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Batch Equivalence Should Preserve Chemical Function, Not Only Fingerprint Similarity: A Multiscale Quality Model for Complex Herbal Preparations Across Manufacturing Drift

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ABSTRACT

Batch-to-batch consistency in complex herbal preparations is commonly judged through identity tests, marker assays, chromatographic fingerprints, and multivariate similarity. These approaches are essential for chemical quality control, yet they do not by themselves establish that manufacturing or storage variation has preserved the chemical features most relevant to biological function. This article develops an original quality-equivalence model that reframes batch equivalence as a multiscale evidential problem rather than a single similarity decision. The analysis distinguishes chemical comparability, process-associated change, exposure relevance, measured functional potency, and higher-order interpretation, while preserving boundaries between association and causation and between analytical compliance and functional equivalence. Evidence from multimodal fingerprinting, process-resolved chemical profiling, effect-oriented constituent weighting, metabolomics, and biological potency testing shows that chemical and functional information can be complementary and, in some settings, discordant. On this basis, the proposed model treats manufacturing drift as meaningful only when its interpretation is supported across the evidence levels relevant to the product's intended quality attributes, rather than whenever any detectable chemical change occurs. Conversely, high fingerprint similarity should not automatically neutralize concern when a function-relevant constituent, chemical domain, exposure determinant, or potency measure has shifted. The model is intended to support lifecycle reasoning, investigation prioritization, and evidence integration rather than to define universal equivalence limits. Its principal boundaries are assay dependence, incomplete constituent attribution, product-specific processing chemistry, confounding by nonmanufacturing sources of variation, and the current absence of prospectively validated cross-product decision thresholds.

Keywords: Herbal medicines, Batch equivalence, Chemical fingerprints, Manufacturing drift, Quality markers, Lifecycle quality management

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Introduction

Complex herbal preparations pose a qualitatively different consistency problem from single-entity medicines. Their measurable composition can reflect botanical source, cultivation, harvesting, extraction, processing, formulation, and storage, while its analytical representation depends on sampling and platform coverage. Contemporary quality-consistency scholarship therefore treats herbal-product variation as a multidimensional analytical problem rather than one reducible to a single marker or chromatographic trace [1]. Yet routine use of

"equivalence" can obscure an important distinction: two batches may be highly similar within a chosen analytical representation without demonstrated equivalence in exposure or biological function. Conversely, detectable chemical differences need not imply loss of relevant function. The problem is therefore interpretive as well as analytical—what changed, at which level, and why should it matter?

Data-rich quality control increases the ability to characterize this problem but does not remove it. Artificial intelligence, bioinformatics, multivariate analysis, and integrated process data can combine spectra, chromatograms, omics features, and manufacturing variables into information-dense quality assessments [2]. Such integration can detect patterns that simpler specifications miss, but model output remains conditional on training data, analytical design, and validation domain. In an equivalence context, computation should therefore organize and predict quality signals, not convert multivariate resemblance into biological sameness. A technically strong classifier may identify batch classes or process states while leaving unanswered whether the discriminating features are pharmacologically important.

The same distinction applies to chemical abundance. A preparation can be well characterized yet incompletely understood if constituents differ in absorption, metabolism, local availability, or access to the relevant biological compartment. Bioavailability-oriented quality approaches place exposure between composition and downstream action, emphasizing that measured content and biologically available material are not interchangeable [3]. Exposure is not universally systemic: locally acting constituents, transformed metabolites, and matrix-dependent release may matter depending on route and intended action. The broader implication is that chemical equivalence should not automatically be interpreted as exposure equivalence, while exposure evidence itself does not establish identical pharmacodynamic consequences.

These boundaries motivate a lifecycle view. Regulatory-science scholarship in traditional medicines emphasizes coordination across source control, manufacturing, analytical evidence, validation, and use context rather than reliance on isolated end-product tests [4]. Building on that premise, this article proposes a multiscale quality-equivalence model for complex herbal preparations across manufacturing drift. The model does not replace established identity, assay, fingerprint, or stability requirements. It organizes what those measurements can establish, where they stop, and when process history, chemical composition, exposure-relevant attributes, and measured function should be integrated. Its purpose is to distinguish acceptable variation from potentially meaningful drift without inventing universal numerical limits or implying regulatory endorsement.

What batch equivalence should mean for complex herbal products

For a complex herbal product, batch equivalence should first be separated into evidential levels. Chemical comparability asks whether specified constituents, fingerprints, or broader profiles remain in an analytically justified state of similarity. Functional comparability asks whether a relevant measured response is preserved under a defined assay. These questions are related but nonredundant. In ReDuNing injection, an integrated strategy combining high-resolution chemical profiling with biological potency and multivariate analysis demonstrated that chemical and functional information can be evaluated jointly rather than treated as interchangeable [5]. The implication is not that every product requires the same potency assay, but that equivalence claims should specify which evidence level has been demonstrated.

Second, chemical differences should not necessarily be weighted equally. A small change in a constituent linked to a relevant effect may warrant more attention than a larger change in an analytically dominant but functionally uninformative feature. An efficacy-oriented effect-constituent index developed for *Paris polyphylla* var. *yunnanensis* illustrates the feasibility of weighting compositional information using measured effect-related evidence in a defined system [6]. Such weighting remains product- and endpoint-specific, and correlated constituents can act as proxies rather than causal drivers. The proposed model therefore uses the broader principle of relevance-weighted drift, not transferable numerical weights.

Third, chemical comparability should be as representation-complete as reasonably possible. Multiple fingerprints and quantitative measurements can cover complementary chemical domains and provide stronger characterization than reliance on a single pattern or marker. A multicomponent strategy applied to Tianma Toutong tablets combined multiple fingerprints, quantitative analysis, and prescription-oriented interpretation to improve chemical quality evaluation [7]. This strengthens confidence in analytical comparability, but analytical breadth is not equivalent to biological relevance: additional peaks or platforms can still omit low-abundance actives, transformation products, or matrix effects.

Finally, the evidential label should remain calibrated to the measurement. Fingerprint similarity accompanied by multi-component quantification can provide strong evidence of chemical consistency, as demonstrated for Yiqing tablets [8]. What it establishes is consistency within the measured analytical space. It does not, without additional evidence, establish preserved exposure, pharmacological potency, or clinical interchangeability. The proposed model therefore reserves "batch equivalence" for a contextual conclusion assembled from the evidence levels required by the intended quality claim, while using "chemical comparability" when only the analytical layer has been demonstrated.

Fingerprint similarity and its limits

Fingerprint similarity is valuable because it preserves pattern information that targeted single-marker assays discard, but its apparent holism is bounded by the analytical representation chosen. Orthogonal modalities can reveal different processing-sensitive chemical domains. For raw and bran-fried Atractylodis Rhizoma, Fourier-transform infrared spectroscopy, HPLC-DAD, and GC-MS fingerprints combined with chemometrics provided complementary discrimination of processing states [9]. A similarity value is therefore not an intrinsic property of a batch pair: it is generated by sample preparation, measurement technology, feature extraction, and comparison logic. Batches judged similar in one analytical space may contain differences visible in another.

The problem is especially clear when relevant chemistry is poorly represented by the dominant small-molecule fingerprint. Processing can alter macromolecular or structurally heterogeneous fractions requiring dedicated analytical treatment. Multi-fingerprint analysis of *Dendrobium huoshanense* polysaccharides detected quality differences across traditional processing stages [10]. Such differences should not automatically be labelled degradation; processing can intentionally create or transform chemical states. The appropriate inference is narrower: domain-aware fingerprint coverage is necessary when manufacturing can alter distinct chemical fractions, and the meaning of those changes requires evidence beyond detectability.

Method dependence also limits universal interpretation of similarity scores. Reviews of herbal fingerprinting show that analytical platform, sample preparation, preprocessing, chemometric method, feature coverage, and validation strategy shape the resulting quality comparison [11]. Consequently, no universal similarity cutoff is proposed here. A threshold can be useful within a validated product-specific method, but it should not be treated as a biological constant. High similarity may coexist with localized movement in a low-abundance or function-relevant feature; lower similarity may reflect benign or intended transformation across abundant chemical regions.

This limitation does not diminish chromatography's central role in herbal quality standards. Pharmacopoeial chromatographic technologies support identification, quantitative assay, and fingerprint control and therefore provide an established foundation for demonstrating chemical identity and consistency [12]. The boundary is evidential rather than adversarial: chromatographic compliance answers chemical questions defined by the monograph and method. It should sit within a broader equivalence architecture when the claim extends to preserved biological function. The proposed model therefore treats fingerprint similarity as strong pattern-level evidence whose interpretation remains linked to analytical coverage, method validation, and the product attribute the similarity decision is intended to protect.

Chemical change across manufacturing and storage

Manufacturing should be interpreted as a trajectory through chemical states rather than a black box between accepted raw material and released product. Process-resolved measurements can identify where compositional movement emerges and whether it is associated with particular unit operations. A pharmaceutical process-omics study of Guanxinning injection used 1H-qNMR-assisted multivariate analysis to characterize profiles across manufacturing stages, showing how process-associated variation can be localized rather than discovered only at final release [13]. For equivalence reasoning, this supports stage-resolved investigation: when a finished batch drifts, the useful question is not only whether its final fingerprint changed, but where the change entered the process and whether that trajectory is reproducible.

Some processing changes can coincide with altered measured function. Black-ginseng research has documented processing-related changes in chemical composition together with changes in measured medicinal effects [14]. Such cases establish the possibility of functionally consequential transformation, but they do not justify assuming every changed peak is causal or every process shift harmful. Multiple constituents change simultaneously, processing can create desirable products, and biological outcomes remain model- and dose-dependent. Meaningful

drift therefore requires a bridge between chemical change and the quality attribute that gives that change significance.

The converse pattern is equally important. LC-MS-based metabolomics and accelerated stability testing of a Chinese herbal spirit detected storage-related chemical change without a necessarily parallel change in the measured functional response [15]. This discordance is not proof that chemical drift is harmless: the selected assay may be insensitive to relevant effects, and accelerated conditions have transfer limits. It does show that "chemical change" and "demonstrated functional change" are different evidential states. An equivalence model must represent that disagreement rather than force both signals into a single similarity verdict.

Attribution is a further constraint. Herbal metabolomes are shaped by botanical origin, growth environment, harvesting, processing, storage, sample handling, and analytical conditions, so a between-batch difference cannot automatically be assigned to manufacturing [16]. Controlled metadata and process-aware comparisons are needed to separate manufacturing drift from upstream biological variation or analytical batch effects. The proposed model therefore adds an alternative-explanation gate before drift is classified as manufacturing-derived. **Table 1** summarizes the evidence states established so far and the boundaries that prevent chemical difference from being overinterpreted.

Table 1. From analytical similarity to potentially meaningful drift: proposed concept-and-evidence classification for herbal batch equivalence

Evidence state	Observation	Supports	Does not establish alone
Pattern comparability	Similar validated fingerprint or marker profile	Chemical consistency in measured space	Preserved exposure or function
Expanded chemical comparability	Concordant orthogonal fingerprints and quantitative domains	Broader coverage of composition	Equal importance of detected features
Process-associated drift	Reproducible chemical change localized to manufacturing or storage	Investigation of where chemistry moved	Causal functional consequence
Chemical–functional concordance	Chemical change accompanies a relevant measured response	Drift may be meaningful in tested context	Causal constituent attribution or clinical equivalence
Chemical–functional discordance	Chemistry changes without parallel assay movement	Need for qualification and assay review	Proof that drift is harmless

Functional relevance of chemical variation

Chemical variation becomes quality-relevant when there is evidence connecting it to a function that matters for the preparation. Spectrum–effect analysis offers one bridge by relating chromatographic or spectrometric features to measured pharmacodynamic responses. In Ling-Gui-Zhu-Gan decoction, spectrum–effect modeling combined with high-resolution mass spectrometry was used to prioritize chemical features associated with an experimental response [17]. Such associations are more informative than fingerprint presence alone, but they remain association evidence: covariance among constituents, extraction behavior, and model structure can cause a feature to track activity without being its causal source. A change in an effect-associated feature should therefore trigger targeted investigation rather than automatic classification as functionally meaningful drift.

The evidential position strengthens when analytical association is followed by biological testing directed at nominated constituents or mechanisms. Work on Gastrodiae Rhizoma combined spectrum–effect relationships with targeted anti-neuroinflammatory investigation, illustrating escalation from correlation-based prioritization toward experimentally constrained attribution [18]. Even this stronger tier remains bounded by the biological system, concentrations, endpoints, and mechanism examined. For batch equivalence, the relevant lesson is procedural: evidence should progress from detection to association and, where necessary, to orthogonal functional confirmation. The model proposed here therefore distinguishes an "effect-linked" chemical feature from a causally established active constituent and avoids making the latter a prerequisite for every routine quality decision.

Exposure can further refine which chemical differences deserve functional attention. Integration of serum pharmacochemistry with chromatographic fingerprints and network-based analysis has been used to nominate candidate quality markers whose plausibility is supported by detection after administration as well as by predicted biological relationships [19]. Absorption narrows the gap between content and potential action, but predicted

network targets remain hypotheses rather than validated mechanisms. Likewise, combined fingerprint, serum, and network evidence has been used to prioritize candidate markers in *Phyllanthus emblica*, demonstrating that chemical detection, systemic exposure, and predicted relevance can be layered without treating them as identical forms of evidence [20].

Accordingly, functional relevance is not a binary property attached permanently to a peak. It is a graded and context-dependent evidential state. A constituent may be chemically stable yet functionally unimportant for the measured endpoint; another may be low in abundance but disproportionately relevant; and a transformation product may become important only after processing or exposure. The proposed equivalence model therefore asks whether observed drift crosses from pattern-level variation into a function-relevant domain, and how securely that transition is supported. **Figure 1** integrates this distinction with the later multiscale, drift-interpretation, and lifecycle arguments.

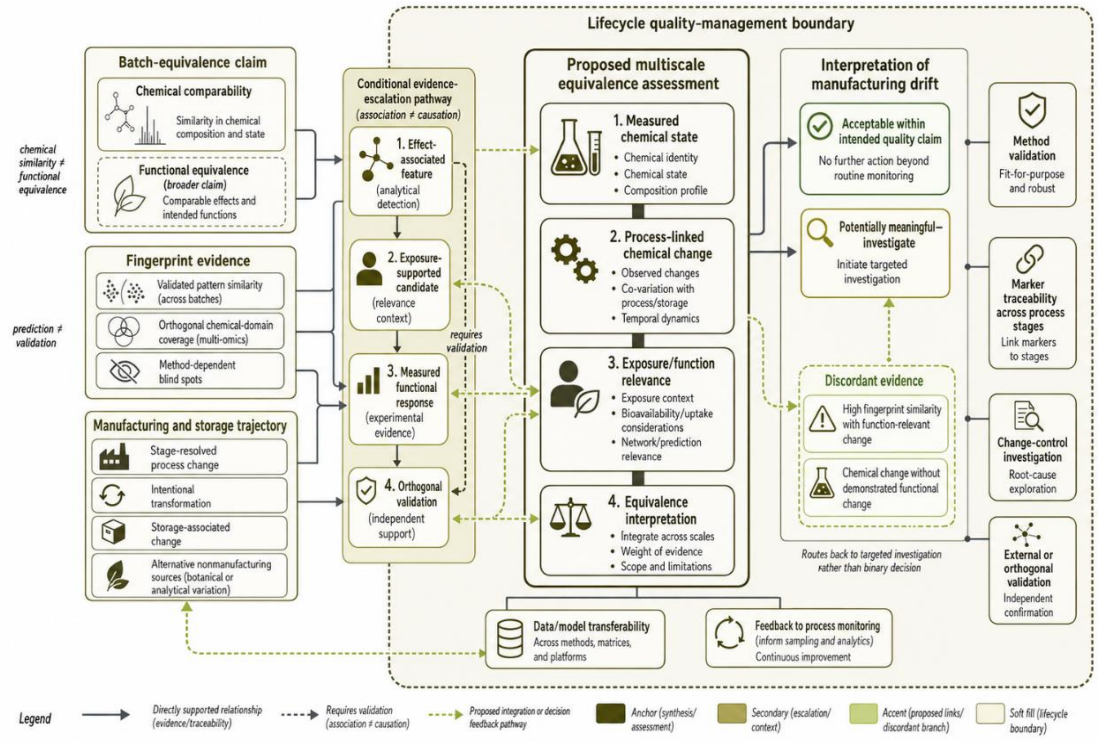

Figure 1. Proposed multiscale architecture for interpreting herbal batch equivalence across chemical, functional, and lifecycle evidence

A multiscale equivalence model

The proposed model begins from a simple constraint: quality evidence should be matched to the level of the equivalence claim. Quality-marker theory has long argued that measurable constituents can be selected with reference to drug properties and effect characteristics rather than analytical detectability alone [21]. This principle is extended here from marker selection to batch interpretation. At the first level, chemical-state equivalence concerns identity, specified content, fingerprints, and broader compositional domains. At the second, process-trajectory equivalence asks whether the route by which that state was reached remains controlled and interpretable. At the third, function-relevance equivalence asks whether changed chemical features alter exposure-relevant or measured functional attributes. These levels are connected, but none is treated as a surrogate for the others.

A multidimensional approach is preferable to compressing heterogeneous evidence into one universal similarity score. Q-marker-centered quality assessment has been proposed as a way of integrating multiple types of quality information into decision-oriented evaluation [22]. The present model retains that integrative logic while rejecting a fixed composite index: evidence strength, measurement error, product mechanism, route, and assay relevance differ too substantially for one weighting scheme to be presumed transferable. Instead, the proposed decision state is categorical and evidence-explicit—what level is comparable, what level is discordant, and what unresolved evidence would change the interpretation.

The model also adds direction through manufacturing time. Quality-marker transitivity and traceability concepts emphasize that quality information can be followed across processing and product transformations rather than assessed only in the finished product [23]. Thus, a final batch that passes a fingerprint criterion can still merit investigation if an unusual process trajectory generated compensating compositional changes or an unmonitored transformation. Conversely, a known process-associated shift can be interpretable when its trajectory, chemical consequence, and relevant function are characterized. This creates a distinction between end-state resemblance and lifecycle equivalence.

Empirical examples justify preserving discordance rather than forcing evidence into one verdict. Integrated chemistry and potency assessment shows that chemical and measured functional information can be jointly evaluated [5]. Stability work demonstrates that measurable chemical change need not be accompanied by a parallel response in the selected functional assay [15]. Layered marker-nomination strategies likewise separate detected chemistry, exposure, and predicted biological relevance [20]. The proposed model therefore treats agreement across levels as stronger support, disagreement as an investigation state, and missing levels as explicit uncertainty—not as implicit equivalence.

Table 2 converts this architecture into a comparative decision matrix without assigning universal numerical limits.

Table 2. Proposed multiscale equivalence matrix for interpreting evidence across herbal-product quality levels

Evidence level	Primary question	Stronger support	Key discordance or boundary
Chemical state	Are measured identity, content, and profiles comparable?	Validated multi-domain analytical agreement	Similarity is method- and coverage-dependent
Process trajectory	Was the chemical state reached through a controlled, traceable path?	Stage-resolved reproducibility and traceable transformations	Similar end states can conceal atypical trajectories
Exposure relevance	Do changed constituents reach the relevant biological context?	Product-appropriate exposure evidence	Absence from systemic exposure may not exclude local action
Functional response	Is a defined quality-relevant response preserved?	Reproducible orthogonal functional evidence	Assay preservation is endpoint- and model-specific
Decision/validation	Does the combined evidence support the intended equivalence claim?	Concordant levels with validated methods and bounded interpretation	Discordance, prediction-only evidence, or transfer outside validation domain

Acceptable versus meaningful manufacturing drift

"Acceptable" drift should not mean merely "undetected" drift, and "meaningful" drift should not mean every statistically detectable difference. Functional prioritization itself can depend on the analytical or modeling method. In carbonized Typhae Pollen, multiple spectrum–effect modeling approaches were used to nominate candidate active ingredients, illustrating that model choice can influence which chemical features appear important [24]. Agreement across methods can strengthen prioritization, but model-selected features remain candidates rather than causal proof. Accordingly, a drift decision should incorporate robustness of feature attribution as well as magnitude of compositional movement.

Evidence becomes more compelling when chemical change concerns constituents supported by biologically relevant exposure and function. Integrated serum pharmacochemistry and pharmacology has been used to investigate absorbed components alongside pharmacological responses [25]. Such evidence is stronger for relevance than fingerprint presence alone, yet remains dependent on biological model, dose, route, and exposure context. The proposed framework therefore classifies drift as potentially meaningful when a reproducible process-associated change affects a quality attribute supported at a function-relevant evidence level, not simply when a peak crosses an arbitrary difference threshold.

Magnitude and significance can consequently diverge. Storage-related chemical changes without a parallel change in a selected functional response show that analytical movement alone does not define demonstrated functional loss [15]. Process-resolved analysis can localize where manufacturing-related chemical movement arises, strengthening attribution of the drift source [13]. Effect-oriented weighting can further indicate that different constituents need not carry equal relevance for quality interpretation [6]. These observations support a conditional decision rule: evaluate source attribution, analytical robustness, relevance of the affected domain, functional or

exposure evidence where appropriate, and uncertainty together. A batch may remain acceptable for a defined quality claim despite measurable benign variation, while a small but reproducible change in a strongly supported function-relevant attribute may warrant investigation. Neither state should be equated automatically with clinical nonequivalence. The practical consequence is that investigation depth should scale with evidential concern rather than with raw analytical distance alone. Replication, orthogonal analysis, process-record review, and targeted functional testing can distinguish an isolated excursion from reproducible quality-relevant drift.

Applications in lifecycle quality management

Lifecycle use requires converting discovery into validated, maintainable evidence. Analytical strategies for quality-marker research distinguish marker discovery from subsequent validation and application, with confidence depending on analytical verification, biological relevance, and context [26]. In the proposed model, a candidate equivalence attribute therefore enters routine change assessment only after its method and intended interpretation are sufficiently validated for the product and process. Evidence used for exploratory investigation can be broader and hypothesis-generating; evidence used for release, comparability, or formal change decisions requires a more constrained claim.

Machine learning can assist this lifecycle architecture by detecting multivariate shifts, combining process and analytical information, or prioritizing unusual trajectories. Current analyses of machine learning in traditional Chinese medicine also identify data quality, interpretability, generalization, and external validation as continuing limitations [27]. The appropriate role is consequently decision support rather than autonomous equivalence adjudication. A model trained on one product, site, instrument configuration, or historical operating range should not be presumed transportable to another without validation, and a discriminative feature should remain analytically interpretable enough to support investigation.

Operationally, the framework can connect monitoring, investigation, and knowledge updating without claiming a universal regulatory pathway. Lifecycle-oriented regulatory science supports integration of manufacturing, evidence, and use context [4]. Quality transitivity and traceability provide a conceptual basis for following relevant attributes across process stages [23]. Data-integration approaches can then organize heterogeneous analytical and manufacturing signals at scale [2]. Together, these premises support a proposed recursive workflow: establish product-specific evidence levels; monitor their validated attributes; investigate discordant movement at its process origin; escalate to exposure or functional testing when the intended claim requires it; and update the control rationale when replicated evidence changes understanding. This is a knowledge-management architecture, not proof that a specific change is acceptable to any regulator. Its useful output is a documented rationale linking the observed deviation to the evidence level actually affected, the uncertainties that remain, and the next measurement capable of resolving them. That structure makes historical batch knowledge reusable when comparable drift patterns recur, while requiring reassessment when process conditions change.

Limitations

The model inherits the incompleteness of the measurements on which it depends. Herbal-product consistency is intrinsically affected by heterogeneous materials, processes, and analytical choices [1]. Fingerprint conclusions vary with platform coverage, preprocessing, feature selection, and validation design [11]. Metabolomic profiles are additionally sensitive to biological origin, sampling, handling, and analytical batch effects [16]. A multiscale framework can make these uncertainty sources visible but cannot eliminate them. It is particularly vulnerable when relevant chemistry lies outside the measured domain or when upstream material variation is insufficiently separated from manufacturing change.

Computational integration creates a second limitation. Machine-learning methods can support high-dimensional pattern recognition, but generalization and explainability remain central constraints [27]. Network-based marker nomination can add biological plausibility while still requiring experimental confirmation of predicted relationships [19]. The framework therefore cannot convert prediction into mechanism by adding more computational layers. Prospective evaluation should test whether its decision structure improves investigation accuracy, reproducibility, or change assessment relative to simpler specifications, preferably across distinct products, manufacturing sites, and analytical platforms.

Finally, functional evidence is assay-bounded. A stability study in which chemical changes are not mirrored by the selected biological measure does not establish preservation of every relevant function [15]. Conversely, combined chemical and potency assessment demonstrates complementarity only for the tested preparation and

assay design [5]. No universal hierarchy specifies which functional assay, exposure measure, marker set, or decision boundary is appropriate for every herbal product. The present framework therefore remains a proposed reasoning architecture. Its value depends on product-specific validation, explicit intended-use claims, transparent treatment of discordance, and willingness to reject or revise individual model elements when prospective evidence does not support them. Difficult cases will include synergistic mixtures whose functional attributes cannot be assigned to stable individual markers, products dominated by local rather than systemic action, and processes in which desired transformation and degradation generate overlapping analytical signatures.

Conclusion

Batch equivalence in complex herbal preparations should be treated as a claim whose evidential meaning depends on the level being compared. Validated fingerprints and quantitative assays remain indispensable for chemical identity and consistency, but their evidential reach should not be extended automatically to preserved exposure, biological function, mechanism, or clinical interchangeability. Manufacturing and storage can generate detectable chemical movement that is intentional, benign, functionally consequential, or difficult to attribute; conversely, high global similarity can conceal localized movement in a potentially important chemical domain.

The proposed multiscale quality-equivalence model organizes these possibilities by keeping chemical state, process trajectory, exposure relevance, measured function, and validation status distinguishable while allowing them to inform one another. It treats concordance across relevant levels as stronger support, discordance as an investigation state, and missing evidence as uncertainty rather than assumed equivalence. Manufacturing drift becomes meaningful through its relationship to a defined quality claim, not through chemical magnitude alone.

This architecture is intended to improve the precision of quality reasoning and lifecycle investigation, not to prescribe universal specifications. Product-specific analytical coverage, assay relevance, transformation chemistry, exposure context, method validation, and transferability remain decisive boundaries. Future prospective work should test whether multiscale interpretation improves the discrimination of benign from quality-relevant drift and whether its evidence transitions can be validated reproducibly across products and manufacturing settings. Such testing should compare the proposed architecture with conventional specification-based decisions, document cases in which evidence levels disagree, and determine whether additional functional or exposure measurements actually change quality conclusions. Until that validation exists, the model is best viewed as a structured, falsifiable framework for asking a more precise question: not whether two complex batches merely look alike analytically, but whether the dimensions of chemistry most relevant to their intended quality have been preserved within an explicitly bounded evidence context.

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