



Review Article

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Real-World Evidence for Biosimilar Interchangeability Across Therapeutic Areas

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ABSTRACT

Biosimilar switching has moved from an isolated clinical question to a recurring feature of biologic treatment. The evidence base now includes randomized switching trials, prospective and retrospective real-world cohorts, systematic reviews, and experience with multiple and biosimilar-to-biosimilar switches. However, “interchangeability” is not a uniform clinical or regulatory construct, and apparently concordant findings can conceal substantial differences in product, disease, switching sequence, immunogenicity assessment, persistence, and implementation context. To evaluate how real-world evidence contributes to judgments about biosimilar interchangeability across therapeutic areas and to identify where evidence can be transferred, where it must remain product- or context-specific, and where uncertainty persists. An umbrella-review framework was used to integrate systematic-review evidence with selected methodological, randomized, analytical, and real-world studies required to interpret switching effectiveness, safety, immunogenicity, persistence, multiple switching, and therapeutic-area variation. Review quality, primary-study overlap, differences in endpoint definitions, and the distinction between analytical, pharmacological, clinical, and implementation evidence were treated as separate dimensions of interpretation. Across therapeutic areas, the assembled evidence is broadly reassuring for appropriately evaluated switches between reference biologics and biosimilars. Controlled studies provide particularly strong support for specified switching schedules, whereas real-world studies add information on persistence, treatment discontinuation, patient experience, mandatory switching, and repeated transitions. Confidence decreases when evidence is transferred between products, switching sequences, indications, assay systems, or health-system contexts that were not directly studied. Real-world evidence strengthens the clinical evidence base for biosimilar switching but does not make interchangeability a context-free property. A defensible interpretation requires convergence across product similarity, clinical effectiveness, safety, immunogenicity, switching sequence, and therapeutic setting while retaining explicit uncertainty when these layers do not align.

Keywords: Biosimilars, Interchangeability, Real-world evidence, Switching, Immunogenicity, Treatment persistence

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INTRODUCTION

Biosimilarity establishes that a biological product is highly similar to its reference product without clinically meaningful differences under the evidentiary framework applicable to its approval, but interchangeability introduces an additional question: whether products can be exchanged in clinical practice under specified

conditions without an unacceptable change in outcome. Regulatory terminology is not globally uniform. European practice has historically separated scientific conclusions concerning switching from national decisions concerning substitution, whereas other jurisdictions have developed specific interchangeability designations or evidentiary pathways [1].

The clinical literature has progressively reduced uncertainty about a single reference-to-biosimilar switch. An early systematic assessment found that available switching studies were predominantly reassuring while identifying limitations in sample size, follow-up, and study design [2]. A broader review spanning multiple biological products similarly found little evidence that switching itself consistently produced loss of efficacy, new safety problems, or increased immunogenicity, although individual studies reported discontinuation or perceived loss of effect [3]. Subsequent synthesis across a substantially larger switching literature reinforced the overall safety and effectiveness signal while also showing that open-label and routine-practice outcomes can diverge from blinded trial experience [4].

The evidentiary problem has nevertheless changed. Routine practice increasingly involves movement not only from a reference product to its biosimilar but also between biosimilars. That distinction matters because biosimilar-to-biosimilar switching is not simply a repetition of the reference-to-biosimilar comparison from which each product obtained approval [5]. Systematic evidence on such cross-switching has been reassuring but has been dominated by observational studies, particularly for infliximab, with substantially thinner evidence for some other molecules [6]. The expansion of biosimilars also creates health-system and patient consequences extending beyond acquisition cost, including treatment access, service organization, patient education, and continuity of care [7].

The central problem is therefore no longer whether switching has ever been studied. It is how evidence generated under different biological products, indications, switching sequences, methodological designs, and implementation conditions should be combined without erasing the boundaries that give each observation meaning. This umbrella review addresses that problem by separating evidence convergence from evidence transferability. The working proposition is that interchangeability in real-world interpretation is strongest when multiple evidence layers converge and weakest when apparently reassuring findings require untested transfer across products, populations, switching schedules, or clinical contexts.

MATERIALS AND METHODS

The review was structured as an umbrella synthesis focused on real-world and clinically applicable evidence concerning biosimilar interchangeability and switching. Reporting logic followed principles of transparent systematic-review reporting described in PRISMA 2020 [8]. Because the present synthesis incorporates reviews with heterogeneous aims and designs, methodological quality was evaluated as a property of the evidence source rather than converted into a numerical surrogate for biological or clinical certainty.

Eligible review evidence was organized around six outcome domains: switching effectiveness, safety, immunogenicity, persistence and discontinuation, multiple switching, and therapeutic-area differences. Methodological sources and selected primary studies were retained when they were needed to resolve an inference that review-level evidence alone could not establish, such as the interpretation of repeated switching, analytical immunogenicity signals, or product-specific trial designs.

No quantitative pooled effect was generated for the umbrella review itself. Findings were instead reconciled by product, therapeutic area, direction and number of switches, study design, outcome definition, and evidentiary level. Clinical outcomes were kept analytically separate from product-quality evidence, immunogenicity assay results, patient-reported experience, regulatory designation, and health-system outcomes.

Review eligibility

Eligible evidence had to address switching or interchangeability involving an approved or proposed biosimilar, or address a methodological issue necessary for interpreting such evidence. Systematic reviews and evidence syntheses formed the principal umbrella-review layer. Randomized trials, prospective or retrospective real-world cohorts, analytical studies, and regulatory or methodological analyses were used selectively where they supplied information not recoverable from higher-level reviews.

Studies were not treated as interchangeable evidence merely because they concerned the same molecule. Reference-to-biosimilar switching, repeated alternating switches, and biosimilar-to-biosimilar transitions were coded as different switching states. Similarly, inflammatory bowel disease, rheumatological disease, psoriasis,

oncology, and other therapeutic contexts were retained separately when disease course, co-treatment, outcome definitions, immunogenicity consequences, or treatment persistence could modify interpretation. Evidence concerning cost, policy, or patient perception was eligible for contextual interpretation but was not used as proof of pharmacological or clinical interchangeability. Analytical similarity was likewise treated as one component of the totality of evidence rather than a substitute for switch-specific clinical evidence.

Search strategy

Search logic combined terms corresponding to *biosimilar*, *interchangeability*, *switching*, *transition*, *multiple switching*, *biosimilar-to-biosimilar*, *real-world evidence*, *effectiveness*, *safety*, *immunogenicity*, *persistence*, and major therapeutic contexts represented in the evidence base. Methodological searches separately targeted umbrella-review conduct, review quality, primary-study overlap, and evidence harmonization.

The available source set did not contain a reproducible database-export ledger sufficient to reconstruct exact database-level retrieval, deduplication, title/abstract exclusion, or full-text exclusion arithmetic. Accordingly, such numbers are not reverse-engineered from the final evidence set and are not reported as though they represented a prospective search-flow count. The synthesis instead limits quantitative statements to numbers reported directly by the included publications themselves.

Review quality appraisal

Review quality was evaluated domain by domain using the methodological principles embodied in AMSTAR 2, including adequacy of search methods, study selection, risk-of-bias assessment, synthesis methods, consideration of heterogeneity, and interpretation of limitations [9]. The purpose was not to generate a single score. A review with a broad search but substantial primary-study overlap, for example, answers a different evidentiary question from a narrower review containing more recent controlled switching data.

Umbrella-review methodology also requires attention to the design diversity of the reviews themselves. Methodological examination of published overviews has shown substantial variation in their aims, eligibility rules, synthesis methods, and handling of overlap [10]. Consequently, review conclusions were interpreted according to the evidence architecture that produced them rather than counted as independent votes for or against interchangeability.

Overlap assessment

Primary-study overlap is particularly important in biosimilar switching because a relatively influential randomized trial or large real-world cohort may appear repeatedly across systematic reviews. Treating each review as an independent replication would therefore inflate the apparent volume of evidence. Corrected covered area and related overlap approaches provide a structured means of identifying this problem, but overlap measures describe duplication rather than methodological quality or clinical validity [11].

Overlap was therefore interpreted at the level of the comparison being made. Repeated inclusion of the same reference-to-biosimilar trial increases synthesis redundancy but does not create additional switching observations. Conversely, an updated review that contains genuinely new biosimilar-to-biosimilar or multiple-switch cohorts can enlarge the evidence base even when it retains older studies.

The clinically important question is what duplicated evidence is being asked to support. Reuse of the same primary study is especially consequential when a review-level conclusion is subsequently transferred to a different therapeutic area, switching sequence, or immunogenicity interpretation.

The principal overlap failure modes and their consequences are summarized in **Table 1**.

Table 1. Failure modes that can make overlapping biosimilar-switch reviews appear more independent than they are

Comparison anchor distorted Immunogenicity relevance	Clinical linkage test Residual interpretation
Overlap failure mode Repeated inclusion of the same pivotal switch trial	

Comparison anchor distorted Evidence volume appears larger without adding patients or switch events	Clinical linkage test Determine whether apparently separate reviews depend on the same trial population
Immunogenicity relevance The same antibody observations may be counted repeatedly	Residual interpretation Concordance is real, but independence of evidence is overstated
Overlap failure mode Trial and extension publication treated as separate populations	
Comparison anchor distorted Follow-up phases can resemble independent comparisons	Clinical linkage test Link publications by original cohort and treatment sequence
Immunogenicity relevance Longer antibody follow-up may be mistaken for replication	Residual interpretation Longer observation adds time, not a new baseline population
Overlap failure mode Multiple reviews dominated by one molecule or disease	
Comparison anchor distorted Breadth of review titles exceeds breadth of underlying evidence	Clinical linkage test Map primary studies by molecule and therapeutic area
Immunogenicity relevance Product-specific immunogenicity experience may dominate the synthesis	Residual interpretation Transfer to underrepresented products remains uncertain
Overlap failure mode Updated review retaining most earlier studies	
Comparison anchor distorted Recency can be mistaken for an entirely new evidence base	Clinical linkage test Separate newly added primary studies from retained legacy evidence
Immunogenicity relevance New assay or antibody observations may be sparse	Residual interpretation Update value depends on the genuinely incremental evidence
Overlap failure mode Broad switching review combined with a narrow disease review	
Comparison anchor distorted The same patients contribute to both general and specialty conclusions	Clinical linkage test Trace shared cohorts before interpreting cross-review agreement
Immunogenicity relevance Disease-specific immunogenicity context may be obscured	Residual interpretation Therapeutic-area confidence must reflect independent disease evidence

Evidence harmonization

Harmonization required more than converting differently labelled outcomes into common headings. The underlying constructs themselves often differ. Clinical remission, disease activity, persistence, treatment discontinuation, adverse events, anti-drug antibodies, pharmacokinetic similarity, and patient satisfaction each occupy a different evidentiary layer. A finding in one layer cannot automatically be substituted for another.

The synthesis therefore used a hierarchy of interpretive separation. First, the switching sequence was retained: a single reference-to-biosimilar transition was not pooled conceptually with repeated alternation or biosimilar-to-biosimilar switching. Second, product and therapeutic-area identity were preserved. Third, efficacy and objective disease-control outcomes were distinguished from persistence, because discontinuation can arise from perceived lack of effect, device preference, administrative policy, availability, or patient expectation as well as pharmacological failure.

Immunogenicity required an additional boundary. Assay positivity is not synonymous with clinically meaningful immune-mediated loss of response. Differences in assay sensitivity, sampling schedules, confirmatory procedures, neutralizing-antibody assessment, baseline antibody status, and drug interference can alter apparent immunogenicity without establishing a clinical difference. Analytical product similarity and clinical switching evidence were therefore treated as connected but non-substitutable components.

Table 2 identifies the main situations in which harmonization could otherwise produce an apparently coherent but scientifically misleading synthesis.

Table 2. Evidence-harmonization failures that can distort interpretation of biosimilar switching

Discordant evidence state	Evidence structure	Discordant evidence state	Decision structure
Different disease-activity measures reported as equivalent effectiveness	Harmonization basis requiring protection Therapeutic-area-specific outcome definition	Treatment persistence treated as efficacy	Harmonization basis requiring protection Reason for discontinuation and switching policy
	Observable signal Similar direction of change measured on non-equivalent scales		Observable signal Higher or lower discontinuation without parallel objective disease worsening
	Functional or clinical relevance May support within-disease stability but not direct cross-disease effect comparison		Functional or clinical relevance May reflect implementation, expectation, device, or access effects
	Resolution endpoint Retain disease-specific interpretation		Resolution endpoint Separate pharmacological failure from treatment attrition
Anti-drug antibody positivity treated as clinical immunogenicity	Harmonization basis requiring protection Assay platform, timing, titre and neutralizing relevance	Single and repeated switching combined	Harmonization basis requiring protection Number, direction and interval of transitions
	Observable signal Different antibody frequencies across methods		Observable signal Similar endpoint averages despite different exposure sequences
	Functional or clinical relevance Clinical importance depends on exposure, neutralization and outcome linkage		Functional or clinical relevance Reassuring single-switch evidence does not establish repeated-switch performance
	Resolution endpoint Require assay-aware clinical interpretation		Resolution endpoint Preserve switching sequence
Mandatory and voluntary switches pooled	Harmonization basis requiring protection Decision context and patient communication	Analytical biosimilarity treated as switch outcome evidence	Harmonization basis requiring protection Product-quality versus clinical evidence layer
	Observable signal Similar disease control with different discontinuation experience		Observable signal Highly similar quality attributes without direct switching observation
	Functional or clinical relevance Implementation context can influence persistence independently of pharmacology		Functional or clinical relevance Supports biosimilarity foundation but not every interchangeability scenario
	Resolution endpoint Retain policy and patient-context boundary		Resolution endpoint Require convergence with switch-specific evidence

The distinction between evidence selection and evidence harmonization is shown in **Figure 1**.

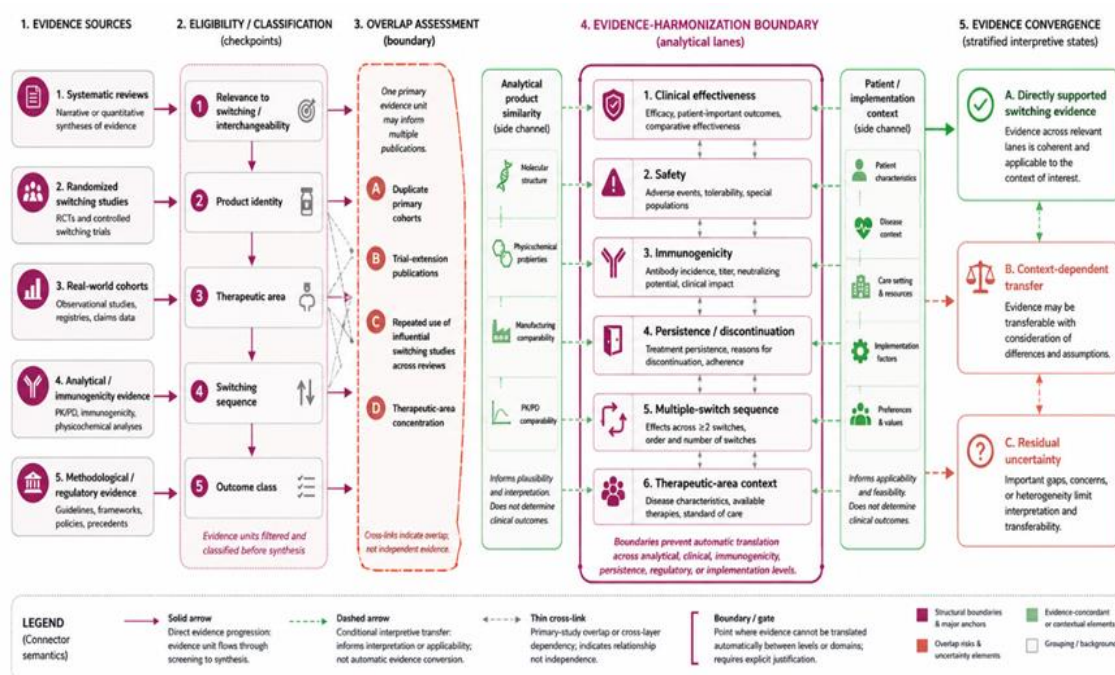


Figure 1. Source-resolved evidence selection and harmonization boundaries for biosimilar switching

RESULTS AND DISCUSSION

Across the assembled literature, evidence was directionally consistent in one central respect: a switch from an originator biologic to an appropriately evaluated biosimilar has generally not produced systematic deterioration in measured effectiveness, safety, or immunogenicity. The strength of that inference, however, varies according to the switching design.

Controlled studies are particularly valuable for distinguishing a pharmacological switch effect from background disease variability and expectation-related effects. Real-world studies add a different type of information. They capture persistence, discontinuation, repeated switching, mandated transitions, treatment-device experience, and routine clinical populations that are incompletely represented in registration programs. Their greater external relevance is accompanied by greater susceptibility to confounding, non-random treatment selection, secular changes, and heterogeneous outcome definitions.

The evidence therefore did not support reducing interchangeability to one pooled clinical outcome. Instead, the synthesis identified convergence when product-specific controlled switching evidence, routine-practice effectiveness, safety, immunogenicity, and persistence pointed in the same direction. Confidence was more conditional where conclusions depended on transferring results across diseases, switching sequences, products, or assay systems.

Switching effectiveness

The NOR-SWITCH trial remains an important controlled test of originator-to-biosimilar switching. Across its pooled disease population, switching from reference infliximab to CT-P13 satisfied the prespecified non-inferiority framework, but the study was not powered to establish non-inferiority separately within each included disease [12]. That distinction is essential: a successful multispecialty trial can support the general plausibility of switching without eliminating disease-specific uncertainty.

Repeated switching has also been examined in controlled settings. In plaque psoriasis, repeated transitions between reference adalimumab and GP2017 did not produce a clinically meaningful deterioration in the principal efficacy, safety, or immunogenicity outcomes evaluated in the trial [13]. Such data strengthen confidence in the studied product and switching schedule, but they do not establish a class-wide property of all adalimumab biosimilars.

Evidence syntheses examining non-medical switching similarly concluded that most studies were reassuring while emphasizing substantial variation in design quality, follow-up, discontinuation, and susceptibility to expectation and implementation effects [14]. Infliximab-specific review evidence has likewise supported

maintenance of effectiveness after a reference-to-biosimilar switch while documenting the predominance of observational designs in parts of the literature [15].

Adalimumab evidence extends across several immune-mediated diseases. A systematic review encompassing rheumatoid arthritis, psoriasis, and inflammatory bowel disease found broadly comparable effectiveness and safety after switching from reference adalimumab to biosimilars, but the evidentiary density differed by indication and could not justify direct extrapolation to every disease in which adalimumab is used [16].

Taken together, these data support a bounded conclusion. Effectiveness after switching is generally maintained in studied settings, and consistent findings across randomized and real-world designs increase confidence. What they establish is performance under defined products, populations, treatment histories, and outcome measurements—not an unrestricted rule that any biosimilar switch in any clinical context must behave identically.

Safety

Safety findings are similarly reassuring, but switching sequence and evidence design remain relevant. Prospective real-world follow-up of successive infliximab biosimilar switches in inflammatory bowel disease did not identify a clear safety penalty attributable to the number of transitions, although observational design prevents the same causal interpretation available from randomization [17].

Controlled multi-switch evidence for adalimumab provides complementary information. In rheumatoid arthritis, repeated switching between PF-06410293 and reference adalimumab produced pharmacokinetic exposure within the study's predefined equivalence framework and did not reveal a meaningful difference in evaluated safety outcomes [18]. Real-world inflammatory bowel disease data after switching from originator adalimumab likewise did not demonstrate an excess of treatment failure attributable to the switch itself [19].

Repeated infliximab transitions have also been examined in routine care. A prospective inflammatory bowel disease cohort found that multiple biosimilar switches were compatible with maintained treatment persistence and clinical or biochemical control during follow-up [20]. Contemporary infliximab synthesis has remained broadly consistent with these findings while emphasizing that evidence quality and switching definitions vary substantially between studies [21].

Recent adalimumab experience outside the United States further illustrates why safety cannot be separated entirely from implementation. The accumulated evidence is generally concordant with clinical trial findings, but device changes, patient education, communication, and local switching policies can influence the experience recorded after a transition [22].

Product-specific interchangeability trials have expanded this controlled evidence. Repeated switching between CT-P17 and reference adalimumab in plaque psoriasis demonstrated pharmacokinetic equivalence under the prespecified study design with similar evaluated efficacy, safety, and immunogenicity profiles [23]. A separate randomized interchangeability study of adalimumab-fkjp likewise found comparable pharmacokinetic and clinical safety outcomes across the tested multiple-switch sequence [24]. These trials materially strengthen the evidence for their respective products but should not be interpreted as direct proof for untested biosimilar pairs. At a broader level, a systematic review and meta-analysis evaluating switching safety across multiple biologics found no material aggregate increase in deaths, serious adverse events, treatment discontinuation due to adverse events, or immunogenicity among switched participants compared with non-switched controls [25]. The appropriate interpretation is reassuring rather than absolute. Aggregated null differences cannot exclude every rare, delayed, product-specific, or population-specific event, and surveillance remains necessary when biosimilars move into new patient populations, repeated-switch sequences, and treatment systems.

The safety evidence therefore supports a layered interpretation: absence of a reproducible switch-associated safety signal across several controlled and real-world settings increases confidence in switching, but that confidence remains tied to the product, sequence, population, observation period, and outcome ascertainment actually studied.

Immunogenicity

Immunogenicity is one of the most consequential yet easily overinterpreted components of interchangeability. A clinically meaningful concern would require more than detection of anti-drug antibodies after switching; the observed response must be interpreted in relation to baseline antibody status, assay characteristics, titres or persistence, neutralizing activity where measured, pharmacokinetic consequences, and relevant clinical

outcomes. Switching evidence therefore becomes strongest when immunogenicity findings remain concordant with exposure, efficacy, and safety rather than when antibody incidence is considered in isolation.

Randomized transition evidence with rituximab illustrates this distinction. In rheumatoid arthritis, transition from reference rituximab to DRL_RI produced low and broadly comparable measured anti-drug antibody incidence together with a similar safety profile under the conditions examined [26]. This finding is reassuring for the studied product and population, but it does not automatically establish the same immunogenicity behavior in oncology, in substantially different concomitant-treatment environments, or after untested repeated-switch sequences.

Analytical interpretation is equally important. Examination of signal-to-noise characteristics in adalimumab biosimilar studies has shown that the apparent frequency and interpretation of anti-drug antibody positivity can depend materially on assay behavior and analytical thresholds [27]. Consequently, numerical differences in antibody positivity should not be elevated directly to evidence of clinically meaningful immunogenicity without demonstrating their functional relevance.

The broader safety synthesis described earlier is consistent with this interpretation: switching has not generated a reproducible aggregate immunogenicity penalty across the studied evidence base. Nevertheless, absence of an aggregate signal is not evidence that every product, population, assay system, or switching sequence carries identical immune risk. The appropriate interchangeability inference is therefore conditional on concordance among analytical immunogenicity, pharmacokinetics where available, clinical effectiveness, and safety.

The principal immunogenicity evidence states are reconciled in **Table 3** so that assay signals, clinical consequences, and unresolved uncertainty are not collapsed into a single binary judgment.

Table 3. Immunogenicity evidence states that alter the interpretation of real-world biosimilar switching

Governing immunogenicity condition	Evidence layer creating the pattern	Comparability interpretation	Decision consequence	Discriminating evidence still required	Proposed synthesis consequence
Scientific anchor	Evidence layer creating the pattern	Comparability interpretation	Decision consequence	Discriminating evidence still required	Proposed synthesis consequence
Similar antibody findings with stable exposure and disease control	Analytical, pharmacokinetic and clinical evidence are concordant	Supports absence of a detectable switch-related immune penalty under studied conditions	Strengthens confidence in the evaluated switching sequence	Continued observation for uncommon or delayed events	Convergent immunogenicity evidence supports transfer only within the studied boundary
Different antibody positivity without clinical or exposure divergence	Assay signal differs while functional outcomes remain stable	Analytical discordance alone is insufficient to infer clinically meaningful immunogenicity	Avoid escalation based solely on antibody frequency	Assay characteristics, titre, persistence, neutralization and exposure linkage	Treat as unresolved analytical discordance rather than clinical failure
Antibody increase accompanied by lower exposure or loss of response	Immunogenicity and clinical or pharmacokinetic evidence align	Potentially clinically relevant immune response requires investigation	Weakens interchangeability confidence for the affected context	Temporal relationship, neutralizing activity and alternative causes of loss of response	Evidence convergence becomes adverse rather than merely analytically discordant
Stable antibodies but higher discontinuation after switching	Immunogenicity evidence and persistence diverge	Immunological mechanism is not established	Evaluate implementation and patient-context explanations separately	Objective disease activity, adverse events, patient experience and switching policy	Persistence should not be used as a surrogate for immune failure

Reassuring single-switch immunogenicity with untested repeated sequence	Evidence exists for one transition state only	Does not directly establish immune equivalence after additional transitions	Preserve switching-sequence uncertainty	Product-specific repeated-switch follow-up	Immunogenicity confidence cannot be automatically propagated across untested sequences
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This reconciliation suggests that immunogenicity should function as a convergence test rather than an isolated gate. **Figure 2** therefore places immune evidence between analytical product similarity and observed clinical performance while retaining explicit boundaries against unsupported transfer.

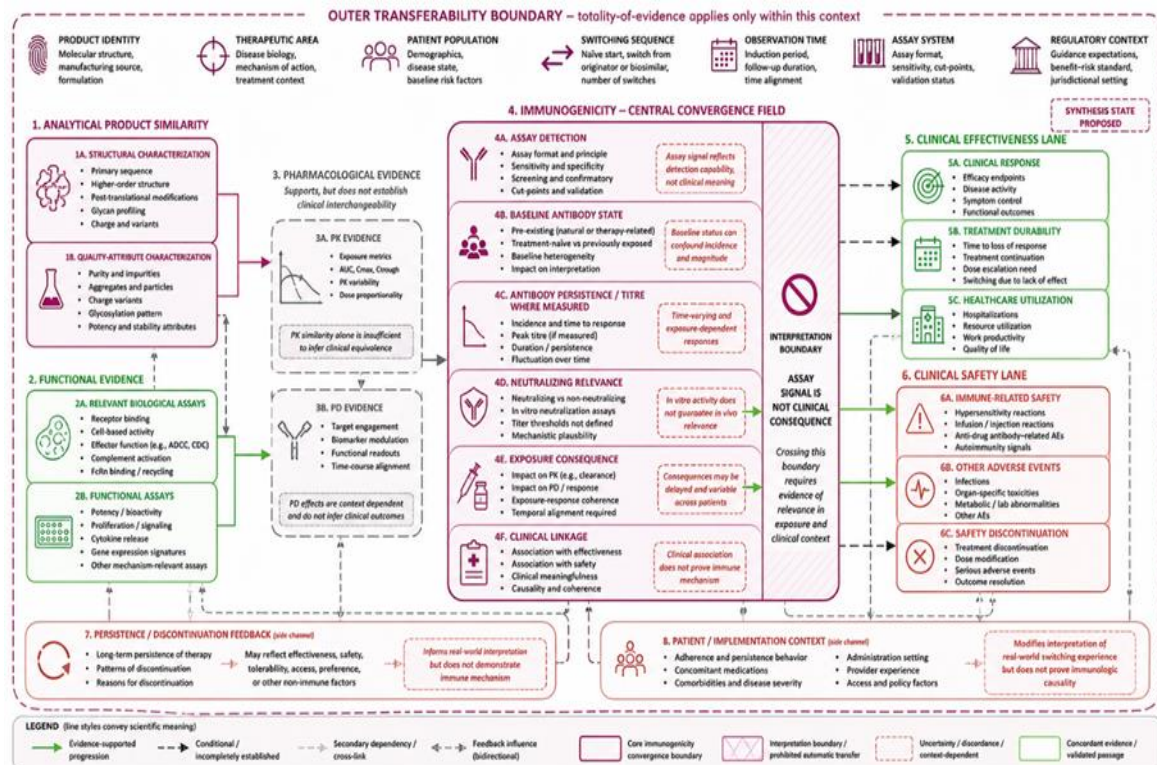


Figure 2. Immunogenicity as the convergence boundary between biosimilar similarity and real-world switching performance

Persistence and discontinuation

Persistence is valuable precisely because it captures phenomena that conventional efficacy endpoints may miss, but it is not a direct proxy for pharmacological interchangeability. Patient perceptions of biosimilars vary substantially across settings, with knowledge, confidence, prior communication, and expectations influencing acceptance of switching [28]. Such evidence makes implementation context clinically relevant without proving that expectation alone causes discontinuation.

Prospective experience after transition to CT-P17 likewise demonstrates that patient satisfaction and treatment experience can remain favorable after switching while also drawing attention to formulation, device, and communication factors that sit outside molecular biosimilarity itself [29]. A patient who discontinues after a switch may therefore represent pharmacological failure, adverse effects, disease fluctuation, device preference, concern about the biosimilar, administrative disruption, or another cause.

For interchangeability assessment, persistence is most informative when reasons for discontinuation are adjudicated alongside objective disease activity, adverse events, drug exposure where available, and immunogenicity. A rise in discontinuation without corresponding clinical or biological deterioration should not automatically be classified as loss of biosimilar effectiveness.

Multiple switching

Multiple switching requires a higher degree of inferential discipline because each additional transition creates a treatment history not necessarily represented by single-switch evidence. Controlled studies reviewed earlier

show that repeated alternation can be evaluated successfully for particular adalimumab products, while observational infliximab cohorts provide complementary experience with successive biosimilar transitions. The distinction from single switching remains important. In rheumatoid arthritis, systematic and network-level evidence supports broadly comparable efficacy and safety after switching among studied TNF-inhibitor reference and biosimilar products [30], but such findings cannot by themselves answer every repeated-switch question. Evidence should therefore be indexed to the actual sequence studied rather than to the molecule name alone.

The proposed synthesis is that evidence accumulates along a switching-sequence gradient: direct evidence for a specific repeated sequence carries greater inferential weight than reassurance borrowed from a single transition involving the same molecule. This does not imply that each additional switch is inherently hazardous; it means that interchangeability confidence should track the treatment sequence actually observed.

Therapeutic-area differences

Therapeutic-area transferability is one of the principal boundaries of real-world interchangeability evidence. Long-term observational experience following mandatory adalimumab switching in inflammatory bowel disease found persistence broadly comparable with originator treatment in the studied setting [31]. This strengthens the IBD evidence base but cannot eliminate residual differences created by disease phenotype, concomitant immunomodulation, prior biologic exposure, or local switching policy.

The importance of therapeutic context becomes still clearer outside immune-mediated inflammatory disease. Real-world comparative evidence for trastuzumab biosimilars in HER2-positive breast cancer has been broadly reassuring for measured effectiveness and safety outcomes [32]. However, such evidence concerns biosimilar use in oncology and does not constitute direct evidence for repeated switching or automatic substitution of trastuzumab products.

Accordingly, evidence transfer should depend on the relationship between product attributes, mechanism of action, clinical endpoint sensitivity, immunogenicity consequences, treatment sequence, and the population in which switching occurs. The resulting boundary conditions are summarized in **Table 4**.

Table 4. Therapeutic-area boundary conditions governing transfer of real-world biosimilar switching evidence

Therapeutic-area evidence case	Boundary	Interpretation and Decision
Scientific anchor	Boundary variable adjacent to interpretation	Product Functional relevance PK Interchangeability endpoint
Inflammatory disease with direct product-specific switch data	Disease activity, concomitant therapy and prior biologic exposure	Product or analytical consideration Same biosimilar and reference pair directly studied
		Functional relevance Clinical control can be assessed within the disease PK or PD consequence Exposure consequences may be interpreted when measured Interchangeability endpoint Strongest support is limited to the studied disease and sequence
Same molecule used across several immune-mediated diseases	Outcome definitions and disease-specific treatment pathways differ	Product or analytical consideration Product similarity is shared across indications
		Functional relevance Mechanism may support extrapolation, but clinical context remains distinct PK or PD consequence Comparable exposure does not erase disease-specific uncertainty Interchangeability endpoint Cross-disease transfer requires qualification

Oncology biosimilar use without repeated-switch evidence	Treatment intent, combination regimen and outcome time scale	Product or analytical consideration Analytical biosimilarity supports product comparability Functional relevance Clinical effectiveness may be reassuring without testing interchangeability directly PK or PD consequence PK similarity may support development evidence Interchangeability endpoint Do not reinterpret biosimilar-use evidence as repeated-switch evidence
Mandatory switch implemented through health-system policy	Communication, access and dispensing context	Product or analytical consideration Product attributes may be unchanged while implementation changes Functional relevance Persistence and patient experience can shift independently of pharmacology PK or PD consequence No PK consequence should be inferred without measurement Interchangeability endpoint Separate policy performance from molecular interchangeability
Evidence transferred to an unstudied product or switching sequence	Product identity and sequence are no longer directly represented	Product or analytical consideration Biosimilars share a reference product but are not identical copies of one another Functional relevance Functional similarity does not create direct cross-switch observation PK or PD consequence PK evidence is product- and study-specific Interchangeability endpoint Retain residual uncertainty rather than assuming class-wide interchangeability

The reviewed evidence supports switching as an increasingly well-characterized component of biosimilar use, but it does not support treating interchangeability as a context-free label. The most defensible inference arises when analytical similarity, appropriate pharmacological evidence, switch-specific clinical outcomes, safety, and immunogenicity converge. Real-world evidence then extends that foundation by testing whether performance remains acceptable under routine treatment histories and implementation conditions.

Health-system effects must remain a separate layer. Biosimilar availability has been associated with substantial changes in adalimumab expenditure across national settings [33], demonstrating the policy relevance of biosimilar adoption without establishing a clinical effect of switching itself. Professional and organizational recommendations on biosimilar switching and interchangeability also remain heterogeneous [34], showing that evidence interpretation is mediated by specialty practice and regulatory context.

Similarly, increasingly sophisticated analytical methods can strengthen evaluation of quality similarity. Glycosylation-oriented assessment of monoclonal-antibody biosimilars illustrates the depth of product-characterization evidence now available [35]. Yet analytical similarity cannot substitute for direct observation of every possible treatment transition. Global regulatory perspectives reinforce this boundary because the terminology and evidence attached to “interchangeability” are jurisdiction dependent [36].

The strongest recent extension of the evidence base concerns biosimilar-to-biosimilar switching. Updated synthesis has identified a substantially larger body of observational cross-switch experience without an evident new safety or effectiveness signal [37]. That accumulation is clinically reassuring, but its predominantly observational character remains relevant. The article therefore proposes a convergence-with-boundaries interpretation: real-world interchangeability confidence increases as independent evidence layers align, but transfer across products, diseases, switch sequences, assay systems, and jurisdictions must remain explicit rather than automatic.

Certainty and transferability of evidence

Certainty is highest for switch scenarios supported directly by controlled product-specific evidence and reinforced by concordant routine-practice observations. It is lower when evidence depends predominantly on uncontrolled persistence outcomes, cross-review repetition of the same primary studies, or extrapolation from one switch sequence to another.

Transferability should therefore be assessed across several independent boundaries. Product identity determines whether the actual biologicals under consideration were studied. Therapeutic area determines whether disease behavior, concomitant therapy, endpoint sensitivity, and immunogenicity consequences are comparable. Switching sequence determines whether evidence concerns a single transition, repeated alternation, or biosimilar-to-biosimilar movement. Finally, regulatory context determines what practical consequence can legitimately be attached to the word interchangeability.

These boundaries do not negate the generally reassuring evidence. They specify the conditions under which that reassurance is scientifically defensible.

Limitations

This umbrella review is limited first by heterogeneity in the underlying literature. Switching definitions, follow-up durations, outcome instruments, reasons for discontinuation, immunogenicity assays, and patient populations are not uniform. Primary-study overlap across reviews can also exaggerate the apparent independence of evidence.

Second, the evidence remains concentrated in selected molecules, particularly TNF inhibitors, and in immune-mediated inflammatory diseases. The volume and maturity of real-world evidence should therefore not be assumed to be equivalent across biologic classes or therapeutic areas.

Third, multiple-switch and biosimilar-to-biosimilar evidence has expanded but remains more observational than the evidence for selected single or controlled repeated-switch scenarios. Residual confounding, policy-driven treatment assignment, secular effects, and patient expectations can influence persistence and discontinuation.

Finally, exact database-level retrieval, deduplication, and screening arithmetic could not be reconstructed reproducibly from the available source materials and therefore was not fabricated. Future umbrella evaluations would benefit from prospectively preserved search exports, explicit overlap matrices, standardized switching-sequence terminology, assay-aware immunogenicity reporting, and longer product-specific follow-up across underrepresented therapeutic areas.

CONCLUSION

Real-world evidence has moved biosimilar switching beyond the question of whether a transition can be clinically acceptable. Across studied products and therapeutic areas, controlled and observational evidence is predominantly reassuring for effectiveness, safety, and immunogenicity, while routine-practice studies add essential information on persistence, repeated transitions, patient experience, and implementation.

The remaining challenge is interpretive rather than simply quantitative. Single switching, repeated switching, and biosimilar-to-biosimilar switching should remain distinct evidence states; analytical similarity, antibody detection, clinical effectiveness, persistence, and regulatory designation should not be treated as interchangeable forms of proof.

The proposed convergence-with-boundaries interpretation provides a disciplined way to use real-world evidence: confidence increases when independent evidence layers agree, but uncertainty should remain visible whenever conclusions require transfer across products, therapeutic areas, switching sequences, populations, assay systems, or regulatory settings. In this form, real-world evidence strengthens interchangeability assessment without converting biosimilarity into an unrestricted assumption of substitutability.

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