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Manufacturing Drift Can Alter the Meaning of Comparability Without Creating a New Biologic

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ABSTRACT

Biological products are manufactured through evolving process histories rather than reproduced as chemically invariant objects. Improvements in cell culture, purification, analytical capability, formulation, scale, site, equipment, and control strategy can alter measured quality attributes even when the therapeutic entity remains clinically continuous. The central problem is therefore not whether a post-change product is analytically identical to its predecessor, but whether observed change alters the evidentiary meaning of comparability. This Current Opinion argues that manufacturing drift should be interpreted through linked but non-equivalent evidence layers: process state, product attribute, structure–function relationship, exposure or immunogenicity relevance, and clinical consequence. Analytical drift can be real without being functionally important; conversely, apparently modest changes can matter when they affect a critical structural feature or mechanism. Comparability should therefore be treated as a lifecycle judgement that can be strengthened, reopened, or escalated as new evidence appears. The article further separates manufacturing-change comparability from biosimilarity and interchangeability, which may use overlapping analytical tools but answer different provenance and regulatory questions. A proposed lifecycle framework is developed around residual uncertainty rather than a universal numerical threshold.

Keywords: Biopharmaceutical comparability, Manufacturing drift, Critical quality attributes, Structure–function relationships, Analytical similarity, Biosimilarity

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INTRODUCTION

Comparability is often discussed as though it were a static demonstration that a product before and after manufacturing change is “the same.” In practice, the evidentiary problem is more conditional. Change can occur at different lifecycle stages, involve different process parameters or control systems, and affect attributes with very different relationships to potency, pharmacokinetics, immunogenicity, or stability. Contemporary comparability practice is therefore risk based: the extent of analytical, nonclinical, or clinical evidence should be proportionate to the nature of the change, the criticality of the potentially affected attributes, and the residual uncertainty relevant to patients [1, 2]. This makes comparability less a binary property of a molecule than a judgement about whether the available evidence is sufficient for a defined post-change state.

That distinction matters because biopharmaceutical heterogeneity is expected. Glycoforms, charge variants, higher-order structural states, aggregates, fragments, and other product-related species can vary within controlled ranges. The presence of analytical variation does not by itself establish clinically meaningful drift, because modern manufacturing control and comparability systems are designed precisely to distinguish manageable variability from changes with potential consequences for safety or efficacy [3]. The opposite error is equally important: analytical change should not be dismissed merely because the product name, primary sequence, or mechanism-of-action label has not changed.

Manufacturing-change comparability also should not be collapsed into biosimilarity. Both can rely on extensive analytical characterization, functional assays, pharmacology, pharmacokinetics, and immunogenicity evidence, but they begin from different product histories and regulatory questions. Comparability asks whether a product remains acceptably continuous across a defined manufacturing change; biosimilarity asks whether an independently developed product is highly similar to a reference product and whether remaining differences are clinically meaningful. The scientific logic overlaps, but the provenance and evidentiary context differ [4]. This article develops that distinction around a narrower proposition: manufacturing drift can change the meaning and evidentiary burden of comparability without implying that a new biologic has necessarily been created.

Manufacturing change and product evolution

Biological manufacturing is not technologically static. Monoclonal antibody production has moved through successive eras of cell-line development, upstream intensification, purification technology, platform standardization, analytical capability, and manufacturing scale [5]. A commercial product can therefore accumulate a history of planned process modifications while remaining under one lifecycle identity. Site transfers, equipment changes, raw-material changes, scale changes, control-strategy updates, purification refinements, and formulation or presentation changes may each alter the process state from which the product emerges.

The relevant consequence is not that every process change produces a materially different molecule, but that a process change creates a new evidentiary comparison. Because recombinant proteins are produced by living systems and can acquire post-translational and higher-order structural heterogeneity, comparability depends on systematic evaluation of the attributes most plausibly affected by the change and on knowledge of their relevance to product performance [6]. “Same product” is therefore not equivalent to perfect molecular identity. It is an evidence-supported conclusion that the post-change state remains sufficiently consistent with the pre-change state for the intended clinical use.

Routine release testing may not expose every difference relevant to lifecycle interpretation. Forced-degradation studies are commonly used to compare degradation pathways and stress responses, particularly when investigators need to determine whether two product states behave similarly outside the narrow release condition [7]. Such studies can be informative when a manufacturing change appears analytically small but could alter conformational or degradation susceptibility. Their interpretation remains conditional: accelerated stress is not a direct surrogate for patient outcome, and stress designs themselves do not justify a universal rule.

Increased analytical sensitivity can also make a product appear to “drift” because the manufacturing system has become more observable. In-line Raman spectroscopy combined with computational modelling has, for example, been used to follow aggregation and fragmentation during a biopharmaceutical process in near real time [8]. A newly visible process-state fluctuation may therefore reflect improved measurement rather than a newly emergent biological problem. Lifecycle comparability must distinguish true product change from improved detection of variation that was previously unmeasured.

Sources of process drift

Process drift can enter the product through multiple molecular routes, and the consequence of each route depends on product architecture. Glycosylation is a prominent example. Glycan composition can influence stability, receptor interaction, clearance, effector function, immunological behaviour, and other properties across therapeutic proteins, although the direction and magnitude of the effect are highly context dependent [9]. A shift in glycan distribution is consequently neither trivial by definition nor clinically important by definition; it requires product-specific interpretation.

Higher-order structure provides a second route by which process environment and product state can interact. Comparative circular-dichroism analysis across therapeutic antibodies has shown molecule-specific structural signatures and sensitivity to environmental conditions such as pH [10]. Such measurements can detect structural

change, but they do not by themselves determine whether the change affects potency or clinical performance. Their evidentiary role is to identify a possible change in state that may require functional adjudication. Charge heterogeneity illustrates the same principle from another direction. Stress-dependent studies of monoclonal antibody charge variants have shown that variant fractions can differ in degradation and aggregation behaviour, and that the relevant pattern depends on the molecule and stress condition [11]. A broad label such as “charge drift” therefore compresses biologically different phenomena. Manufacturing drift should instead be decomposed into the specific modification, location, stability consequence, and plausible functional pathway before its meaning for comparability is assigned.

Analytical drift versus functional drift

The most important interpretive boundary is between detecting an analytical difference and demonstrating a functional consequence. Extensive orthogonal characterization of the proposed ecilizumab biosimilar SB12 showed how multiple structural and functional methods can converge on a high-similarity conclusion when the evidence is mutually consistent [12]. This is the simplest comparability state: analytical and functional evidence point in the same direction, leaving relatively little unresolved uncertainty.

More difficult cases occur when a measurable physicochemical difference persists. Structure–activity analysis of BAT1806/BIIB800 and reference tocilizumab identified differences in attributes including glycation, yet the investigated differences did not produce relevant effects in the tested biological functions [13]. The inferential lesson is narrow but important. Detection of a difference establishes analytical nonidentity; it does not establish functional drift. The correct next question is whether the difference changes a function relevant to the product’s mechanism, disposition, stability, or immunological behaviour.

The converse is equally important. Charge-variant analysis of IgG2 therapeutics demonstrated that modifications within one broad analytical category can have markedly different consequences depending on their molecular origin and location. In one setting, a charge variant had little functional impact, whereas another modification could alter a functionally important interaction [14]. Thus, neither the size of a chromatographic shift nor membership in a named CQA class is sufficient to determine meaning. Structure–activity context matters.

Recent biosimilar characterization studies reinforce the asymmetry between analytical and functional drift. Minor physicochemical differences in RGB-19 products were not accompanied by changes in the functional properties examined [15]. In the RGB-14 denosumab program, quality-parameter shifts were observed across reference-product material of different expiry status without a corresponding change in measured biological activity [16]. Together with the BAT1806 evidence, these studies support only a bounded conclusion: in those products and assays, some measured analytical differences were not associated with impairment of the tested functions [13, 15, 16]. They do not justify a general rule that analytical drift is harmless.

For lifecycle interpretation, three states should therefore remain distinct. First, an analytical-only state exists when a reproducible difference is detected but relevant functional testing remains concordant. Second, a functionally relevant state exists when the changed attribute is linked to altered potency, binding, stability, exposure-related behaviour, or another product-relevant function. Third, an unresolved state exists when analytical discordance is established but the structure–function evidence is inadequate, contradictory, or insufficiently sensitive. The third state is especially important because it is where comparability should be reopened rather than prematurely declared lost or preserved.

Critical quality attribute relationships

A critical quality attribute is meaningful only through the consequence it is intended to control. Comparative characterization of trastuzumab products illustrates why this matters: products can look broadly similar while still showing differences across structural, stability, and functional measurements, and those differences cannot be ranked correctly without considering their relationship to biological activity [17]. A CQA therefore should not be interpreted as a fixed checklist item whose mere movement across an analytical range automatically determines comparability.

Orthogonal analytical strategies reduce this problem by interrogating the product through partially independent evidence layers. Contemporary analytical-similarity practice combines primary structure, higher-order structure, glycosylation, charge, size heterogeneity, impurity profiles, binding, potency, and other assays because no single platform resolves every uncertainty [18]. The value of orthogonality is not the number of assays itself; it is the ability of different measurements to test different explanations for the same observed change.

The same caution applies to computational summaries. Automated glycosimilarity methods can integrate complex glycan profiles efficiently, but their decision value depends on the adequacy of the reference distribution. A recent glycosimilarity tool demonstrated useful computational integration while also showing that limited innovator-batch data constrained the definition of definitive tolerance limits [19]. A composite index can therefore summarize evidence without becoming a universal regulatory threshold.

This article proposes a claim-to-test interpretation for manufacturing drift. A changed attribute should first be classified by what product property it represents, then linked to the minimum observation needed to show that the change is real, the strongest plausible alternative explanation, and the most discriminating functional or stability test. Only after those steps should the result be translated into a comparability consequence. The framework is deliberately nonnumeric because the literature does not support one universal magnitude of change that separates acceptable drift from loss of comparability.

The adjudication problem is compressed in **Table 1**, which separates what has been observed from what must still be demonstrated before a manufacturing-drift signal can legitimately change the comparability conclusion.

Table 1. Adjudicating CQA Drift Before It Changes a Comparability Conclusion

CQA classification basis	Minimum observation establishing a real shift	Strongest plausible alternative explanation... Permitted comparability interpretation	Article-level discriminating test Lifecycle trigger Residual evidence gap
Manuscript-derived drift scenario Glycan-distribution movement			
Product- and site-specific relationship to stability, clearance, receptor interaction, or effector function	Reproducible orthogonal glycan-profile difference across suitable lots	Strongest plausible alternative explanation Sampling variability, analytical-method change, or reference-lot distribution Permitted comparability interpretation Analytical drift only if relevant functions remain concordant; functionally relevant drift if a supported pathway changes	Article-level discriminating test Determine whether the affected glycoform changes a product-relevant function or stability pathway Lifecycle trigger for reassessment Persistent shift, expansion beyond historical product state, or new functionally sensitive evidence Residual evidence gap Clinical meaning where analytical and functional evidence do not fully close uncertainty
Manuscript-derived drift scenario Higher-order structural difference			
Conformational state linked to stability or activity	Reproducible structural signal under qualified conditions	Strongest plausible alternative explanation Method sensitivity, solution-condition effect, or reversible stress response Permitted comparability interpretation Structural discordance alone is insufficient for clinical inference	Article-level discriminating test Orthogonal structural confirmation plus product-relevant functional or stability challenge Lifecycle trigger for reassessment Reappearance across lots, stress amplification, or association with degradation Residual evidence gap Whether the observed conformation occurs under relevant manufacturing, storage, or use conditions
Manuscript-derived drift scenario Charge-variant redistribution			

Molecular origin and location of the modification rather than charge category alone	Reproducible change in variant fractions with chemical identity characterized	Strongest plausible alternative explanation	Article-level discriminating test
		Benign processing heterogeneity or functionally silent modification	Variant-specific binding, potency, stability, or mechanistic assay selected for the affected domain
		Permitted comparability interpretation	Lifecycle trigger for reassessment
		Consequence depends on the modification's structure–activity relationship	New variant, sustained enrichment, altered degradation propensity, or mechanistic signal
			Residual evidence gap
			Transfer from in-vitro functional effect to patient relevance
Manuscript-derived drift scenario			
Degradation or aggregation divergence			
Relationship to stability, immunogenicity risk, potency, or delivery	Difference confirmed under release, stability, or justified challenge conditions	Strongest plausible alternative explanation	Article-level discriminating test
		Artificial stress pathway with limited relevance to actual storage or use	Compare degradation mechanism and product-relevant consequences under realistic and challenge conditions
		Permitted comparability interpretation	Lifecycle trigger for reassessment
		Concern increases when divergence is mechanistically coherent and relevant to product exposure	Change in shelf-life behaviour, process excursions, or a new instability pattern
			Residual evidence gap
			Magnitude of patient-facing risk at clinical exposure
Manuscript-derived drift scenario			
Multivariate profile shift without one dominant CQA			
Convergence across several weak but potentially related signals	Consistent multidomain difference beyond expected analytical variation	Strongest plausible alternative explanation	Article-level discriminating test
		Correlated assay noise, undersampled reference range, or method transition	Determine whether independent evidence layers converge on one mechanistic or functional interpretation
		Permitted comparability interpretation	Lifecycle trigger for reassessment
		Proposed: retain an unresolved state until convergence or discordance is explained	Accumulating weak signals across successive lots or methods
			Residual evidence gap
			Whether combined weak signals represent one biological change or unrelated analytical variation

The same logic is easier to recover visually when the evidence layers and their boundaries are shown simultaneously. **Figure 1** therefore places the CQA relationship field at the centre of a nested interpretation architecture rather than presenting manufacturing drift as a linear sequence from process change to clinical effect.

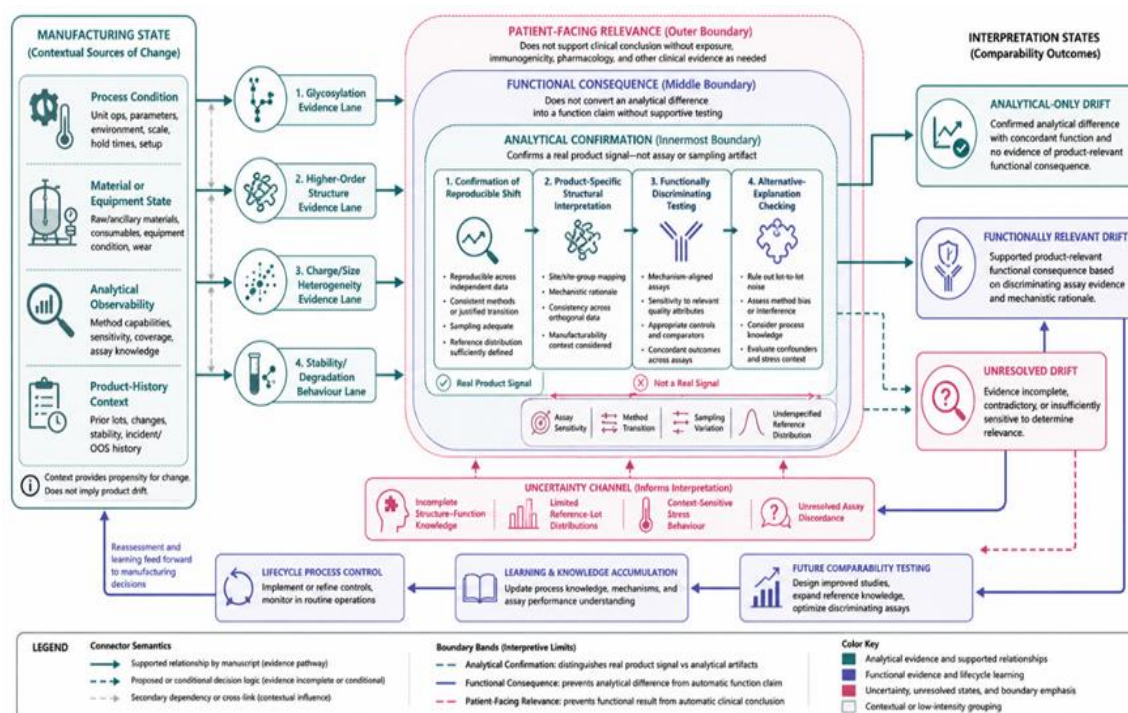


Figure 1. Where a Detected Quality Shift Changes—and Does Not Change—the Meaning of Comparability

Clinical relevance of observed change

Clinical relevance is not an automatic downstream property of analytical difference. A risk-based clinical-pharmacology approach to monoclonal-antibody manufacturing changes has argued that the need for PK, PD, or immunogenicity evidence should depend on the potential impact of the affected CQA and on when the change occurs in development [20]. This logic prevents two opposite errors: demanding a clinical efficacy study for every detectable manufacturing difference, or assuming that analytics alone always eliminate uncertainty.

Exposure can also be altered by changes that do not originate primarily in the molecular structure of the biologic. For subcutaneous biologic-device combination products, a structured assessment of CMC and pharmacokinetic risk has been proposed to determine whether a product or device change warrants a dedicated PK comparability study [21]. The broader implication is that functional drift should not be confined to receptor-binding or potency assays. Delivery, absorption, and exposure can become the relevant bridge between manufacturing state and patient consequence.

Immunogenicity creates another difficult boundary. A recent ustekinumab case analysis found that analytical information combined with single-dose PK evidence was capable of identifying comparative immunogenicity patterns that were also observed in comparative efficacy studies [22]. That result supports targeted streamlining in a defined product class, not a universal elimination of clinical immunogenicity evidence. The adequacy of an earlier evidence layer depends on whether it is sufficiently sensitive to the specific uncertainty that remains.

Clinical escalation should therefore be question specific. If the changed attribute has a well-understood function and orthogonal testing remains concordant, additional clinical evidence may contribute little. If the change plausibly affects exposure, immunogenicity, target engagement, or an incompletely characterized mechanism, clinical evidence can become decisive. Comparability is preserved not because a clinical study was or was not performed, but because the remaining uncertainty has been addressed with evidence suited to the risk.

Comparability versus biosimilarity

Biosimilarity and manufacturing-change comparability share an important scientific principle: neither requires absolute molecular identity. Biosimilar development instead proceeds through a stepwise totality-of-evidence strategy in which extensive analytical and functional similarity provides the foundation and later studies address residual uncertainty [23]. That logic is useful for thinking about manufacturing drift because it emphasizes evidence convergence rather than a single decisive assay.

The two questions nevertheless remain different. In a manufacturing-change exercise, the pre-change and post-change materials belong to one product history and are compared because the manufacturing state has changed.

In biosimilarity, an independently developed candidate is compared with a reference product whose manufacturing history is not shared. The same analytical technology may be used, but the prior knowledge, provenance, and regulatory framing are different.

Switching and interchangeability add still another layer. A systematic review of biosimilar switching literature showed why outcomes after transition between products form a distinct clinical evidence question, with heterogeneity and evidence gaps that cannot be resolved merely by repeating structural characterization [24]. In the United States, interchangeability further asks whether the biosimilar can be expected to produce the same clinical result and whether repeated switching creates additional risk relative to remaining on the reference product [25]. Those questions are not equivalent to determining whether a manufacturer has maintained comparability after a process change.

Product-specific biosimilar programs illustrate both the power and limits of analogy. The GP2017 adalimumab program integrated analytical, functional, pharmacokinetic, and clinical evidence into a totality-of-evidence argument [26]. A separate natalizumab program similarly combined structural and functional characterization with PK, PD, and clinical evidence to support biosimilarity in a different therapeutic setting [27]. These programs show that evidence layers can converge while retaining different inferential roles; they do not establish that every biologic or every manufacturing change requires the same package.

For the present argument, biosimilarity is therefore best treated as a neighbouring evidentiary model rather than a synonym for comparability. Manufacturing drift can require more, less, or different evidence depending on what changed and what remains uncertain. The next section develops that proposition as a proposed lifecycle comparability framework in which evidence requirements are tied to decision state rather than to the mere detection of difference.

A lifecycle comparability framework

A lifecycle view treats comparability as a sequence of evidence states rather than a one-time declaration. Experience from biosimilar development has increasingly supported tailoring evidence requirements to molecular complexity and residual uncertainty instead of applying the same clinical package to every product [28]. For manufacturing change, the principle can be adapted more narrowly: the question at each point is what uncertainty the observed change creates and which evidence layer can resolve it.

The proposed framework therefore begins with the historical product state and the process change that altered it. If analytical evidence remains concordant across relevant CQAs, the product can remain in a controlled-continuity state, subject to routine lifecycle surveillance. If a reproducible analytical difference appears but relevant functional evidence remains concordant, the state becomes analytical discordance with resolved function. That conclusion is conditional rather than permanent: new lots, stability behaviour, process excursions, or more sensitive assays can reopen the question. Risk-based comparability principles support this reassessment logic [1]. A different state arises when the structure–function relationship remains unclear. Here, comparability is not necessarily lost, but neither should it be assumed. Additional mechanistic, stability, exposure, or immunogenicity evidence should be selected according to the uncertainty that remains. Global comparability principles favour such risk-weighted evidence over automatic escalation [4]. When a functional consequence is demonstrated, the question shifts from whether drift exists to whether its magnitude, persistence, and patient-facing relevance remain compatible with the product's established clinical profile.

This state-based view also prevents chronology from being mistaken for causality. A later manufacturing state may differ from an earlier one because of process evolution, analytical-method replacement, reference-lot aging, or a combination of these factors. Reassessment should therefore ask whether the same signal persists when methods are bridged and whether it co-varies with a mechanistically plausible product property. Evidence from forced-degradation comparability work supports using challenge conditions as one supplementary way to interrogate latent divergence, while keeping stress behaviour separate from direct clinical prediction [7]. Likewise, temporal shifts observed in reference-product quality parameters without loss of measured biological activity show why “later” cannot simply be translated into “worse” [16]. In the proposed framework, time is a context for interpreting drift, not an independent proof of consequence.

Table 2 translates these lifecycle states into a decision ledger so that a manufacturing difference is linked to what is known, what remains unresolved, the action that remains permissible, and the observation that should reopen assessment.

Table 2. Decision States for Reopening or Sustaining Lifecycle Comparability

Controlled continuity Analytical discordance with resolved function Unresolved structure–function discordance			
Decision state	Controlled continuity	Analytical discordance with resolved function	Unresolved structure–function discordance
Governing condition	No reproducible CQA discordance after appropriate comparison	Reproducible attribute shift with concordant relevant function	Real analytical change with incomplete or conflicting functional interpretation
Information already sufficient	Process-change context and orthogonal analytical evidence	Identity of change, analytical confirmation, and function-sensitive testing	Existence of the shift and plausible affected pathway
Residual uncertainty	Undetected or future drift	Longer-term stability or untested context	Consequence for activity, exposure, immunogenicity, or stability
Permissible lifecycle action	Maintain comparability with routine control and surveillance	Maintain comparability while tracking the changed attribute	Keep assessment open and add targeted evidence
Observation triggering reassessment	New recurring signal, process excursion, or stability divergence	Expansion of shift, new degradation behaviour, or functional divergence	Convergent evidence toward benign or consequential interpretation
Manufacturing-drift consequence	Drift not established	Analytical drift does not yet alter functional meaning	Comparability meaning remains unsettled
Functionally relevant drift Clinically consequential state			
Decision state	Functionally relevant drift	Clinically consequential state	
Governing condition	Attribute shift linked to a product-relevant functional change	Functional change supported by evidence of meaningful patient-facing consequence	
Information already sufficient	Reproducible structure–function association	Analytical, functional, and clinically relevant evidence converge	
Residual uncertainty	Patient-facing magnitude and clinical relevance	Residual population or use-context uncertainty	
Permissible lifecycle action	Escalate evidence and reconsider controls or change strategy	Reassess acceptability of the post-change state	
Observation triggering reassessment	Exposure, immunogenicity, pharmacology, or clinical concern	Further confirmation, mitigation, or regulatory decision	
Manufacturing-drift consequence	Comparability requires stronger justification	Continuity cannot be assumed solely from product identity	

Decision thresholds and residual uncertainty

The proposed framework deliberately avoids a universal numerical threshold. Comparability thresholds are meaningful only relative to a defined CQA, its historical distribution, assay performance, mechanism, and potential consequence. A small change at a functionally sensitive site may matter more than a larger movement in a weakly consequential attribute. Structure–activity evidence for charge variants makes that asymmetry clear [14].

Residual uncertainty should therefore be treated as the quantity that drives escalation. Orthogonal evidence can reduce uncertainty, but a composite metric should not be allowed to hide weak reference distributions or unresolved mechanisms. The limitations reported for automated glycosimilarity assessment illustrate why a useful summary measure cannot automatically become a regulatory boundary [19]. Where uncertainty shifts toward exposure, pharmacodynamics, or immunogenicity, targeted clinical-pharmacology evidence becomes more informative than further repetition of structurally similar assays [20]. The threshold is thus evidentiary sufficiency for the specific risk, not a universal amount of molecular difference.

Regulatory implications

Regulatory comparability already places analytical assessment at the foundation of manufacturing-change evaluation, while the amount of additional evidence varies with the change and product context [2]. The proposed lifecycle framework does not replace that practice. Its purpose is to make explicit why a detected difference can have different regulatory meanings depending on whether it is analytically confirmed, functionally resolved, clinically relevant, or still uncertain.

The same discipline is needed when borrowing concepts from biosimilarity. Interchangeability, particularly in the United States, adds switching-specific questions that should not be imported into ordinary manufacturing comparability [25]. Conversely, experience from biosimilar development can support more efficient evidence generation when residual uncertainty has genuinely been addressed. Product-specific analyses of immunogenicity and clinical-pharmacology evidence suggest that later studies may sometimes add little when earlier evidence is sufficiently sensitive [22]. Streamlining should therefore mean removing redundant evidence, not lowering the standard for resolving relevant uncertainty.

CONCLUSION

Manufacturing drift should not be interpreted as a synonym for loss of product identity. A biologic can move analytically across its lifecycle while remaining functionally and clinically continuous, but that conclusion must be demonstrated rather than presumed. The decisive question is what an observed difference means in relation to product function, exposure, immunogenicity, stability, and patient risk. The proposed lifecycle framework organizes those questions as evidence states that can remain stable, be reopened, or require escalation. Its value is not a new numerical cutoff, but a clearer separation of detection, functional consequence, clinical relevance, and regulatory judgement. Comparability is therefore best understood as a continuing evidence-supported claim about product continuity, not as proof of molecular immobility.

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