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Mechanism-Based Extrapolation across Biosimilar Indications, Patient Populations, Dosing Regimens, and Residual Scientific Uncertainty in Regulatory and Clinical Contexts

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ABSTRACT

Indication extrapolation allows a biosimilar to be used in approved reference-product indications that were not independently tested in comparative efficacy trials. Its scientific justification, however, cannot rest on analytical similarity, shared target identity, pharmacokinetic equivalence, or clinical similarity in one sensitive population alone. This original framework article proposes a mechanism-based evidence pathway integrating reference-product knowledge, comparative analytical and functional evidence, indication-specific mechanisms of action, target-expression and disease-pathway context, exposure and regimen bridging, population and immunogenicity modifiers, residual scientific uncertainty, evidence coherence, and post-authorization evidence updating. The framework treats residual uncertainty as an explicit scientific object whose source, potential consequence, affected scope, and feasible resolution strategy must be documented. It distinguishes conditionally supported extrapolation from situations requiring targeted additional evidence or leaving the extrapolation claim unsupported under the current evidence package. Immunogenicity is framed as a context-dependent interaction among product attributes, patient characteristics, disease state, concomitant treatment, route, treatment duration, prior exposure, and assay performance. Clinical communication, traceability, and post-authorization monitoring are included because evidentiary adequacy does not guarantee correct interpretation or implementation. The principal contribution is a transparent, non-empirical architecture connecting product comparison to indication-, population-, and regimen-specific decision boundaries. The framework does not constitute a validated predictive model, clinical recommendation, regulatory determination, or universal development standard. Prospective operationalization, inter-rater reproducibility testing, product-class adaptation, and empirical validation are required before formal use.

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

Biopharmaceutical performance emerges from interactions among molecular structure, post-translational attributes, biological targets, manufacturing processes, exposure conditions, and patient biology. A biosimilar is therefore not established through molecular identity but through a comparative demonstration that observed differences do not create clinically meaningful differences. This assessment is commonly organized as a totality-

of-evidence exercise in which analytical, functional, pharmacokinetic, immunogenicity, and, where necessary, comparative clinical evidence progressively address remaining uncertainty [1].

Indication extrapolation extends this comparative logic beyond the population and disease directly studied during development. It uses reference-product knowledge and biosimilar comparative evidence to justify use in additional approved indications when the scientific argument is coherent. The practice developed within an evolving regulatory framework informed by analytical science, clinical pharmacology, immunogenicity assessment, lifecycle experience, and post-authorization monitoring [2]. Yet accumulated experience does not make every extrapolation equivalent because products, mechanisms, routes, doses, treatment durations, and patient populations differ.

The prevailing framing becomes inadequate when one favorable comparison is treated as sufficient. Analytical similarity can reveal close correspondence across critical quality attributes but may not resolve every clinically relevant function. Pharmacokinetic equivalence can provide a sensitive comparison of systemic exposure but may not represent tissue distribution or regimen-specific pharmacology. Comparative efficacy trials may be less sensitive than analytical or pharmacological methods for detecting product-related differences and may add little when earlier evidence has already resolved the material uncertainty [3]. Conversely, reducing clinical testing without explicitly examining mechanism, population, and dosing differences risks replacing inefficient evidence generation with unsupported inference.

This article develops an original, non-empirical indication-extrapolation framework. It distinguishes biosimilar evaluation from manufacturing comparability, analytical similarity from clinical equivalence, indication extrapolation from interchangeability, and scientific justification from regulatory or clinical decision authority. The framework organizes what is directly demonstrated, what is transported from reference-product knowledge, what is mechanistically inferred, what remains uncertain, and what evidence could alter the conclusion. It builds on the continuing refinement of biosimilar evaluation toward product-specific and question-specific scientific judgment [4].

Scientific basis and controversy of indication extrapolation

The scientific basis of extrapolation begins with the comparative purpose of biosimilar development. Once analytical and functional evidence has established close similarity, later studies should address unresolved questions rather than re-establish the reference product's complete benefit–risk profile. Confirmatory efficacy trials may have limited discriminatory or incremental value when sensitive analytical methods and comparative pharmacokinetics have already resolved the product-related uncertainties such trials could plausibly detect [5]. This does not imply that efficacy trials are always unnecessary; they remain relevant when mechanisms are incompletely characterized, analytical differences remain unexplained, or the available pharmacological model is insufficiently sensitive.

Reference-product knowledge provides the second foundation. Established mechanisms, dose–response relationships, pharmacokinetics, safety, immunogenicity, and lifecycle experience define the context in which biosimilar differences are interpreted. Experience with extrapolation during the development and lifecycle management of original biologics shows that evidence can be transported across populations or disease settings when the relevant mechanisms and exposure relationships are sufficiently understood [6]. Nevertheless, biosimilar extrapolation remains a comparative inference: reference-product experience cannot substitute for demonstrating biosimilarity.

A further controversy arises from conceptual conflation. Biosimilarity concerns the relationship between a proposed product and its reference product. Indication extrapolation concerns whether that relationship and the reference-product evidence support use in an unstudied approved indication. Switching concerns a change between products during treatment, whereas interchangeability may have a jurisdiction-specific legal meaning governing substitution. These determinations overlap scientifically but are not equivalent [7].

The central dispute is therefore not whether extrapolation is acceptable in principle, but how residual uncertainty should be identified and resolved. One position emphasizes that sensitive analytical and pharmacological evidence usually makes indication-specific efficacy trials redundant. Another emphasizes that mechanisms may vary across diseases, populations, and treatment conditions in ways not represented by one development program. The proposed framework integrates both positions by treating extrapolation as a structured inference whose strength depends on coherence across product attributes, mechanisms, target context, exposure, population factors, and immunogenicity.

Proposed mechanism-based extrapolation framework

The framework begins with the principle that evidence generation should be tailored to the uncertainty remaining after each comparative stage. Tailored development has been proposed as an alternative to uniform study requirements because products, mechanisms, assays, and programs do not leave the same questions unresolved [8]. The present framework extends this principle from study selection to the architecture of the extrapolation argument itself.

Figure 1 presents the original conceptual synthesis for mechanism-based evidence pathway for biosimilar indication extrapolation, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

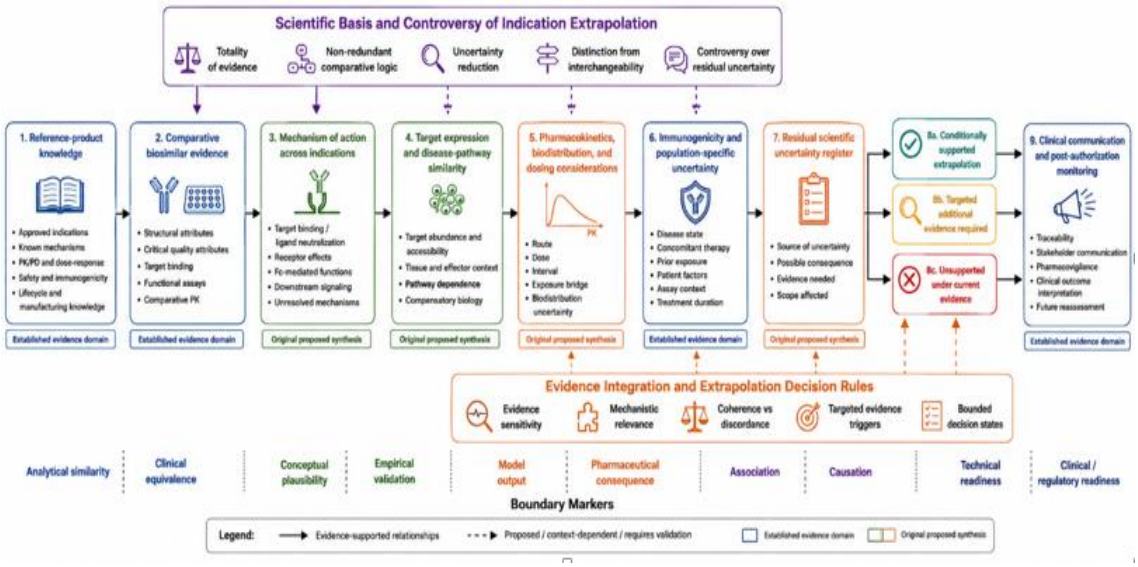

Figure 1. Mechanism-Based Evidence Pathway for Biosimilar Indication Extrapolation.

The first framework layer contains two distinct inputs. The reference-product knowledge anchor includes approved uses, established and hypothesized mechanisms, clinical pharmacology, dose–response information, safety, immunogenicity, and lifecycle evidence. The biosimilar comparative profile includes structural attributes, critical quality attributes, physicochemical properties, receptor or ligand binding, cell-based function, and comparative pharmacokinetics. These inputs must remain distinguishable because reference-product knowledge cannot replace biosimilarity evidence, while analytical similarity cannot recreate the reference product's full clinical history. Regulatory analyses indicate that development requirements may vary according to product class, analytical uncertainty, pharmacology, and the likelihood that additional evidence will resolve a meaningful question [9].

The second layer is a proposed mechanism-concordance profile. It separates target binding, ligand neutralization, receptor blockade or activation, Fc-mediated functions, downstream signaling, cellular effects, and incompletely characterized mechanisms. Each mechanism is mapped to the indications in which it is principal, contributory, uncertain, or probably non-determinant. Comparative efficacy outcomes should then be interpreted according to whether they address a defined unresolved question rather than according to their conventional position near the end of development [10].

The third layer comprises the target and disease-pathway concordance profile, the exposure and regimen bridge, and the population and immunogenicity modifier. These domains ask whether target expression, tissue accessibility, effector-cell involvement, pathway dependence, dose, route, interval, pharmacokinetic covariates, treatment duration, concomitant therapy, and immune context support transport of the comparative conclusion. Across tailored-development proposals and regulatory analyses, the incremental value of routine confirmatory efficacy testing is lowest when analytical, functional, and clinical-pharmacology evidence has already resolved the material comparative uncertainties [8–10].

The final layer is a proposed residual scientific uncertainty register. Each uncertainty is documented according to source, plausible mechanism, possible consequence, affected indication or population, and feasible resolution strategy. The register produces three conceptual states: conditionally supported extrapolation, targeted additional

evidence required, or extrapolation unsupported under the current evidence package. These states are not regulatory determinations and do not use numerical thresholds.

Mechanism of action across indications

Mechanism of action may compress several distinct molecular and cellular processes. For monoclonal antibodies and fusion proteins, relevant activities can include antigen or ligand binding, receptor occupancy, signaling blockade, ligand neutralization, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, receptor internalization, apoptosis, and secondary effects on inflammatory pathways. Mechanism-relevant binding and functional assays can determine whether a proposed biosimilar preserves activities associated with the reference product's known biological functions [11].

The framework therefore rejects a binary definition of mechanism concordance. Analytical similarity must integrate multiple structural and functional attributes, particularly where different quality attributes influence different biological activities. A multidimensional comparison can reveal whether observed variation is analytically expected, functionally neutral, or potentially relevant to an indication-dependent mechanism [12]. Numerical identity is not required, but differences must be interpreted according to analytical uncertainty, biological relevance, assay sensitivity, and clinical context.

A mechanism-based extrapolation argument must also preserve discordant evidence rather than absorb it into an overall similarity conclusion. Rituximab case comparisons illustrate that structural resemblance alone does not eliminate questions about functional activity, pharmacokinetics, or the clinical relevance of specific product differences [13]. Such observations do not establish clinical inferiority or justify ranking biosimilars. They show why measured attributes must be connected to functional consequences and indication-specific mechanisms.

The proposed indication-specific mechanism-contribution map assigns known or plausible mechanisms to four descriptive states: principal, contributory, uncertain, or not presently considered clinically determinant. The assignment should be justified through reference-product pharmacology, functional evidence, disease biology, and exposure relationships. Extrapolation becomes more plausible when functions that are principal or contributory across indications have been adequately compared. It becomes less secure when an important mechanism is poorly represented by the assays, population, or regimen used during development.

Target expression and disease-pathway similarity

Target expression is relevant only when interpreted together with localization, accessibility, downstream signaling, and the therapeutic role of the target in the disease pathway. A target may be present in several indications while differing in abundance, soluble versus membrane-bound form, tissue penetration, receptor density, or dependence on accessory immune mechanisms. Longitudinal variation in antibody-dependent cellular cytotoxicity-related attributes of trastuzumab shows why critical quality attributes must be connected to the functions they influence and to the settings in which those functions matter [14].

The framework separates target concordance from disease-pathway concordance. Target concordance concerns whether the biosimilar and reference product engage the same target with comparable binding and functional properties. Disease-pathway concordance concerns whether target engagement has a sufficiently similar therapeutic role across the studied and extrapolated indications. Infliximab biosimilar development illustrates how shared tumor necrosis factor biology can be considered together with analytical, functional, pharmacokinetic, immunogenicity, and reference-product evidence [15].

Clinical evidence in one indication must not be treated as direct evidence for every extrapolated indication. In adalimumab biosimilar development, comparative clinical evidence in a sensitive indication supplemented a broader analytical, functional, pharmacokinetic, and immunogenicity package [16]. The studied indication can therefore serve as a discriminatory clinical setting without becoming a biological proxy for every disease.

The proposed target and disease-pathway concordance profile includes target abundance, target form, tissue accessibility, pathway dependence, effector-cell involvement, compensatory biology, and the relative contribution of each mechanism. Each dimension is described as concordant, plausibly transportable with stated assumptions, materially uncertain, or discordant. These categories expose the basis of inference but do not constitute validated thresholds.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in mechanism-based extrapolation across biosimilar indications, patient populations.

Table 1. Definitions, components, relationships, and intended uses in Mechanism-Based Extrapolation across Biosimilar Indications, Patient Populations

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Reference-product anchor	Context-free inference	Indications, mechanisms, PK/PD, safety	**Proposed starting context**	Defines assumptions	Verified product knowledge [2]	Incomplete knowledge	Informs, not proves, extrapolation
Comparative profile	Global similarity masking differences	Structure, CQAs, binding, function, PK	**Proposed attribute–function linkage**	Identifies unresolved differences	Orthogonal assays [11]	Insensitive methods	Analytical similarity is not clinical equivalence
Mechanism profile	Target identity treated as sufficient	Binding, receptor and Fc functions, signaling	**Proposed indication-specific map**	Makes inference testable	Functional pharmacology [12]	Unknown mechanisms	Plausibility is not clinical proof
Target–pathway profile	Disease heterogeneity	Expression, accessibility, pathway dependence	**Proposed contextual concordance**	Tests biological transportability	Disease-specific evidence [14]	Shared target but different pathway	No universal threshold
Exposure–regimen bridge	Cross-regimen transport	PK, route, dose, interval, covariates	**Proposed exposure bridge**	Bounds regimen inference	Sensitive PK [17]	Tissue-exposure mismatch	PK does not validate every regimen
Population–immunogenicity modifier	Variable immune response	Disease, therapy, exposure, assays	**Proposed confidence modifier**	Identifies evidence gaps	Integrated immune evidence [18]	Rare events or assay limitations	No individual prediction
Residual uncertainty register	Hidden assumptions	Source, consequence, scope, evidence need	**Original explicit register**	Supports revision	Decision-relevant evidence [10]	Omitted uncertainty	Not a numerical score
Decision and monitoring layer	Binary or static conclusions	Coherence, discordance, traceability, surveillance	**Proposed bounded states and updating**	Links evidence to scope	Fit-for-purpose evidence [19]	False coherence or poor traceability	Not approval or prescribing advice

Pharmacokinetics, biodistribution, and dosing considerations

Comparative pharmacokinetics is often among the most sensitive clinical components of biosimilar development because systemic exposure can reveal product-related differences without the variability introduced by disease progression or subjective endpoints. A three-arm comparison of ABP 501 and reference adalimumab in healthy subjects illustrates how a sensitive population can support comparative exposure assessment [17]. The same design, however, does not directly represent patients with inflammatory disease, altered protein turnover, concomitant therapy, or target-mediated disposition.

The framework therefore treats pharmacokinetic similarity as the basis of an exposure bridge rather than as a universal surrogate for clinical similarity. Route, formulation, dose, interval, absorption kinetics, target concentration, and treatment duration can change exposure relationships. Comparison of subcutaneous and intravenous CT-P13 in rheumatoid arthritis demonstrates that changes in route and regimen create distinct pharmacokinetic and administration contexts requiring direct characterization [20].

Modeling and simulation may integrate population covariates, dosing schedules, target-mediated disposition, and exposure–response relationships when direct studies cannot represent every setting [21]. Their value depends on model structure, parameter identifiability, data quality, calibration, sensitivity analysis, and external evaluation. A modeled bridge is therefore inferential rather than observed confirmation of equal tissue distribution or therapeutic outcome.

Biodistribution introduces a further boundary because serum concentration may not represent local exposure at the therapeutic site. The framework requires an explicit statement about whether systemic PK is an adequate proxy for the clinically relevant compartment and whether receptor-mediated uptake, tissue permeability, disease

anatomy, or local target burden could alter the inference. Where these mechanisms are poorly characterized, uncertainty should remain visible.

Immunogenicity and population-specific uncertainty

Immunogenicity is not a fixed product property expressed uniformly across patients. It emerges through interactions among molecular attributes, aggregates or impurities, route, dose, treatment duration, disease state, immune competence, background therapy, prior exposure, assay sensitivity, and sampling strategy. The NOR-SWITCH trial provided multi-indication evidence concerning a switch from reference infliximab to CT-P13 and informed aggregate evaluation of efficacy, safety, and immunogenicity [22]. It was not designed to establish certainty for every disease subgroup or individual patient.

Broader switching evidence has generally not shown a consistent aggregate loss of efficacy or a new safety signal attributable to switching from a reference medicine to a biosimilar. Interpretation remains limited by heterogeneous populations, switch protocols, follow-up periods, assays, and outcome definitions [23]. Reassuring aggregate evidence must therefore be distinguished from proof that every switch sequence or treatment context carries identical uncertainty.

Regulatory evaluation of biosimilar monoclonal antibodies and fusion proteins similarly indicates that immunogenicity and interchangeability questions require integrated consideration of product, patient, treatment, and assay evidence [18]. Across randomized switching evidence, systematic clinical synthesis, and regulatory evaluation, no consistent new safety or immunogenicity signal has been identified at the aggregate level, although study heterogeneity and context-specific uncertainty remain [18, 22, 23].

The proposed population and immunogenicity modifier documents disease-related immune activation, background therapy, prior biologic exposure, route, interval, duration, and anti-drug-antibody assay performance. It does not generate an individual risk score. It identifies whether population differences are likely to leave the comparative conclusion unchanged, require a qualified assumption, or create a discrete evidence gap.

Evidence integration and extrapolation decision rules

Evidence integration requires more than assembling favorable analytical, functional, pharmacokinetic, and clinical findings. Each finding must be weighted according to sensitivity, mechanistic relevance, reproducibility, and fitness for the precise question. Evidentiary principles developed for pharmacodynamic biomarkers show that a measurement is informative only when its context of use and relationship to biological activity are adequately justified [19].

The type and extent of clinical evidence supporting biosimilar approvals have varied according to product characteristics, available comparative methods, and the questions remaining after quality and pharmacokinetic assessment [24]. This variation supports a purpose-sensitive approach rather than a single minimal package for every biologic. Historical approval patterns provide context but are not automatic precedents for a different molecule, route, mechanism, or indication.

Evidence coherence must be distinguished from superficial uniformity. Switching studies may point in a reassuring direction while differing substantially in design, follow-up, immune-response assessment, and clinical context [25]. The framework defines coherence as the absence of an unexplained contradiction among evidence sources that are sufficiently sensitive and relevant to the same comparative question.

The proposed rules produce three bounded states. Conditionally supported extrapolation applies when evidence is coherent and remaining uncertainty is unlikely to alter the comparative conclusion within the specified indication, population, and regimen. Targeted additional evidence required applies when a discrete uncertainty could change the inference and can be tested sensitively. Unsupported under current evidence applies when material discordance, uncharacterized mechanism, inadequate exposure bridging, or unresolved safety concern prevents a defensible inference.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for mechanism-based extrapolation across biosimilar indications, patient populations.

Table 2. Testable propositions, evidence requirements, and validation criteria for Mechanism-Based Extrapolation across Biosimilar Indications, Patient Populations

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
Product evidence	Establish relevant similarity	CQA, function, and PK evidence enter mechanism layer	Supplies empirical foundation	Orthogonal assays detect relevant differences [11]	Insensitive assays	Analytical scientists and reviewers	No progression with unexplained relevant differences
Mechanism concordance	Preserve relevant activities	Functional evidence mapped by indication	Links product to disease context	Reproducible mechanism map	Target identity mistaken for equivalence	Pharmacologists and disease experts	Conceptual until operationally tested
Target–pathway context	Test disease transportability	Expression and pathway evidence enter uncertainty register	Modifies mechanism confidence	Disease-specific justification	Target presence treated as causation	Translational and clinical experts	No universal cutoff
Exposure bridge	Test regimen transport	PK, PK/PD, route, dose, and covariates	Modifies clinical transportability	Calibrated and externally evaluated models [21]	Serum PK treated as tissue exposure	Clinical pharmacologists and modelers	Model output remains inferential
Population–immunogenicity	Test contextual immune uncertainty	Patient, treatment, exposure, and assay data	Interacts with switching and monitoring	Reproducible prospective classification [18]	Rare events or assay interference	Immunologists, clinicians, and statisticians	No individual or universal guarantee
Uncertainty register	Make assumptions explicit	Source, consequence, scope, and resolution	Integrates upstream layers	Consistent independent classification	Omission or double counting	Multidisciplinary assessment team	No automatic score
Decision state	Produce bounded conclusion	Coherent or discordant evidence produces one state	Determines scope or targeted evidence	Transparent case-based reproducibility [19]	False assurance or excessive testing	Assessors justify evidence weighting	Not approval or treatment advice
Post-authorization update	Reassess emerging evidence	Traceable outcomes and safety data	Extends prior assessment	Product-identifiable data and procedures [26]	Confounding or under-reporting	Shared surveillance responsibility	No signal is not retrospective proof

Clinical communication and post-authorization monitoring

A scientifically defensible extrapolation argument may still fail in practice when clinicians and patients do not understand how biosimilar evidence is generated. Stakeholder research indicates that understanding of comparative development affects confidence, acceptance, and interpretation of indication extrapolation [27]. Communication should therefore distinguish directly observed biosimilar evidence, inherited reference-product knowledge, mechanistic inference, and residual uncertainty.

Implementation also requires governance. Traceability, coordinated switching processes, documentation of the dispensed product, shared responsibilities, and access to balanced information influence whether clinical outcomes can be interpreted appropriately [28]. The framework therefore separates the scientific extrapolation conclusion from operational decisions to initiate, substitute, or switch treatment.

Post-authorization monitoring can update uncertainties that cannot be completely resolved before broad clinical use. Long-term real-world safety evidence can identify unexpected reporting patterns and contribute to continuing evaluation [26]. Sustained confidence in extrapolated use depends jointly on informed stakeholder communication, implementation safeguards, and traceable postauthorization safety evidence [26–28].

The proposed evidence-update pathway is forward-only. New analytical findings, manufacturing changes, pharmacovigilance signals, switching outcomes, or disease-specific observations are assessed for relevance to the

residual uncertainty register. A finding may leave the prior inference unchanged, strengthen confidence within its boundary, trigger targeted investigation, or justify narrowing the claim. Human scientific judgment remains necessary because surveillance cannot automatically separate product effects from confounding, disease variation, or contextual influences.

Limitations and unresolved questions

The first limitation concerns causal interpretation after switching or extrapolated use. Symptoms, discontinuation, and perceived loss of effect can arise through pharmacological differences, disease fluctuation, expectations, communication, healthcare-system processes, or combinations of these mechanisms. Nocebo effects are an important non-pharmacological consideration in switching from originator biologics to biosimilars [29]. Their existence does not justify dismissing patient-reported outcomes or attributing every unfavorable event to expectation.

A second limitation is the translation gap between scientific evidence and decision use. Prescribers may remain uncertain about analytical similarity, pharmacodynamic evidence, extrapolation, switching, or interchangeability even when the underlying regulatory reasoning is coherent [30]. The framework may improve transparency but cannot guarantee understanding, acceptance, or consistent implementation.

A third limitation is that tailored development retains important exceptions. Additional evidence may remain necessary when mechanisms are incompletely characterized, assays do not represent a relevant function, population heterogeneity cannot be bounded, or safety and immunogenicity concerns remain unresolved [31]. The framework does not specify universal weights, thresholds, readiness levels, or acceptable residual-risk values.

Future research should operationalize each construct and test inter-rater reproducibility. Evaluation should include retrospective case reconstruction, prospective protocol design, deliberately discordant analytical scenarios, model-based sensitivity analysis, disease-specific mechanism review, and assessment of how the framework changes evidence selection. Until such work is completed, the framework remains explanatory and hypothesis-generating rather than an operational standard.

CONCLUSION

Mechanism-based indication extrapolation requires more than confirmation that a biosimilar resembles its reference product or acts on the same nominal target. The proposed framework connects comparative analytical and functional evidence to indication-specific mechanisms, disease-pathway context, exposure and dosing-regimen bridging, population and immunogenicity modifiers, evidence coherence, and explicit residual uncertainty. Its central contribution is to make the inferential structure visible: what is demonstrated, what is transported from reference-product knowledge, what is mechanistically inferred, what remains uncertain, and what evidence could alter the conclusion. The three proposed decision states preserve the distinction between conditional scientific support, a need for targeted evidence, and an inference unsupported under the available evidence. Clinical communication, traceability, and post-authorization monitoring extend the architecture into practice without converting it into a clinical recommendation or regulatory determination. Empirical operationalization and validation remain necessary before formal use.

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