassessment. Discordant evidence should trigger discrimination between competing explanations rather than automatic failure. Importantly, evidence generated at one level should modify confidence in another only when a scientifically defensible transfer relationship exists.

A dynamic comparability framework

We propose representing biosimilarity as a durable historical bridge between two defined approval-era product states, followed by two independently controlled lifecycle trajectories. Within each trajectory, validated manufacturing controls and serial comparability remain primary. Cross-product reassessment becomes informative only when a new signal challenges an assumption on which the existing bridge depends.

Escalation should proceed through falsification gates. First establish that the signal is analytically real and not created by assay or reference-system change. Next determine whether the affected attribute is mechanism-relevant and whether function changes concordantly. Only unresolved biologically plausible differences should progress to pharmacokinetic, immunogenicity, or clinical interrogation. Conversely, credible downstream evidence can return the analysis upstream and reopen product-state or assay questions. This framework is proposed synthesis rather than an empirically validated decision rule; it intentionally contains no universal numerical thresholds.

The evidence patterns below require different conclusions, which is why a reconciliation grid is more useful than a single binary judgment.

Table 3. Reconciling Discordant Lifecycle Evidence Without Repeating the Original Biosimilarity Exercise

Observed configuration		Mechanism and competing diagnosis	Corrective discrimination
Dynamic comparability inference scenario / Clinical linkage	Comparability interpretation	Residual uncertainty / Lifecycle trigger	Decision consequence / Lifecycle synthesis consequence
Dynamic comparability inference scenario: Stable analytics and function after a manufacturing change Clinical linkage: Existing bridge remains applicable	Controlled lifecycle evolution	Residual uncertainty: Routine background uncertainty Lifecycle trigger: Documented manufacturing change	Decision consequence: Continue established control Lifecycle synthesis consequence: No re-demonstration of biosimilarity
Dynamic comparability inference scenario: Analytical movement without functional consequence Clinical linkage: None established	Difference does not yet challenge the clinical bridge	Residual uncertainty: Attribute criticality and future trajectory Lifecycle trigger: Persistent reproducible trend	Decision consequence: Targeted surveillance Lifecycle synthesis consequence: Maintain comparability while testing the unresolved attribute
Dynamic comparability inference scenario: Concordant critical-attribute and functional change Clinical linkage: Plausible but unproven	Existing bridge requires focused stress testing	Residual uncertainty: Human biological consequence Lifecycle trigger: Cross-level concordance	Decision consequence: Escalate to PK, immunogenicity, or clinically relevant evidence Lifecycle synthesis consequence: Comparability confidence becomes conditional
Dynamic comparability inference scenario: Clinical or immune signal without product concordance Clinical linkage: Observed downstream signal	Drift cannot be inferred	Residual uncertainty: Product causality Lifecycle trigger: Credible postmarket signal	Decision consequence: Investigate product and competing contextual causes Lifecycle synthesis consequence: Attribution remains open
Dynamic comparability inference scenario: Discordant reference and biosimilar temporal trajectories with both products individually controlled	Historical biosimilarity is not automatically revoked	Residual uncertainty: Meaning of cross-product separation Lifecycle trigger: Mechanistically relevant separation	Decision consequence: Assess whether divergence affects a clinically relevant attribute Lifecycle synthesis consequence: Re-comparison is conditional, not routine

**Clinical linkage: No automatic
clinical consequence**

Regulatory implications

A dynamic framework should simplify evidence use rather than create a new recurring approval exercise. International stakeholder work has already identified substantial support for greater regulatory convergence, reliance on analytical and pharmacokinetic evidence, and reconsideration of development requirements that add limited information [27]. Lifecycle comparability is compatible with that direction when it makes escalation more selective and its rationale more traceable.

The regulatory value would be explicit documentation of why a temporal signal stops at analytical surveillance, advances to functional testing, or justifies human reassessment. Such traceability could also clarify when apparently discordant evidence represents measurement instability, expected product variability, or a genuinely unresolved biological question. The proposal does not require continuous re-matching of commercial biosimilars to current reference lots and should not be interpreted as a new regulatory standard. Its purpose is to connect existing comparability science, pharmacovigilance, and biosimilar totality-of-evidence reasoning across time.

CONCLUSION

Biosimilarity is established at approval, but comparability reasoning cannot be temporally frozen. Reference products and biosimilars can evolve while remaining well controlled, and measurable change is not synonymous with clinically meaningful drift. A lifecycle approach should preserve the original biosimilarity bridge, separate measurement change from product change, and escalate only when credible evidence crosses analytical, functional, pharmacological, immunogenicity, or clinical boundaries. The proposed dynamic comparability framework is therefore a method for managing residual uncertainty, not for repeatedly proving biosimilarity.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Aithal R, Majedi OM, McCarthy D, Atouf F, Peckham N. Review of quality attributes and analytical methods used for comparative analytical assessment of monoclonal antibodies as part of successful biosimilar approvals in the United States and European Union. *BioDrugs*. 2026;40(4):713-32. doi:10.1007/s40259-026-00786-w
2. Park JP, Oh H, Woollett GR. Why product drift is not an issue for biosimilars/biologics: Start the same, stay the same. *BioDrugs*. 2026. doi:10.1007/s40259-026-00796-8
3. Blümel M, Cordoba-Rodriguez R, Carroll JA, Beardsley RL, Maggio F, Wylie D, et al. Patient-centric comparability assessment of biopharmaceuticals. *J Pharm Sci*. 2024;113(6):1415-25. doi:10.1016/j.xphs.2024.02.010
4. Selmaj K, Roth K, Höfler J, Vitzthum K, Derlacz R, von Richter O, et al. Introducing the biosimilar paradigm to neurology: The totality of evidence for the first biosimilar natalizumab. *BioDrugs*. 2024;38(6):755-67. doi:10.1007/s40259-024-00671-4
5. Liu Y, Xie J, Li Z, Mei X, Cao D, Li S, et al. Demonstration of physicochemical and functional similarity of the biosimilar BAT1806/BIIB800 to reference tocilizumab. *BioDrugs*. 2024;38(4):571-88. doi:10.1007/s40259-024-00662-5
6. Saleem R, Cantin G, Wikström M, Bolton G, Kuhns S, McBride HJ, et al. Analytical and functional similarity assessment of ABP 710, a biosimilar to infliximab reference product. *Pharm Res*. 2020;37(6):114. doi:10.1007/s11095-020-02816-w

7. Li Z, Du X, Wang YMC. A survey of FDA approved monoclonal antibodies and Fc-fusion proteins for manufacturing changes and comparability assessment. *Pharm Res.* 2024;41(1):13-27. doi:10.1007/s11095-023-03627-5
8. Lee JJ, Lee N, Seo YJ, Kim I. Consistency of product quality for SB5, an adalimumab biosimilar. *BioDrugs.* 2023;37(2):271-7. doi:10.1007/s40259-023-00581-x
9. Kang HN, Wadhwa M, Knezevic I, Burns C, Griffiths E. The importance of World Health Organization international reference standards in the product life cycle of biosimilars. *Ann N Y Acad Sci.* 2024;1540(1):225-34. doi:10.1111/nyas.15217
10. Webster CJ, George KL, Woollett GR. Comparability of biologics: Global principles, evidentiary consistency and unrealized reliance. *BioDrugs.* 2021;35(4):379-87. doi:10.1007/s40259-021-00488-5
11. Solti K, Timári S, Faludi T, Iliás A, Hegedüs R, Pataj Z, et al. Comprehensive physico-chemical and functional similarity assessment of intravenous and subcutaneous RGB-19 drug products as proposed biosimilars to tocilizumab reference product. *BioDrugs.* 2025;39(5):675-96. doi:10.1007/s40259-025-00734-0
12. Garai ÁS, Hüse D, Fizil Á, Zólyomi Z, Lehoczki G, Kis A, et al. Comprehensive physico-chemical and functional similarity assessment study of RGB-14-P and RGB-14-X drug products as proposed biosimilars to denosumab reference products. *BioDrugs.* 2025;39(5):697-724. doi:10.1007/s40259-025-00738-w
13. Kim S, Song J, Park S, Ham S, Paek K, Kang M, et al. Drifts in ADCC-related quality attributes of Herceptin: Impact on development of a trastuzumab biosimilar. *MAbs.* 2017;9(4):704-14. doi:10.1080/19420862.2017.1305530
14. Lee JH, Paek K, Moon JH, Ham S, Song J, Kim S. Biological characterization of SB3, a trastuzumab biosimilar, and the influence of changes in reference product characteristics on the similarity assessment. *BioDrugs.* 2019;33(4):411-22. doi:10.1007/s40259-019-00362-5
15. Shibata H, Harazono A, Kiyoshi M, Saito Y, Ishii-Watabe A. Characterization of biosimilar monoclonal antibodies and their reference products approved in Japan to reveal the quality characteristics in post-approval phase. *BioDrugs.* 2025;39(4):645-67. doi:10.1007/s40259-025-00722-4
16. Liu Y, Xie J, Li Z, Mei X, Cao D, Li S, et al. Comparative structure activity relationship characterization of the biosimilar BAT1806/BIIB800 to reference tocilizumab. *BioDrugs.* 2025;39(2):307-20. doi:10.1007/s40259-024-00698-7
17. Lee J, Kang HA, Bae JS, Kim KD, Lee KH, Lim KJ, et al. Evaluation of analytical similarity between trastuzumab biosimilar CT-P6 and reference product using statistical analyses. *MAbs.* 2018;10(4):547-71. doi:10.1080/19420862.2018.1440170
18. Schiestl M, Roy N, Trieb M, Park JP, Guillen E, Woollett G, et al. Analytical data and single-dose PK are sufficient to conclude comparable immunogenicity for biosimilars: An ustekinumab case study. *BioDrugs.* 2025;39(5):769-76. doi:10.1007/s40259-025-00733-1
19. Bouguen G, Gossec L, Abitbol V, Senbel E, Bonnaud G, Roblin X, et al. Patient satisfaction and experience with CT-P17 following transition from reference adalimumab or another adalimumab biosimilar: Results from the real-world YU-MATTER study. *BioDrugs.* 2024;38(6):867-78. doi:10.1007/s40259-024-00681-2
20. Mamori T, Tanioka M, Takada K, Hamano H, Tsukioki T, Takahashi Y, et al. Real-world comparative analysis of trastuzumab originator and biosimilars: Safety, efficacy, and cost effectiveness. *BioDrugs.* 2025;39(1):131-42. doi:10.1007/s40259-024-00686-x
21. Tesser JRP, Charabaty A, Hebert AA. Switching from adalimumab reference product to and among adalimumab biosimilars outside the USA: Insights for US clinicians. *BioDrugs.* 2025;39(4):591-606. doi:10.1007/s40259-025-00719-z
22. Cohen HP, Bodenmueller W. Additional data in expanded patient populations and new indications support the practice of biosimilar-to-biosimilar switching. *BioDrugs.* 2024;38(3):331-9. doi:10.1007/s40259-024-00655-4
23. Cohen HP, Hachaichi S, Bodenmueller W, Kvien TK, Danese S, Blauvelt A. Switching from one biosimilar to another biosimilar of the same reference biologic: A systematic review of studies. *BioDrugs.* 2022;36(5):625-37. doi:10.1007/s40259-022-00546-6
24. Barbier L, Ebberts HC, Declerck P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: A systematic review. *Clin Pharmacol Ther.* 2020;108(4):734-55. doi:10.1002/cpt.1836

25. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: A systematic literature review of clinical outcomes. *Drugs*. 2018;78(4):463-78. doi:10.1007/s40265-018-0881-y
26. McKinnon RA, Cook M, Liauw W, Marabani M, Marschner IC, Packer NH, et al. Biosimilarity and interchangeability: Principles and evidence: A systematic review. *BioDrugs*. 2018;32(1):27-52. doi:10.1007/s40259-017-0256-z
27. Car E, Barbier L, Schwarzenberger I, Huys I, Simoens S, Vulto AG. Toward regulatory convergence and streamlined biosimilar development: Recommendations from an international qualitative study. *BioDrugs*. 2025;39(6):943-55. doi:10.1007/s40259-025-00746-w