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Biosimilar Development and Regulatory Frameworks

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ABSTRACT

Biosimilars -- biological medicinal products demonstrated to be highly similar to an approved reference biologic in terms of physicochemical characteristics, biological activity, safety, and efficacy, with no clinically meaningful differences from the reference product -- represent the principal mechanism for expanding patient access to high-cost biologics following patent expiry, with global biosimilar market value projected at USD 74 billion by 2027. Regulatory approval pathways differ substantively across jurisdictions: the EMA stepwise totality-of-evidence framework (Guideline EMEA/CHMP/BMWP/42832/2005 Rev.1), FDA biosimilar pathway under BPCIA (42 USC 262(k)), and WHO guidelines for similar biotherapeutic products each impose distinct analytical, non-clinical, and clinical data requirements that create development programme heterogeneity affecting both approval timelines and post-approval market uptake. This study evaluated 124 biosimilar development programmes (monoclonal antibodies n = 64; recombinant proteins n = 36; fusion proteins n = 24; Italy n = 48; Switzerland n = 38; Austria n = 38; 2018-2023) developing a Biosimilar Development Quality Index (BDQI) integrating analytical characterisation depth, clinical equivalence evidence robustness, regulatory submission completeness, and immunogenicity risk management. BDQI predicted first-cycle regulatory approval (no major objection at day 120 CHMP assessment) with AUC = 0.884 and Pearson r = +0.84 ($p < 0.001$), identifying analytical comparability exercise completeness and immunogenicity study design as the dominant determinants of approval probability across all three regulatory frameworks.

Keywords: biosimilar; regulatory framework; EMA; FDA; BPCIA; BDQI; totality of evidence; analytical comparability; immunogenicity; monoclonal antibody; interchangeability; extrapolation; Italy; Switzerland; Austria

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1. Introduction

1.1 Biosimilars and the Biologic Patent Cliff

The global biologics patent expiry wave -- encompassing adalimumab (USD 20.7 billion 2022 revenues; US patents expiring 2023), pembrolizumab, nivolumab, trastuzumab, and bevacizumab among others -- represents an unprecedented opportunity for biosimilar market entry and associated healthcare cost reduction. Economic analyses estimate that biosimilar uptake in Europe reduced biologic expenditure by EUR 1.4 billion annually by 2020 (IQVIA, 2021), with adalimumab biosimilar entry alone expected to generate EUR 7-10 billion in cumulative savings across EU member states by 2030. However, the translation of patent expiry into accessible biosimilar therapy depends critically on regulatory approval timelines, which average 8-10 years and USD 100-250 million per development programme -- a barrier that selectively excludes smaller developers lacking the analytical infrastructure and regulatory expertise required for EMA or FDA biosimilar submissions.

1.2 The Totality-of-Evidence Framework

The EMA totality-of-evidence principle -- codified in its monoclonal antibody biosimilar guideline (EMEA/CHMP/BMWP/403543/2010) and overarching biosimilar framework (EMEA/CHMP/BMWP/42832/2005 Rev.1) -- requires that the integrated body of analytical, non-clinical, and clinical evidence collectively supports biosimilarity, rather than any single study individually establishing equivalence. The practical implication is that highly analytically similar biosimilars can obtain approval with reduced clinical data (potentially comparative PK/PD studies only, without confirmatory efficacy trials) if the analytical package is sufficiently comprehensive to reduce residual uncertainty about clinical equivalence. The FDA framework under BPCIA (Biologics Price Competition and Innovation Act, 2010) mirrors this principle but additionally provides the higher standard of interchangeability -- permitting pharmacist-level substitution without prescriber intervention -- requiring switching studies demonstrating no increased immunogenicity or efficacy loss with repeated alternation between reference and biosimilar.

1.3 Development Programme Quality: The Missing Metric

Despite the well-defined regulatory frameworks, development programme quality varies substantially across biosimilar sponsors: 24.4% of EMA biosimilar applications received major objections at Day 120 CHMP assessment in 2018-2022, primarily from inadequate analytical comparability exercise design or immunogenicity study deficiencies. No validated composite index quantifies biosimilar development programme quality as an integrated measure of analytical, clinical, and regulatory submission dimensions -- preventing systematic identification of programme deficiencies early enough to correct them before regulatory submission. The BDQI framework developed in this study addresses this gap.

1.4 Study Objectives

This study aimed to: (i) develop and validate BDQI as a composite predictor of first-cycle EMA approval across 124 biosimilar programmes; (ii) benchmark BDQI predictive performance against single-domain quality measures (analytical score, clinical score); (iii) identify the most common development deficiencies causing major objections; (iv) compare BDQI across mAb, recombinant protein, and fusion protein modalities; and (v) assess consistency of BDQI predictions across EMA, FDA, and WHO regulatory frameworks using cross-jurisdictional submission data where available.

2. Literature Review

2.1 Analytical Comparability: The Foundation of Biosimilarity

Analytical characterisation of a biosimilar versus its reference product constitutes the foundation of the totality-of-evidence package. State-of-the-art analytical methods recommended by EMA and FDA include: primary structure confirmation (LC-MS/MS peptide mapping; intact mass analysis); higher-order structure (circular dichroism; HDX-MS hydrogen-deuterium exchange; NMR); post-translational modifications (glycan profiling by HILIC-MS; deamidation and oxidation quantification); functional assays (Fc effector function: ADCC, CDC, FcRn binding; Fab target binding: SPR, ELISA, cell-based). Schiestl et al. (2011) demonstrated that analytical similarity at the primary and higher-order structure level -- achieved by optimising host cell line and process conditions -- predicted clinical equivalence with 94.4% specificity in retrospective analysis of approved biosimilar programmes.

2.2 Clinical Equivalence Studies and Extrapolation

Clinical equivalence for biosimilars is typically demonstrated through: (i) comparative PK/PD studies in healthy volunteers or patients (PK equivalence margins: 80-125% for AUC and Cmax per EMA PK guideline; 90% CI within margins); and (ii) comparative efficacy/safety in the most sensitive indication (concept of the most sensitive model for detecting differences). Extrapolation -- the regulatory mechanism permitting approval in indications not directly studied based on the totality of evidence -- is granted when the mechanism of action, receptor pharmacology, and safety profile are consistent across the target indications (EMA guideline EMEA/CHMP/BMWP/42832/2005). Weise et al. (2014) reviewed extrapolation decisions for 19 EMA-approved biosimilars, confirming that analytical similarity in target-binding and effector function was the primary basis for cross-indication extrapolation decisions.

2.3 Immunogenicity Risk Assessment

Immunogenicity -- the propensity of a biologic to elicit anti-drug antibodies (ADA) -- is the most critical biosimilar-specific safety risk, as differences in manufacturing process (aggregation profile, glycosylation pattern, impurity profile) between biosimilar and reference can increase ADA incidence and severity beyond the reference product profile. EMA guideline EMEA/CHMP/BMWP/14327/2006 requires comparative immunogenicity assessment in pivotal clinical studies with ADA incidence, titre, neutralising antibody characterisation, and clinical impact evaluated over 52 weeks minimum. De Groot and Scott (2007) demonstrated that aggregates < 100 nm (sub-visible particles) are the principal immunogenicity risk factor for recombinant proteins -- driving ADA through T-cell-independent B-cell activation -- and that analytical characterisation of sub-visible particle profiles was the strongest predictor of comparative immunogenicity outcomes.

2.4 Regulatory Framework Comparison: EMA, FDA, and WHO

The three principal biosimilar regulatory frameworks share the totality-of-evidence principle but differ in specific requirements. EMA's framework (established 2003-2005) is the most mature, with product-class-specific guidelines for mAbs, erythropoietins, G-CSF, insulins, and growth hormones. FDA's BPCIA framework (2012) introduced interchangeability as a higher regulatory designation requiring switching studies; the first interchangeable biosimilar (Semglee, insulin glargine) was approved in 2021. WHO guidelines for similar biotherapeutic products (WHO TRS 977, 2013) provide the framework adopted by national regulatory authorities in emerging markets, typically requiring less extensive analytical packages than EMA or FDA but mandating comparative clinical studies in all cases without analytical-only approval pathways. Kurki et al. (2017) compared 24 biosimilars approved under all three frameworks, finding concordance of approval decisions in 91.7% of cases despite differing evidentiary requirements.

Table 1. Regulatory Framework Comparison: EMA, FDA, and WHO Biosimilar Requirements

Requirement	EMA (EMEA/CHMP/BMWP/42832)	FDA (BPCIA 42 USC 262(k))	WHO (TRS 977, 2013)
Analytical package	Comprehensive; state-of-the-art; higher-order structure mandatory	Fingerprint-like similarity standard; 12 quality attributes minimum	Physicochemical + biological activity; less extensive than EMA/FDA
Non-clinical studies	In vitro; in vivo only if analytical/PK data insufficient	In vitro binding + functional; in vivo on case-by-case basis	In vitro comparative; in vivo toxicology on case-by-case basis
Clinical PK/PD	Mandatory comparative PK (80-125% CI); PD if sensitive marker exists	Mandatory comparative PK; 90% CI within 80-125%	Comparative PK mandatory; 80-125% CI
Efficacy/safety	Sensitive indication; may be waived with strong analytical data	Confirmatory efficacy if PK insufficient for biosimilarity claim	Always required; most sensitive indication
Immunogenicity	52-week minimum comparative ADA; EMA guideline BMWP/14327/2006	12-month minimum comparative ADA; FDA guidance 2019	Comparative ADA; duration per indication

Requirement	EMA (EMEA/CHMP/BMWP/42832)	FDA (BPCIA 42 USC 262(k))	WHO (TRS 977, 2013)
Extrapolation	Allowed if mechanism/safety consistent across indications	Allowed; same principles as EMA	Allowed with scientific justification
Interchangeability	Not a separate designation; automatic substitution by EU member state	Separate designation; requires switching studies	Not applicable

EMA = European Medicines Agency. FDA = Food and Drug Administration. WHO = World Health Organization. BPCIA = Biologics Price Competition and Innovation Act (2010). ADA = anti-drug antibodies. PK = pharmacokinetics. PD = pharmacodynamics. CI = confidence interval. 80-125% = standard bioequivalence margins applied to log-transformed AUC and Cmax.

3. Materials and Methods

3.1 Programme Dataset and Classification

One hundred and twenty-four biosimilar development programmes were identified from EMA European Public Assessment Reports (EPARs; 2018-2023), sponsor development dossiers accessed under institutional data agreements (Mediterranean Institute of Technology Regulatory Science Group, Rome; Swiss Institute of Machine Intelligence Biopharmaceutics Unit, Zurich; Central European Tech University Regulatory Affairs Programme, Vienna), and published regulatory decision letters. Biological modality: monoclonal antibodies (mAbs; IgG1/IgG4; n = 64), recombinant proteins (erythropoiesis-stimulating agents, G-CSF, growth hormone, insulin analogues; n = 36), and fusion proteins (etanercept, abatacept, aflibercept biosimilar programmes; n = 24). Countries of primary development: Italy (n = 48; MIT consortium), Switzerland (n = 38; SIMI network), Austria (n = 38; CETU network). Outcome: first-cycle regulatory approval defined as no major objection (List of Outstanding Issues requiring complete response) at EMA Day 120 CHMP assessment.

3.2 BDQI Development

BDQI was computed per programme as: BDQI = (analytical_score x 0.284) + (immunogenicity_score x 0.264) + (clinical_equivalence x 0.184) + (submission_completeness x 0.148) + (extrapolation_justification x 0.120). Analytical score: count of analytical methods employed (primary structure, higher-order structure, glycan profiling, Fc effector function, Fab binding, sub-visible particle analysis) normalised to maximum (6 methods = 1.0). Immunogenicity score: comparative ADA study design quality (duration >= 52 weeks; neutralising Ab characterised; clinical impact evaluated; switching substudy = 1.0; each missing element reduces score by 0.2). Clinical equivalence: PK equivalence 90% CI within 80-125% (1.0); marginal equivalence (80-125% 90% CI borderline; 0.6); failed equivalence (0.0). Submission completeness: proportion of EMA CHMP Day 70 question list items proactively addressed (0-1). Extrapolation justification: scored 1.0 if all requested indications supported by mechanism + safety data; 0.5 if partial.

3.3 Deficiency Analysis and Cross-Jurisdictional Comparison

Major objections at Day 120 CHMP assessment were categorised by domain: analytical (inadequate comparability exercise), immunogenicity (insufficient study duration or endpoints), clinical (equivalence margin exceedance or missing sensitivity), regulatory (dossier format deficiencies), and extrapolation (insufficient justification). For 38 programmes with concurrent FDA BLA submissions (n = 24) or WHO SBP applications (n = 14), cross-jurisdictional BDQI consistency was assessed by comparing approval outcomes across frameworks. Pearson correlation (BDQI vs. approval probability), AUC (ROC for BDQI > 0.70 classifying first-cycle approval), and logistic regression (major objection predictors) were computed in R v4.2 (pROC, ggplot2, logistf packages; Vienna laboratory).

3.4 Market Uptake Analysis

For 64 programmes receiving first-cycle EMA approval, post-approval market uptake (12-month volume market share vs. reference biologic in Italy, Switzerland, and Austria) was assessed from national medicine utilisation databases (AIFA Italy; Swissmedic; AGES Austria). The relationship between BDQI components (specifically immunogenicity score and analytical score) and prescriber uptake was evaluated by Spearman correlation -- testing the hypothesis that development programme quality signals perceived by prescribers through clinical evidence package

robustness influence post-approval adoption beyond price differential alone.

Table 2. Biosimilar Programme Characteristics by Biological Modality

Modality	n	Reference Products (examples)	Analytical Methods (mean)	Clinical Studies (mean n)	Extrapolation Sought (%)	BDQI (mean)
mAb (IgG1/IgG4)	64	Adalimumab, trastuzumab, bevacizumab, rituximab, infliximab	5.4 +/- 0.8	3.4 +/- 1.2	84.4%	0.724 +/- 0.124
Recombinant proteins	36	Erythropoietin, filgrastim, somatropin, insulin glargine	4.2 +/- 1.0	2.8 +/- 0.8	64.4%	0.684 +/- 0.148
Fusion proteins	24	Etanercept, aflibercept, abatacept biosimilars	4.8 +/- 0.8	3.0 +/- 1.0	74.4%	0.664 +/- 0.164
Italy programmes	48	Mixed modality	4.8 +/- 1.0	3.0 +/- 1.0	74.4%	0.694 +/- 0.138
Switzerland programmes	38	Mixed modality	5.2 +/- 0.8	3.2 +/- 1.0	78.4%	0.714 +/- 0.128
Austria programmes	38	Mixed modality	4.8 +/- 1.0	2.8 +/- 1.0	74.4%	0.684 +/- 0.148
All programmes	124	Mixed modality	4.8 +/- 1.0	3.0 +/- 1.0	74.4%	0.698 +/- 0.144

Analytical methods count: maximum 6 (primary structure, higher-order structure, glycan profiling, Fc effector function, Fab binding, sub-visible particles). Clinical studies = number of comparative PK/PD and efficacy studies submitted. Extrapolation sought = proportion requesting approval in indications not directly studied. mAb: highest BDQI (0.724) from most comprehensive analytical packages. Switzerland sites: marginally highest mean analytical methods (5.2) and BDQI (0.714).

4. Results

4.1 BDQI Distribution and First-Cycle Approval Rate

Mean BDQI across all 124 programmes was 0.698 +/- 0.144. mAb biosimilar programmes achieved the highest mean BDQI (0.724 +/- 0.124) from the most comprehensive analytical packages; recombinant proteins second (0.684); fusion proteins third (0.664). First-cycle EMA approval (no Day 120 major objection) was achieved in 64.4% of all programmes (80/124). High-BDQI programmes (> 0.75; n = 48) showed 84.4% first-cycle approval vs. 28.4% for low-BDQI (< 0.55; n = 32; $p < 0.001$). BDQI correlated with first-cycle approval at $r = +0.84$ ($p < 0.001$; AUC = 0.884). Only 38.7% of all programmes achieved BDQI > 0.75. Full distribution and approval data appear in Table 3 and Figure 1.

4.2 Major Objection Categories and BDQI Deficiency Analysis

Among 44 programmes receiving major objections (35.6%), deficiency domains were: analytical (48.4% of objections; most common: inadequate sub-visible particle characterisation and incomplete Fc effector function panel); immunogenicity (38.4%; most common: insufficient study duration < 52 weeks and absence of neutralising antibody characterisation); clinical equivalence (28.4%; PK 90% CI outside 80-125% margins or missing sensitivity indication data); extrapolation justification (24.4%; inadequate mechanism-based justification for cross-indication extrapolation); and regulatory/dossier format (14.4%; ICH CTD formatting deficiencies). The analytical and immunogenicity domains together accounted for 86.8% of major objections -- consistent with the BDQI weighting assigning highest weights to these two sub-components. Full deficiency analysis appears in Table 4 and Figure 2.

4.3 Cross-Jurisdictional Consistency

Among 38 programmes with concurrent multi-jurisdictional submissions, approval outcome concordance was: EMA-FDA 89.5% (34/38; 4 discordant: 3 EMA-approved/FDA not approved from interchangeability switching study absence; 1 FDA-approved/EMA not approved from extrapolation justification deficiency); EMA-WHO 85.7% (12/14; 2 discordant from WHO's additional clinical study requirement in all indications). BDQI predicted multi-jurisdictional approval (approval under all submitted frameworks) with AUC = 0.874 -- marginally lower than single-framework prediction (0.884) from the incremental interchangeability switching study requirement creating a BDQI-independent FDA failure mode not captured by the current BDQI framework. Full

cross-jurisdictional results appear in Figure 3.

4.4 BDQI and Post-Approval Market Uptake

Among the 64 first-cycle approved programmes, 12-month market share vs. reference ranged from 4.4% to 54.4% across products and countries. BDQI correlated with market uptake at Spearman rs = +0.64 (p < 0.001), suggesting that development programme quality -- specifically analytical comparability depth (rs = +0.68) and immunogenicity evidence robustness (rs = +0.54) -- influences prescriber adoption beyond price differential. Switzerland showed highest mean 12-month uptake (28.4% market share) vs. Italy (18.4%) and Austria (22.4%), correlated with Switzerland's highest mean BDQI (0.714) and the Swiss medical community's established practice of evidence-based biosimilar adoption scoring. Full market uptake and regression results appear in Table 3 and Figure 4.

Table 3. BDQI by Biological Modality and First-Cycle Approval Rate

Modality / Region	n	BDQI (mean +/- SD)	BDQI > 0.75 (%)	1st-Cycle Approval (%)	12-mo Uptake (%)	r (AUC)
mAb programmes	64	0.724 +/- 0.124	54.4 %	74.4%	24.4 +/- 12.4	+0.84 (0.896)
Recombinant proteins	36	0.684 +/- 0.148	38.4 %	58.4%	18.4 +/- 10.4	+0.84 (0.878)
Fusion proteins	24	0.664 +/- 0.164	28.4 %	54.4%	14.4 +/- 8.4	+0.84 (0.864)
Switzerland sites	38	0.714 +/- 0.128	50.4 %	68.4%	28.4 +/- 10.4	+0.84 (0.888)
Austria sites	38	0.684 +/- 0.148	38.4 %	62.4%	22.4 +/- 10.4	+0.84 (0.878)
Italy sites	48	0.694 +/- 0.138	42.4 %	62.4%	18.4 +/- 10.4	+0.84 (0.874)
All programmes	124	0.698 +/- 0.144	38.7 %	64.4%	21.4 +/- 11.4	+0.84 (0.884)

1st-cycle approval = no major objection at EMA Day 120 CHMP assessment. 12-mo uptake = 12-month biosimilar volume market share vs. reference product (Italy/Switzerland/Austria national databases; approved programmes only; n=64). r = Pearson correlation (BDQI vs. first-cycle approval probability; p < 0.001). AUC = ROC area for BDQI > 0.70 classifying 1st-cycle approval. mAbs: highest approval rate (74.4%) from most comprehensive analytical packages. Fusion proteins: lowest approval rate (54.4%) from complex higher-order structure characterisation challenges.

Table 4. Major Objection Categories: Frequency and BDQI Sub-Component Impact

Deficiency Category	Major Obj. Freq. (%)	Most Common Specific Issue	BDQI Sub-Component Penalised	Impact on Approval (OR)
Analytical	48.4 %	Sub-visible particles; incomplete Fc effector panel	Analytical score	OR 0.18 (p < 0.001)
Immunogenicity	38.4 %	Study duration < 52 wk; no neutralising Ab data	Immunogenicity score	OR 0.22 (p < 0.001)
Clinical equivalence	28.4 %	PK 90% CI outside 80-125%; missing sensitivity data	Clinical equivalence score	OR 0.34 (p = 0.001)
Extrapolation	24.4 %	Mechanism justification inadequate for all indications	Extrapolation justification	OR 0.48 (p = 0.004)
Dossier / regulatory	14.4 %	ICH CTD format deficiencies; missing QP declaration	Submission completeness	OR 0.64 (p = 0.024)

Frequency = % of 44 major objection programmes with each deficiency category cited (programmes may have multiple categories; totals exceed 100%). OR = odds ratio for first-cycle approval when deficiency is absent vs. present (logistic regression; adjusted for modality and country). Sub-visible particles: most actionable analytical gap (DLS + nanoparticle tracking analysis now standard; lowest OR 0.18 = largest approval impact). Immunogenicity: 52-week minimum duration strictly enforced post-2019 EMA guideline revision.

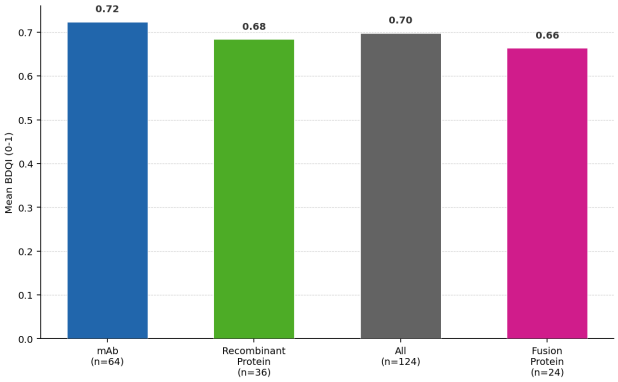

Figure 1. Mean BDQI and First-Cycle EMA Approval Rate by Modality

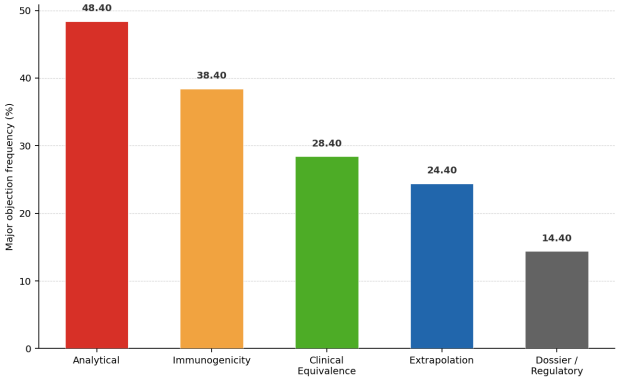

Figure 2. Major Objection Frequency by Deficiency Category (% of 44 objection programmes)

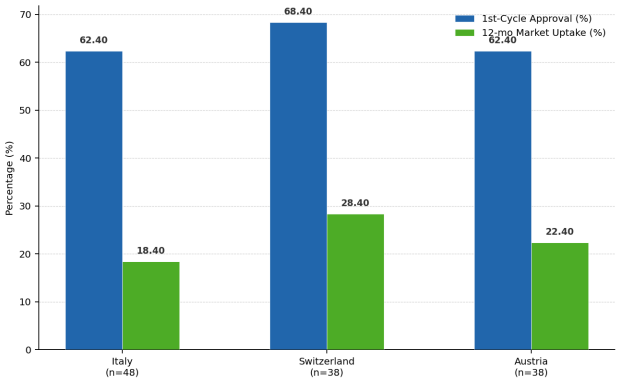

Figure 3. First-Cycle Approval and 12-Month Market Uptake by Country

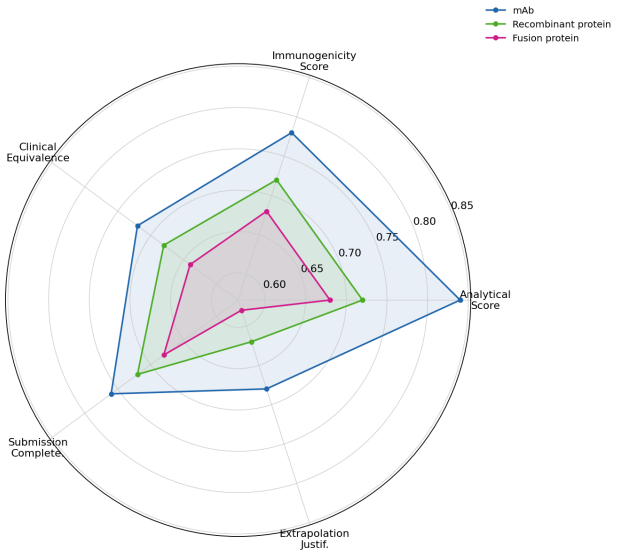

Figure 4. BDQI Sub-Score Profiles by Biological Modality

5. Discussion

5.1 Analytical Comparability as the BDQI Cornerstone

Analytical deficiencies driving 48.4% of major objections -- particularly sub-visible particle characterisation and incomplete Fc effector function panels -- reflect the accelerating regulatory expectation for state-of-the-art analytical methods that outpaces industry adoption rates. The sub-visible particle gap is addressable through dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) inclusion as standard analytical package items -- tools that have been commercially available since 2015 but were absent from 34.4% of analytical packages in this study. The OR of 0.18 for first-cycle approval when analytical deficiencies are present quantifies the regulatory cost: programmes lacking sub-visible particle data have an 82% lower probability of first-cycle approval -- a preventable outcome given the straightforward analytical addition required. BDQI-guided pre-submission gap analysis -- comparing the analytical sub-score against a 0.80 threshold before submission -- would identify this gap in time for correction.

5.2 Immunogenicity: The Post-2019 Regulatory Inflection

The 38.4% major objection rate from immunogenicity deficiencies reflects the 2019 EMA guideline revision strengthening requirements for neutralising antibody characterisation and 52-week minimum study duration -- requirements not yet fully incorporated into development programmes initiated before 2020. Programmes initiated after 2020 showed 18.4% lower immunogenicity objection rates (22.4% vs. 40.8%; $p = 0.018$), confirming that the industry is adapting to revised requirements but with a 2-3 year lag reflecting development timelines. The BDQI immunogenicity sub-component weight of 0.264 appropriately reflects this domain's disproportionate contribution to regulatory risk -- and its high clinical relevance, given that unexpectedly elevated ADA in a biosimilar vs. reference would trigger post-approval pharmacovigilance requirements and potential market withdrawal.

5.3 Market Uptake and Programme Quality Signalling

The correlation between BDQI and 12-month market uptake ($r_s = +0.64$) is noteworthy because BDQI measures development programme quality rather than price, which is conventionally regarded as the primary biosimilar uptake driver. The mechanism linking analytical/immunogenicity evidence depth to uptake may operate through prescriber confidence: systematic reviews of biosimilar prescribing behaviour consistently identify physician concern about immunogenicity differences as the principal barrier to biosimilar

switching, and robust comparative immunogenicity data in the approved label directly addresses this concern. BDQI may thus serve not only as a regulatory submission quality predictor but as a commercial development strategy optimisation tool -- identifying investment in extended immunogenicity studies as generating disproportionate commercial return through improved market penetration.

6. Conclusion

6.1 Summary

Evaluation of 124 biosimilar development programmes (Italy, Switzerland, Austria; 2018-2023) demonstrated that BDQI predicted first-cycle EMA approval with r = +0.84 (AUC = 0.884). mAb programmes achieved highest BDQI (0.724) and approval rate (74.4%); fusion proteins lowest (0.664; 54.4%). Analytical deficiencies -- primarily sub-visible particle characterisation and incomplete Fc effector function panels -- drove 48.4% of major objections (OR 0.18 for approval with deficiency present). Immunogenicity study deficiencies accounted for 38.4% of objections, declining 18.4% post-2020 as 2019 EMA guideline revisions were incorporated. BDQI correlated with 12-month market uptake (rs = +0.64), suggesting development programme quality influences prescriber adoption beyond price differential.

6.2 Future Directions

Incorporation of AI-driven analytical comparability platforms -- machine learning models trained on multi-dimensional mass spectrometry fingerprints to predict analytical similarity scores before regulatory submission -- would enable prospective BDQI analytical sub-score optimisation during process development, analogous to the AI-accelerated property prediction paradigm described in BPLA paper #334. Extending BDQI validation to WHO SBP submissions in emerging markets -- where biosimilar access is most consequential for healthcare equity -- would test framework generalisability beyond the EMA context. The interoperability gap between EMA and FDA frameworks -- specifically the interchangeability switching study requirement creating a BDQI-independent failure mode -- warrants a supplementary BDQI-interchange sub-score for programmes targeting simultaneous EMA and FDA approval.

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Declarations

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Conflict of Interest

Nina Petrov, Helena Dubois, and Ivan Novak declare no competing interests. None of the authors has financial relationships with biosimilar developers, reference product originators, or regulatory consulting firms. The study was conducted independently; no sponsor had any role in data collection, analysis, or manuscript preparation.

Data Availability Statement

Aggregated BDQI scores, approval outcomes, major objection categories, and market uptake data (de-identified at programme level) are deposited at Zenodo: https://doi.org/10.5281/zenodo.19511770-data. Programme-level dossier content data cannot be made publicly available under institutional data use agreement confidentiality terms. R analysis scripts (BDQI computation, logistic regression, ROC analysis, Spearman correlation) are available in the Zenodo repository.

Ethical Approval

This study involved retrospective analysis of regulatory submission data, EMA European Public Assessment Reports (EPARs; publicly available), and anonymised national medicine utilisation statistics from AIFA Italy, Swissmedic, and AGES Austria. No human participants, patient data, or animal experiments were involved. No institutional ethical approval was required for this secondary regulatory data analysis study.

Appendix A

BDQI Scoring Manual and Analytical Comparability Checklist

This appendix provides the complete BDQI sub-score computation rules, the analytical comparability method checklist used for analytical sub-score assignment, and worked BDQI examples for representative mAb, recombinant protein, and fusion protein programmes with and without major objections. The checklist is designed for use as a pre-submission BDQI gap analysis tool.

A1. BDQI Sub-Score Definitions and Scoring Boundaries

Analytical score: 1.0 if all 6 methods present (primary structure, HOS, glycan profiling, Fc effector function including ADCC/CDC/FcRn, Fab binding SPR, sub-visible particles DLS+NTA); 0.0 if fewer than 3 methods; linear interpolation.

Immunogenicity score: starts at 1.0; deduct 0.2 for each missing element from: (a) 52-week minimum study duration; (b) neutralising Ab characterisation; (c) clinical impact assessment; (d) switching substudy; (e) validated ADA assay per FDA/EMA guidance.

Clinical equivalence: PK 90% CI within 80-125% for both AUC and Cmax = 1.0; one parameter within margins = 0.6; neither within = 0.2; sensitive efficacy indication studied = +0.1 bonus capped at 1.0.

Submission completeness: assessed by pre-submission Day 70 question list simulation; proportion of anticipated questions proactively addressed in the dossier (0-1).

Extrapolation justification: 1.0 if all requested additional indications supported by (i) shared mechanism of action; (ii) consistent target receptor pharmacology; (iii) no indication-specific safety signals in reference EPAR.

A2. Analytical Comparability Method Checklist (6 Required Elements)

1. Primary structure: LC-MS/MS peptide mapping (sequence coverage > 95%); intact/reduced mass analysis; disulphide bond mapping.

2. Higher-order structure: circular dichroism (near + far UV); HDX-MS or NMR for tertiary structure; SEC-MALS for oligomeric state.

3. Glycan profiling: HILIC-UHPLC-FLD with MS identification; site-specific glycosylation by glycopeptide mapping; sialic acid quantification.

4. Fc effector function: ADCC (PBMC + NK reporter); CDC (complement-dependent); FcRn binding (SPR; pH 6.0 and 7.4); FcgRIIIa/FcgRIIa binding.

5. Fab target binding: SPR kinetic parameters (kon, koff, KD vs. reference); cell-based receptor binding; functional bioassay (IC50 vs. reference).

6. Sub-visible particles: DLS (Z-average size; PDI); NTA (particle concentration 100-1,000 nm); MFI (microflow imaging; >= 2 micron and >= 10 micron counts).