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PERSPECTIVES

Net Present Value Impact of FDA's Phase 3 Waivers on Monoclonal Antibody Biosimilar Development

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Background: The FDA's October 2025 guidance proposes waiving Phase 3 comparative efficacy studies for biosimilars when analytical and pharmacokinetic similarity are demonstrated.

Methods: We conducted a net present value (NPV) analysis comparing traditional biosimilar development pathways (with Phase 3 comparative efficacy studies) to streamlined pathways utilizing FDA's Phase 3 waiver framework. The model incorporates industry-benchmarked cost data (Phase 3 studies: $20–28M), development timelines (Phase 3 duration: 1–3 years). Economic outcomes were evaluated across three monoclonal antibody biosimilar programs representing high-, moderate-, and lower-complexity scenarios. Sensitivity analysis evaluated parameter variation across realistic ranges.

Results: Waiving Phase 3 studies reduces development costs by $25 million per program (18% reduction) and shortens timelines by 1.5 years (21% reduction). Risk-adjusted NPV improves by $25 million (29%), and minimum viable peak sales threshold decreases from $300 million to $250 million.

Conclusion: Phase 3 waivers can substantially reduce development costs (~$25M average), accelerate timelines (~1.5 years), and improve NPV (~25–29%) for well-characterized monoclonal antibody biosimilars meeting FDA's analytical similarity and pharmacokinetic equivalence criteria. Economic benefits are conditional on robust analytical data, regulatory approval of waiver requests, and appropriate product selection (Tier 1/2/3 classification). Real-world realization requires post-implementation surveillance of FDA approval patterns, achieved cost reductions, and timeline compression beginning 2026–2027.

Keywords: biosimilar NPV, antibody cost reduction, phase 3 waiver

On October 29, 2025, the US Food and Drug Administration (FDA) issued a draft guidance revising the agency's approach to biosimilar development.[1] The guidance proposes waiving comparative efficacy studies when comprehensive analytical characterization and pharmacokinetic similarity are demonstrated. This regulatory update reflects the agency's recognition that large phase 3 efficacy trials may not provide additional meaningful information when preceded by robust analytical and pharmacokinetic assessments and add substantial cost and time to development programs.

Understanding the Regulatory Shift

In April 2015, FDA released "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", establishing the regulatory framework for biosimilars under section 351(k) of the Public Health Service Act. This pathway was authorized by Congress in 2010 through the Biologics Price Competition and Innovation Act (BPCIA). The 2015 guidance established requirement for: comparative analytical studies, pharmacokinetic/pharmacodynamic studies, immunogenicity assessment, and Phase 3 comparative clinical efficacy studies. Phase 3 studies were expected to demonstrate that proposed biosimilar had equivalent clinical efficacy to reference product under specified conditions of use. In 2018, FDA released minor update to 2015 guidance acknowledging that sponsors could request Phase 3 waiver

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on case-by-case basis, but provided limited guidance on when waiver would be approved. This resulted in most sponsors still conducting Phase 3 to ensure regulatory predictability.

The FDA (in October 2025 guidance document) proposes that Phase 3 comparative efficacy studies may not be necessary when: (1) the proposed biosimilar demonstrates robust analytical similarity to the reference product, (2) human pharmacokinetic studies show equivalence, and (3) immunogenicity assessments are conducted appropriately. This is a significant departure from the 2015–2024 regulatory paradigm, which treated Phase 3 studies as standard requirement for most biosimilar development programs.

The FDA guidance does not eliminate clinical testing; rather, it recognizes that comparative efficacy studies—trials comparing clinical outcomes between biosimilars and reference products—may contribute limited additional value when preceded by robust analytical similarity and pharmacokinetic equivalence studies. Clinical pharmacokinetic studies and immunogenicity assessments remain required, but phase 3 efficacy trials, typically requiring 300–700 patients, can now be waived under appropriate circumstances.

Other regulatory authorities had already established more flexible approaches before FDA's October 2025 guidance. The European Medicines Agency permitted case-by-case flexibility on Phase 3 requirements beginning in 2018. Health Canada adopted a risk-based regulatory framework that allows consideration of Phase 3 waiver requests. The World Health Organization established the scientific rationale supporting an analytical-focused paradigm for biosimilar development. These international precedents provided important validation for FDA's policy shift toward Phase 3 waivers.

Despite growing regulatory acceptance of Phase 3 waivers, published quantitative economic evaluations are limited. By bridging regulatory science and development economics, this work enables evidence-based decision-making for biosimilar developers, investors, and policymakers regarding Phase 3 waiver adoption.

This distinction has economic implications. Phase 3 comparative efficacy studies typically cost $20–28 million and require 1–3 years to complete, representing a significant component of biosimilar development expenses.[1,2] In contrast, Phase 1 pharmacokinetic studies cost $9–13 million and can be completed in 6–12 months. Eliminating phase 3 trials while maintaining phase 1 studies preserves clinical safety data while addressing a development component that adds substantial time and cost.

Focus on Monoclonal Antibody Biosimilars

This analysis focuses specifically on monoclonal antibody (mAb) biosimilars for several important reasons. From a regulatory perspective, the FDA's October 2025 guidance explicitly addresses monoclonal antibodies first, as they have well-characterized mechanisms of action and established analytical methods supported by robust post-market safety and efficacy data from sixty approved mAb biosimilars. Economically, monoclonal antibodies represent approximately sixty percent of the current biosimilar development pipeline and target high-value therapeutic areas such as oncology and immunology, where reference product markets range from three to five billion dollars annually. These large market sizes enable multiple developers to pursue competing programs, making the economic impact of Phase 3 waivers most substantial in this product category. Regarding generalizability, the findings presented here apply strongly to other well-characterized biologics such as fusion proteins and hormone analogs. However, the results have limited applicability to novel biologic classes, locally-administered products, and drugs with unknown mechanisms of action. Gene therapies, cell and tissue products, and highly variable biologics fall outside the scope of this analysis and would require separate regulatory and economic assessment.

The Economic Burden of Comparative Efficacy Requirements

Biosimilar development requires substantial investment, typically $100–250 million over 6–8 years.[2] A net present value (NPV) analysis of monoclonal antibody biosimilar programs revealed that clinical development accounts for 57% of total costs, with phase 3 comparative efficacy studies representing a substantial portion of clinical expenses.[2] Waiving phase 3 efficacy studies could reduce development costs by $20–30 million/program and shorten development timelines by 1–3 years.[1] For comprehensive NPV methodology specification and parameter justification, see Ranbhor & Kulkarni (2025), which provides the analytical framework applied in this Perspective.

These cost reductions may influence market dynamics. Development programs with lower cost requirements enable broader participation in biosimilar development, potentially increasing market competition and affecting pricing.

The projected economic benefits ($25M cost savings, 1.5-year timeline reduction) are contingent on specific organizational and regulatory conditions. Real-world realization requires: (1) FDA approval of Phase 3 waiver requests based on robust analytical data quality, (2) sponsor analytical expertise and platform investment to support Phase 3-waived pathway, (3) manufacturing capability enabling accelerated timeline execution, and (4) financial flexibility to invest upfront in analytical/CMC development. Programs lacking these prerequisites may achieve reduced or zero benefits despite regulatory waiver availability. This manuscript projects average portfolio-level outcomes; individual program benefits will vary substantially based on product-specific circumstances and sponsor capabilities.

Scientific Foundation for Waiving Efficacy Studies

The FDA's revised approach is informed by evidence that analytical similarity coupled with pharmacokinetic equivalence can predict clinical efficacy. A review of biosimilar approvals revealed that biosimilars demonstrating robust analytical similarity and pharmacokinetic (PK) equivalence consistently meet comparative efficacy criteria.[3] This pattern suggests that comparative efficacy studies may serve a confirmatory rather than discriminatory role in biosimilarity assessment.

Modern analytical technologies can detect structural differences at 1–2% resolution, while clinical efficacy trials typically employ equivalence margins of 15–20%.[3] High-resolution mass spectrometry, hydrogen-deuterium exchange, and multidimensional nuclear magnetic resonance provide detailed molecular characterization. Cell-based potency assays demonstrate coefficients of variation below 5%, compared with 15–30% for clinical outcomes under inflammatory conditions.

Importantly, this scientific principle already governs manufacturing changes for originator biologics. Under International Council for Harmonisation Q5E guidelines, manufacturers implement substantial process modifications without clinical efficacy testing when analytical comparability is established. The FDA's acceptance of the idea that structurally comparable post-change biologics will perform clinically equivalently applies equally to biosimilars demonstrating high analytical similarity and PK equivalence.

Investment Implications and Market Impact

Sensitivity analyses from NPV modeling show how waiving comparative efficacy studies affects investment decisions (Table 1). Eliminating phase 3 efficacy requirements while maintaining phase 1 PK and immunogenicity studies improves risk-adjusted NPV by approximately $25 million/program while reducing development timelines by 1.5

Table 1 Impact of Waiving Comparative Efficacy Studies on Biosimilar Development Economics[a,c]

Parameter	with Phase 3 CESs	without Phase 3 CESs	Change, %
Total development cost	$140M	$115M	−18
Clinical development cost	$40M	$12M	−70
Development timeline	7 years	5.5 years	−21
Risk-Adjusted NPV	$85M	$110M	+29
Internal rate of return (%)	16.5	18.5	+2.0 pp
Minimum viable peak sales	$300M	$250M	−17[b]

Notes: [a]Based on monoclonal antibody biosimilar case study analysis.[1,2] [b]A lower minimum threshold enables more biosimilar programs to achieve economic viability. [c]Based on base case assumptions of 10% discount rate, 70% success probability, 25% market share, and 35% price discount—contingent on FDA waiver approval and sponsor analytical capability.

Abbreviations: CESs, comparative efficacy studies; NPV, net present value; pp, percentage points.

years. These improvements lower the minimum viable market size threshold from $300 million to $250 million in peak annual sales, potentially expanding the range of economically feasible biosimilar targets.

Market entry timing affects competitive position. Analysis shows that first-to-market biosimilars typically capture greater market share than later entrants do.[2] Accelerated timelines from waiving comparative efficacy studies may provide timing advantages. Earlier market entry by 12–18 months can improve competitive positioning through extended market presence before additional competitors enter.

Manufacturing optimization becomes more influential in development economics when clinical trial costs decrease. With phase 3 efficacy costs eliminated, process development and manufacturing efficiency represent a larger proportion of value creation. Companies with established analytical and manufacturing capabilities may have competitive advantages in this environment.

When Comparative Efficacy Studies Remain Necessary

The FDA guidance appropriately identifies scenarios where comparative efficacy data may still be required: biologics with unknown mechanisms of action, products with high intrinsic heterogeneity insufficiently characterized by current analytical methods, locally administered products where pharmacokinetic studies are not relevant, and products with known clinically significant safety or immunogenicity concerns.[4] These exceptions ensure that the streamlined pathway applies only when analytical and pharmacokinetic data provide sufficient evidence of biosimilarity.

Strategic Considerations

The FDA's updated approach affects strategic planning for biosimilar developers. Implications include earlier pipeline decisions, modified timing for commercial manufacturing commitments, and increased emphasis on analytical method development capabilities. For payers and health systems, streamlined biosimilar pathways may contribute to increased market competition, although actual price effects depend on multiple market factors.

The October 2025 guidance represents alignment between regulatory requirements and current analytical capabilities. By waiving phase 3 efficacy studies when comprehensive analytical characterization and pharmacokinetic equivalence are established while maintaining phase 1 clinical studies for safety and immunogenicity assessment, the FDA has revised the biosimilar development pathway. Based on published research showing that phase 3 comparative efficacy studies cost $20–28 million and require 1–3 years to complete, these changes may reduce development costs and timelines, potentially affecting the economics of biosimilar development and market entry decisions.

This analysis demonstrates that Phase 3 waivers expand the number of economically feasible biosimilar programs—enabling developers to pursue mid-market indications ($600M-2B reference products) previously deemed uneconomic. However, economic feasibility is distinct from healthcare impact. Whether accelerated biosimilar development translates to lower patient prices, improved access, or healthcare system cost savings depends on: (1) competitive intensity and biosimilar proliferation, (2) payer/prescriber adoption and utilization patterns, (3) pricing negotiation dynamics, and (4) broader healthcare policy context. Monitoring real-world pricing, market share, and utilization patterns (2026–2030) essential to assess whether Phase 3 waivers achieve intended patient access and cost management objectives.

Disclosure

The authors report no conflicts of interest in this work.

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