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A Living Comparability Protocol for Biopharmaceutical Manufacturing Processes That Continuously Evolve without Losing Product Understanding across Product Lifecycles

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ABSTRACT

Biopharmaceutical manufacturing processes evolve through scale changes, equipment replacement, raw-material variation, site transfers, analytical modernization, process intensification, and post-approval optimization. Conventional comparability plans are commonly structured around a defined change and a prespecified evidence package, but repeated and interacting changes can fragment product knowledge across development and commercial lifecycles. This article proposes a living comparability protocol as an original adaptive-comparability framework for maintaining traceable product understanding while manufacturing processes continue to evolve. The protocol connects a version-controlled knowledge baseline, change classification, impact hypotheses, dynamic critical-quality-attribute weighting, tiered analytical and functional evidence, continuous process and product monitoring, requalification rules, and governance controls. Continuous monitoring is treated as a learning mechanism rather than as passive data collection: observations are interpreted against prior variability, mechanistic expectations, assay capability, and unresolved uncertainty. Protocol versioning records how assumptions, attribute priorities, analytical methods, acceptance rationales, and evidence requirements change over time. Requalification is triggered when accumulated evidence invalidates a prior assumption, alters an attribute's relevance, reveals analytical blind spots, or weakens confidence in the existing control strategy. Governance and regulatory communication are organized around transparent change histories, explicit uncertainty statements, predefined escalation logic, and documented human accountability. The original contribution is therefore not a new analytical test or regulatory pathway, but a proposed architecture for preserving comparability reasoning across sequential manufacturing changes. The framework requires prospective testing using real product histories, orthogonal analytical evidence, functional studies, monitoring performance, and decision-concordance assessments. It does not establish clinical equivalence, interchangeability, regulatory acceptability, or universal applicability.

Key words: *Biopharmaceuticals, Biosimilars, Comparability, Analytical similarity, Immunogenicity, Interchangeability*

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INTRODUCTION

Biopharmaceutical products are defined not only by their amino-acid sequence but also by higher-order structure, post-translational modifications, impurity profiles, biological activity, formulation, and process-dependent

variability. Demonstrating similarity or comparability therefore requires multiple analytical and biological tools rather than reliance on a single test or product characteristic [1].

Comparability is generally used to determine whether a manufacturing change has adversely affected product quality, safety, or efficacy, whereas analytical similarity is commonly applied within biosimilar development to compare a proposed product with its reference product. Although both depend on structured evidence and product understanding, their evidentiary questions, development contexts, and decision consequences are not identical [2].

Comparability must also remain distinct from interchangeability. Analytical and functional similarity may support a totality-of-evidence assessment, but interchangeability additionally concerns the consequences of substitution or switching within a defined legal and clinical context. It cannot be inferred automatically from manufacturing comparability or analytical similarity alone [3].

This Original Adaptive-Comparability Framework Article proposes a living comparability protocol for manufacturing processes that undergo sequential, overlapping, or cumulative change. The framework is an original conceptual synthesis rather than an empirical study, regulatory guideline, or validated decision system. Its purpose is to preserve traceable product and process understanding by linking baseline knowledge, change hypotheses, attribute prioritization, evidence escalation, monitoring, version control, and governance across the lifecycle.

Why fixed comparability plans are insufficient for evolving processes

A fixed comparability plan normally begins with a defined change, evaluates anticipated effects, and closes once an agreed evidence package supports a conclusion. This event-based structure becomes less reliable when the reference state itself evolves. Documented shifts in antibody-dependent cellular cytotoxicity-related attributes of trastuzumab reference material illustrate how product characteristics may drift over time even when the product remains clinically established [4].

Manufacturing changes may influence several quality dimensions simultaneously, including charge variants, glycosylation, aggregation, potency, binding, and process-related impurities. Comparative studies of monoclonal antibodies therefore rely on orthogonal analytical methods and integrated interpretation rather than one-dimensional pass-or-fail testing [5]. A static plan may capture the immediate change while failing to preserve how successive changes reshape the evidentiary context.

Quality-attribute criticality is also conditional rather than permanent. Attribute ranking depends on biological relevance, structure–function knowledge, assay capability, observed variability, and uncertainty about clinical consequence. Rational tiering can organize analytical similarity assessments, but its validity depends on the assumptions and evidence used to assign attributes to particular levels of concern [6].

The central limitation is therefore not that fixed plans lack scientific value, but that they are weak at retaining temporal relationships among changes, assumptions, evidence, and decisions. A plan may remain internally coherent while becoming externally outdated as methods improve, process capability changes, new failure modes emerge, or accumulated modifications alter the relevance of the original baseline. The proposed protocol treats comparability as a continuously maintained knowledge state rather than a succession of isolated reports.

Proposed living comparability protocol

A living comparability protocol is proposed as a version-controlled architecture that connects product knowledge, process knowledge, change histories, impact hypotheses, attribute priorities, analytical evidence, monitoring observations, and governance decisions. Knowledge management is essential to biopharmaceutical development and lifecycle management because scientific conclusions depend on preserving relationships among data, assumptions, process understanding, and control strategies [7].

The protocol begins with an approved knowledge baseline but does not treat that baseline as immutable. Each manufacturing change generates a structured impact hypothesis describing what could change, through which mechanism, which quality attributes may be affected, what evidence could detect the effect, and what uncertainty would remain after testing. The hypothesis is updated when new analytical or manufacturing observations conflict with prior expectations.

A second layer links comparability testing with timely process and product information. Real-time release testing and advanced process analytics demonstrate the potential to use manufacturing information more directly in quality decisions, although implementation depends on validated methods, process understanding, data integrity, and appropriate control strategies [8]. Within the proposed protocol, rapid data availability informs escalation but does not replace orthogonal confirmation or human review.

Monitoring technologies can generate information on process parameters and quality attributes during development and manufacturing, but sensor performance, sampling design, model transferability, and interpretive context remain important limitations [9]. The protocol therefore separates data acquisition from evidentiary sufficiency: an observation becomes decision-relevant only after its provenance, analytical validity, mechanistic meaning, and relationship to product quality have been assessed.

Figure 1 presents the original conceptual synthesis for living comparability protocol across a biopharmaceutical lifecycle, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

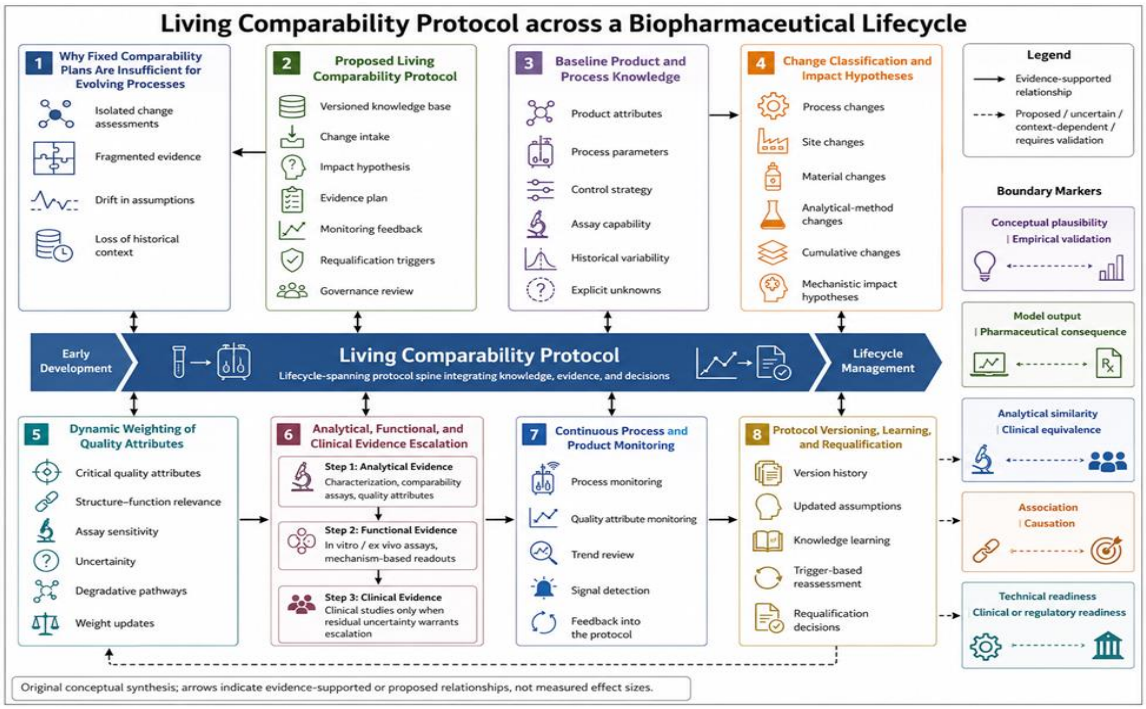

Figure 1. Living Comparability Protocol across a Biopharmaceutical Lifecycle

Baseline product and process knowledge

The baseline is the protocol's current, version-specific representation of what is known about the product, process, analytical methods, and control strategy. Integrated and continuous biomanufacturing frameworks emphasize that upstream operations, downstream purification, process controls, and product-quality measurements must be understood as connected elements rather than independent manufacturing stages [10].

The product component should describe identity, primary and higher-order structure, glycosylation, charge heterogeneity, aggregation, impurities, potency, binding, and other attributes relevant to the molecule's mechanism and clinical performance. Comparative-assessment experience shows that approved biosimilar programs use broad analytical portfolios, but the selected methods and attributes vary with molecular properties, available knowledge, and the intended similarity question [11].

The process component should capture material inputs, unit operations, parameter ranges, equipment, scale, site, hold conditions, sampling strategies, method capability, and known sources of variability. Published biosimilarity assessments do not always report quality attributes with consistent completeness or terminology, which can limit independent interpretation and cross-product learning [12]. A living protocol therefore requires controlled definitions and traceable links between evidence and conclusions.

The proposed baseline is not a claim that every relevant mechanism is known. It should include explicit unknowns, unresolved structure–function relationships, analytical limitations, and assumptions inherited from earlier development stages. Each baseline version should identify the evidence supporting its contents, the conditions under which that evidence remains applicable, and the observations that would trigger reassessment. Its function is to provide a defensible reference state for future comparison, not to freeze product understanding permanently.

Change classification and impact hypotheses

Change classification should begin with the affected product–process relationship rather than administrative labels such as minor or major. Post-approval manufacturing histories show that biologic products undergo repeated changes involving sites, processes, specifications, methods, and control strategies [13].

For each change, the proposed protocol requires an impact hypothesis linking the intervention to plausible effects on process performance, molecular attributes, biological function, and residual uncertainty. Comparability studies after antibody–drug-conjugate manufacturing changes illustrate the value of integrating structural, purity, conjugation, and functional evidence [14].

Classification is proposed across four non-exclusive dimensions: direct product impact, indirect process-mediated impact, cumulative interaction with earlier changes, and detectability using the current analytical system. Emerging generations of biosimilars may create additional challenges when reference-product evolution and historical evidence complicate selection of the comparison state [15].

These classifications are decision-organizing constructs, not validated predictors of clinical consequence. A low-risk classification cannot substitute for evidence, and a high-risk classification does not establish harm. Classification should determine what must be investigated, not predetermine the comparability conclusion.

Dynamic weighting of quality attributes

Critical-quality-attribute weighting should change when new evidence alters biological relevance, observed variability, assay sensitivity, or confidence in the reference state. Characterization of SB3 showed that changes in reference-product characteristics can affect how similarity evidence is interpreted [16].

The protocol therefore proposes version-specific weights rather than permanent rankings. Multi-attribute mass-spectrometric methods can measure several molecular characteristics within one analytical workflow, supporting more integrated assessment of patterns that may be missed by isolated tests [17].

Weighting should also account for formulation and degradation pathways. Industry case studies on polysorbate degradation demonstrate that apparently secondary excipient changes may influence particles, protein stability, or method interpretation under product-specific conditions [18].

Dynamic weighting does not assign numerical clinical risk without supporting evidence. It identifies where evidence should be concentrated and where uncertainty remains consequential. Attribute importance must remain conditional on mechanism, molecule, process, formulation, analytical capability, and intended decision use.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in a living comparability protocol for biopharmaceutical manufacturing processes that..

Table 1. Definitions, components, relationships, and intended uses in A Living Comparability Protocol for Biopharmaceutical Manufacturing Processes That.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Versioned knowledge baseline	Fragmented lifecycle knowledge	Product attributes, process history, methods and control strategy	Proposed linkage of each conclusion to its evidentiary version	Preserves traceability across sequential changes	Verified analytical, process and historical records	Outdated or incomplete baseline	Does not prove that all clinically relevant mechanisms are known
Change-impact hypothesis	Testing disconnected from plausible causation	Change description, affected operations and prior failure modes [13, 14]	Proposed pathway from change to process, attribute and functional consequences	Directs proportionate investigation	Mechanistic rationale plus confirmatory evidence	Incorrect or overly narrow hypothesis	Organizes testing but does not establish causality
Dynamic attribute weighting	Permanent criticality rankings	Structure–function knowledge, drift, assay capability and degradation pathways [16, 18]	Proposed updating of attribute priority when evidence changes	Focuses evidence on decision-relevant uncertainty	Orthogonal analytical and functional support	Weighting may reflect incomplete knowledge	Does not create validated numerical risk
Analytical integration	Isolated tests miss	Conventional assays and multi-	Combined interpretation of	Improves pattern	Qualified methods and	Shared method bias	Analytical similarity is

	correlated change	attribute methods [17]	complementary measurements	recognition and consistency assessment	independent confirmation	or model dependence	not clinical equivalence
Evidence escalation	Uniform testing regardless of risk	Hypothesis strength, attribute relevance and unresolved uncertainty	Proposed progression from analytical to functional and, when necessary, clinical evidence	Avoids both under-testing and automatic clinical testing	Product-specific justification at every escalation stage	Premature closure or unnecessary escalation	Escalation does not guarantee regulatory acceptance
Monitoring and requalification	Conclusions become stale after closure	Continued process and product observations	Proposed feedback into hypotheses, weights and protocol versions	Maintains lifecycle relevance	Prospective monitoring and governance review	Data accumulation without learning	Monitoring signals require investigation before decision use

Analytical, functional, and clinical evidence escalation

Evidence escalation should begin with sensitive analytical characterization and progress only when uncertainty relevant to function, safety, or clinical performance remains unresolved. Data-driven evaluations of biosimilar monoclonal antibodies support tailoring clinical programs to the residual uncertainty remaining after analytical and functional assessment [19].

The proposed first tier includes identity, structure, heterogeneity, purity, impurities, formulation, stability, and process-related attributes. The second tier adds receptor binding, potency, effector functions, and other mechanism-relevant assays when analytical differences require biological interpretation.

Clinical evidence should not be treated as an automatic final tier. Arguments for streamlined biosimilar development emphasize that comparative efficacy trials may add limited discriminatory value when comprehensive analytical and functional evidence has already resolved meaningful uncertainty [20].

A tailored program must nevertheless remain conditional on molecule, mechanism, population, residual uncertainty, and decision context [21]. The protocol does not presume that analytical evidence always suffices or that clinical testing is always necessary; it requires a documented justification for stopping or escalating.

Continuous process and product monitoring

Continuous monitoring extends comparability beyond the formal closure of a change. Continued-performance programs should verify that analytical procedures remain capable, relevant, and controlled throughout their lifecycle [22].

Product monitoring should integrate predefined attributes with emerging signals. Multi-attribute methods may strengthen purity and heterogeneity surveillance, but they require qualified data processing, method control, and interpretation alongside orthogonal assays [23].

Reference materials and standardized analytical protocols can improve comparability of measurements across laboratories and time. The NIST monoclonal-antibody peptide-mapping protocol illustrates how carefully defined procedures can support reproducible characterization [24].

The proposed monitoring loop distinguishes detection, investigation, interpretation, and action. A trend does not itself prove product deterioration, and absence of a detected trend does not prove absence of change. Monitoring must remain sensitive to analytical drift, sampling limitations, process adaptation, and changing knowledge.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for a living comparability protocol for biopharmaceutical manufacturing processes that..

Table 2. Testable propositions, evidence requirements, and validation criteria for A Living Comparability Protocol for Biopharmaceutical Manufacturing Processes That.

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

Baseline initialization	Establish current product and process understanding	Verified records enter a versioned baseline	Supplies context for all later hypotheses	Independent reconstruction of baseline conclusions	Missing provenance	Subject-matter review and data verification	Documentation completeness is not scientific completeness
Change intake	Convert a proposed change into testable questions	Change description flows to impact-hypothesis layer	Activates attribute weighting and evidence planning	Experts can reproduce the rationale from recorded inputs	Administrative classification replaces scientific analysis	Manufacturing, analytical and quality experts	A recorded hypothesis is not a validated mechanism
Analytical assessment	Detect and characterize differences	Samples and data flow through qualified methods [23, 24]	Feeds functional assessment and monitoring	Method suitability, reproducibility and orthogonal agreement	Method drift or shared analytical bias	Laboratory execution and independent review	Analytical comparability does not establish clinical equivalence
Functional escalation	Determine biological relevance	Analytical differences inform mechanism-relevant assays	May close uncertainty or trigger further evidence	Assay relevance, sensitivity and interpretable controls	Assay lacks relationship to product mechanism	Bioassay scientists and product experts	In vitro similarity does not guarantee identical clinical outcomes
Clinical escalation	Address unresolved clinically meaningful uncertainty	Residual uncertainty informs tailored clinical questions [19-21]	Must remain linked to preceding evidence	Prespecified question and decision relevance	Insensitive or redundant clinical design	Clinical, statistical and regulatory judgement	Clinical evidence is not automatically required or sufficient
Monitoring and requalification	Test persistence of prior conclusions	Lifecycle observations return to the protocol baseline [22]	Updates weights, assumptions and versions	Timely detection and documented response to meaningful change	Signal overload or delayed action	Cross-functional governance	Monitoring performance must be demonstrated prospectively

Protocol versioning, learning, and requalification

Protocol versioning records changes to assumptions, attribute priorities, methods, acceptance rationales, and unresolved uncertainties. Post-approval characterization of reference and biosimilar monoclonal antibodies demonstrates that product-quality understanding can continue to develop after authorization [25].

Each version should preserve the prior state, the evidence prompting revision, the responsible decision-makers, and the implications for earlier conclusions. Versioning must permit retrospective reconstruction rather than silently replacing previous interpretations.

Requalification is proposed when an assumption is invalidated, an analytical method changes materially, an attribute acquires new biological relevance, or accumulated changes weaken confidence in the existing baseline. Evolution of the European biosimilar framework illustrates that evidentiary expectations can themselves change as scientific and regulatory experience accumulates [26].

Requalification does not imply repeating the complete development program. Its scope should be proportional to the affected knowledge links and residual uncertainty. The trigger logic, however, requires empirical evaluation for sensitivity, specificity, feasibility, and consistency across products.

Governance and regulatory communication

Governance should assign ownership for baseline maintenance, change hypotheses, analytical interpretation, escalation decisions, and protocol approval. Reviews of biosimilarity and interchangeability show that these concepts rely on different evidence and should not be merged within communication or decision records [27].

Regulatory communication should distinguish observed data, mechanistic interpretation, original proposed reasoning, unresolved uncertainty, and the requested decision. This structure can make disagreements traceable without presenting the protocol as a substitute for applicable requirements.

Switching evidence illustrates why terminology and context matter. Systematic evaluation of switching between reference biologics and biosimilars found a generally reassuring evidence base while also identifying heterogeneity in designs, products, and follow-up [28].

Accordingly, governance should prevent manufacturing comparability conclusions from being extended automatically to switching, interchangeability, indication extrapolation, or clinical substitution. Those decisions require their own legal, scientific, and clinical foundations.

Limitations and implementation priorities

The framework may fail if organizations lack data integrity, stable terminology, qualified methods, cross-functional ownership, or willingness to revise established assumptions. Reviews of switching among biosimilars also show that evidence breadth does not eliminate product-specific and design-specific uncertainty [29].

Implementation priorities are prospective testing against historical change cases, blinded expert comparison, evaluation of missed and false escalation signals, method-transfer studies, and assessment of whether versioning improves decision traceability. Biosimilar-to-biosimilar switching evidence further emphasizes the need to separate accumulated class-level reassurance from conclusions about a particular transition [30].

CONCLUSION

The proposed living comparability protocol reframes comparability as a maintained lifecycle knowledge system rather than a sequence of isolated change assessments. It connects versioned product and process understanding, explicit impact hypotheses, dynamic attribute weighting, proportionate evidence escalation, continuous monitoring, requalification, and accountable governance. The framework is an original conceptual synthesis that requires product-specific, prospective, and independent validation. It does not establish analytical similarity, clinical equivalence, interchangeability, regulatory acceptability, or deployment readiness, but offers a testable architecture for preserving scientific reasoning as biopharmaceutical manufacturing processes evolve.

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