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Novel Perspectives on Biologics and Biosimilars: History, Gaps and Future Advancements

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Abstract: ***Biologics have greatly changed the narrative in oncology, immunology, endocrinology, and dermatology practices. Biosimilars, which are highly similar to high quality approved biologics, provide sustainable access and competition. This review evaluated important historical events, regulatory frameworks (EMA, FDA, WHO), therapeutic uptake, market constraints, methodology aspects (analytical similarity, extrapolation and interchangeability), covigilance requirements, and emerging spaces (biobetters; bispecifics; ADCs; AI for development; manufacturing 4.0). We draw upon evidence from key reviews and policy analysis to identify areas for which continued gaps exist—long-term safety and immunogenicity; pharmacovigilance transparency; international regulatory inconsistency; patient and clinician acceptance—and advocate for a research agenda to improve, equitable, patient-centered availability of biologics and biosimilars.***

Keywords: biologics, biosimilars, pharmacovigilance, immunogenicity, interchangeability, market access, AI/ML, health economics.

I. INTRODUCTION

Biologics are relatively large, structurally complicated therapies produced in living systems such as monoclonal antibodies, recombinant proteins, vaccines and advanced modalities at the interface with cell and gene therapies. Biosimilars are developed to be highly similar to a licensed reference biologic and features no clinically meaningful difference in safety, purity, and potency. The rise of biosimilars represents the maturation of analytical technologies, regulatory guidance and the need for heavy economic pressure to increase access to high-priced modalities. This review combines knowledge from the methodological, clinical, regulatory and economic literature to describe the current state of the art, provide an inventory of gaps and consider opportunities in the short-term.

II. HISTORICAL EVOLUTION OF BIOLOGICS AND BIOSIMILAR

The landscape of biologics has transformed from early protein therapies and vaccines, to recombinant DNA technology with advances in the controls for manufacturing, analytics and targeting in clinical use. The 1990s and early 2000s saw the further acceleration of mAb platforms for oncology and immune diseases, and in 2006 the European Union facilitated a regulatory pathway for biosimilars with the approval of the first wave of products, then later in the US under the "Biologics Price Competition and Innovation Act" (BPCIA), with waves of approval advancing from hormones and growth factors, to complex glycoproteins and mAbs, and multiple-switch studies began to emerge with supporting evidence.

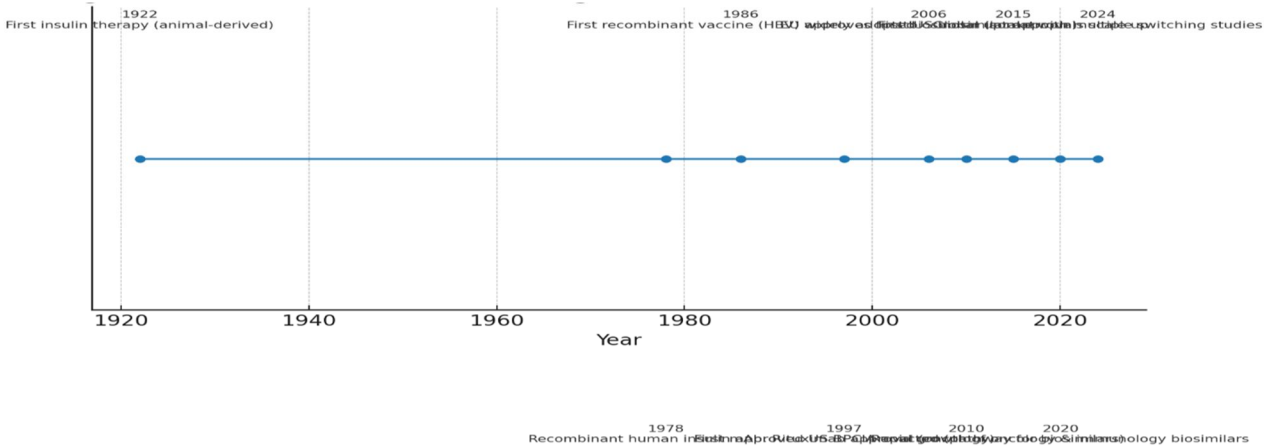

Fig. 1 Historical timeline of Biologics and Biosimilars

III. REGULATORY FRAMEWORK AND METHODOLOGICAL CONSIDERATIONS

While the EMA's stepped comparability approach and the FDA's totality of evidence paradigm reflect similar scientific principles: strong analytical similarity, limited nonclinical data, and limited clinical confirmation, differences remain around interchangeability and associated definitions, naming and traceability, indication extrapolation and post-approval conditions. WHO guidance may help to narrow discordance of regional packages, but diversity is significant. Methodologically, the ability to apply new levels of analytical sophistication such as mass spectrometry, higher-order structure differentiation, glycan characterization and bioassays to assess similarity can facilitate risk-based reduction in clinical burden without compromising safe use.

TABLE 1.
COMPARATIVE OVERVIEW of BIOSIMILAR REGULATORY ELEMENTS

Element	EMA (EU)	FDA (US)	WHO	Notes/Gaps
Analytical similarity	Stepwise, product-class guidance	Totality-of-evidence	Framework for LMIC alignment	Technique sensitivity and acceptance thresholds
Clinical confirmation	Equivalence/non-inferiority designs	Targeted trials; PK/PD emphasis	Encourages risk-based design	Debate on necessity for some endpoints
Interchangeability	No separate legal status	Formal designation possible	Not addressed explicitly	Study designs and multiple-switch data
Naming/traceability	Distinct names + batch traceability	Nonproprietary + suffix	Advocates strong pharmacovigilance	Global consistency and EHR capture
Extrapolation	Permitted with justification	Permitted with justification	Supported via scientific rationale	Transparency and stakeholder trust

IV. THERAPEUTIC APPLICATIONS

Biosimilars have seen more advancement in immune mediated diseases and oncology than any other therapeutic area, with a swift increase in experimentation in endocrinology and dermatology. The real-world data confirms that non-medical switching is safe and effective in stable patients for a number of different conditions; however, shared-decision making and nocebo minimization will continue to be paramount in helping strengthen adherence.

TABLE 2.
SELECTED THERAPEUTIC AREAS, REFERENCE BIOLOGICS, and REPRESENTATIVES BIOSIMILARS

Therapeutic Area	Reference Biologics (examples)	Representative Biosimilars	Key Evidence/Notes
Oncology	Trastuzumab, Bevacizumab, Rituximab	Trastuzumab-dkst, Bevacizumab-awwb, Rituximab-abbs	Comparable efficacy; switching studies; cost savings
Rheumatology/IBD	Infliximab, Adalimumab, Etanercept	Infliximab-dyyb, Adalimumab-atto, Etanercept-szzs	Multiple RCTs + RWE support non-inferiority
Dermatology	Ustekinumab, Etanercept	Etanercept-szzs	Improved access in psoriasis; adherence emphasis
Endocrinology	Insulin glargine	Insulin glargine-yfgn	PK/PD-driven approvals; device usability matters

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V. MARKET DYNAMICS AND BARRIERS TO ADOPTION

Initial economic factors are influenced by high fixed cost, production acting complexity, patent thickets, dismissed litigation strategies, and tendering practices. Acceptance by provider and patients, contracting practices (rebates, formulary structure), and supply reliability also will influence uptake. Advance of entry also depends on jurisdictions with clear interchangeability policies, procurement reform applicable to non-cannabis products, and primary education campaigns.

TABLE 3.
BARRIERS to BIOSIMILARS UPTAKE and POTENTIAL REMEDIES

Barrier	Manifestation	Potential Remedy
Patent thickets & litigation	Delayed market entry	Patent reform; earlier resolution pathways
Information gaps & nocebo	Hesitancy to switch	Education, shared decision-making, clear labeling
Contracting & rebates	Lock-in to reference products	Transparent tendering; multi-winner bids
Traceability limitations	Pharmacovigilance uncertainty	Distinct naming + batch capture in EHRs
Manufacturing scale-up	Supply interruptions	Redundant suppliers; quality-by-design

VI. CLINICAL and METHODOLOGICAL CHALLENGES

The use of sophisticated analytics to perform similarity assessments will shift the focus away from needing large efficacy trials. Key clinical questions are: (i) how to plan switching and multiple-switch designs; (ii) how to monitor immunogenicity and risk; (iii) how to choose relevant endpoints that are sensitive enough to detect clinically meaningful differences; (iv) the influence of real-world evidence on regulatory and HTA decisions. There are opportunities to address efficiency in trials through adaptive designs, enhanced PK/PD programs, and standardized patient-reported outcomes.

VII. COVIGILANCE AND POST-MARKETING SURVEILLANCE

Efficient covigilance relies on the accurate identification of product and batch numbers, consistent reporting of adverse events, and the interconnectivity of data across registries, electronic health records (EHRs), and claims. Active surveillance and rapid-cycle learning analytics can identify rare safety signals. Being transparent about switching and multiple-switch histories improves the interpretability of product use and safety data.

TABLE 4.
CORE ELEMENTS of a ROBUST COVIGILANCE SYSTEM for BIOLOGICS / BIOSIMILARS

Element	Operationalization	Outcome
Traceability	Distinct naming + batch/lot capture	Accurate signal attribution
Active surveillance	Registries, EHR-triggered follow-up	Early detection of rare AEs
Data standards	Common identifiers and terminologies	Interoperability across systems
PROs & adherence	Routine collection in clinics	Nocebo mitigation; better outcomes
Transparency	Switch history and product coding	Interpretable RWE for decisions

VIII. NOVEL DIRECTION AND FUTURE ADVANCEMENTS

The term innovation has a broad scope which includes next-generation antibodies (bispecifics, trispecfics), antibody-drug conjugates, Fc engineering, and long-acting depot systems. Biobetters are intended to provide improved PK/PD or decreased immunogenicity in comparison to their predecessors. At the same time, AI/ML is facilitating the design of next-generation candidates, epitope prediction, glycoengineering approach, and the manufacturing process (i.e., PAT/QbD). Digital twins, and increasing automation to assure consistent quality going forward. Access in an equitable manner will depend on prices, value based procurement and transfer of technology to LMICs.

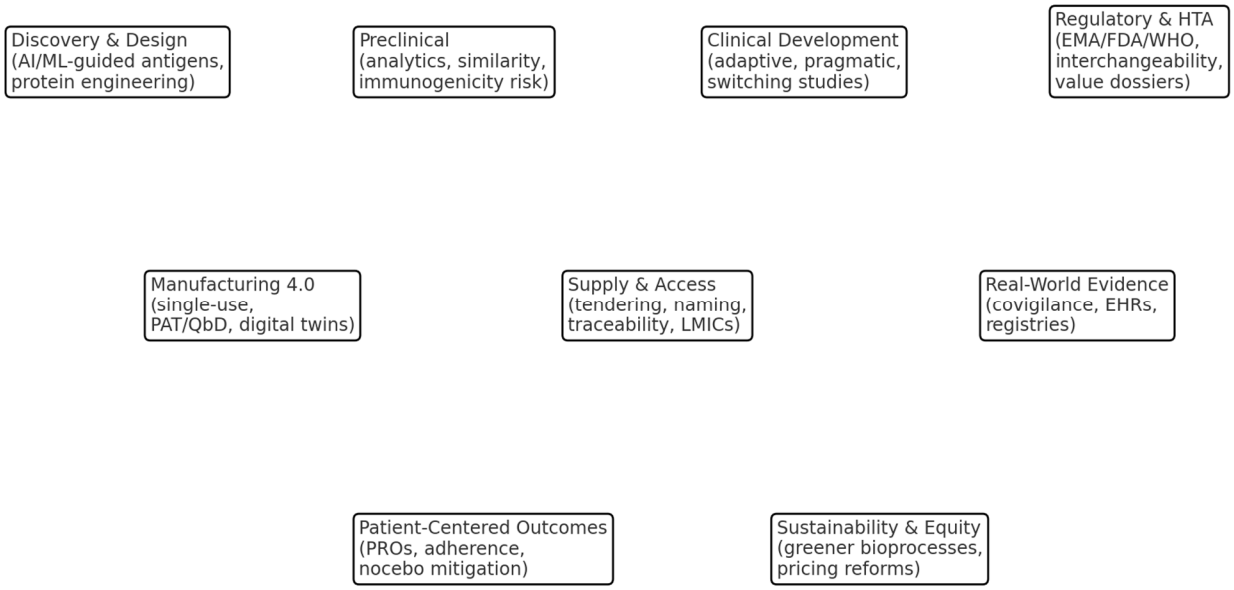

Fig. 2 Future landscape for biologics and biosimilars

IX. IDENTIFIED GAPS AND RESEARCH ROADMAPS

It will take a coordinated effort to align regulators, HTAs, industry, clinicians, and patient communities to close the evidence and implementation gaps. The table below summarizes the key gaps and points of action.

Table 5.
PRIORITY GAPS MAPPED to ACTIONS and STAKEHOLDERS

Gap	Actionable Next Step	Primary Stakeholders	Indicative Metrics
Long-term safety & immunogenicity	Prospective RWE registries with standardized PROs	Regulators, HTA, clinicians	Signal detection time; adherence
Switching & interchangeability clarity	Consensus protocols for multiple-switch trials	Regulators, sponsors	Consistent outcomes across switches
Traceability in PV	Mandate batch capture in EHR/claims	Health systems, payers	Proportion of AEs with batch data
Education & nocebo	National campaigns & decision aids	Professional bodies, patient groups	Switch acceptance; persistence
Manufacturing resilience	Supplier diversification; PAT adoption	Industry, regulators	Supply interruption rates
Global harmonization	Alignment with WHO biosimilar guidance	National agencies	Time-to-approval, duplication reduced

X. CONCLUSION

Biosimilars have progressed from cautious experimentation, to now being routinely deployed in many high-burden diseases. The scientific convergence on analytical similarity, along with real world evidence trending, demonstrates feasibility for broader use and responsible extrapolation. Future development will also be shaped by smarter development (AI/ML), robust covigilance, procurement reform, and patient-centered implementation in an effort to realize affordability without sacrificing safety or quality.

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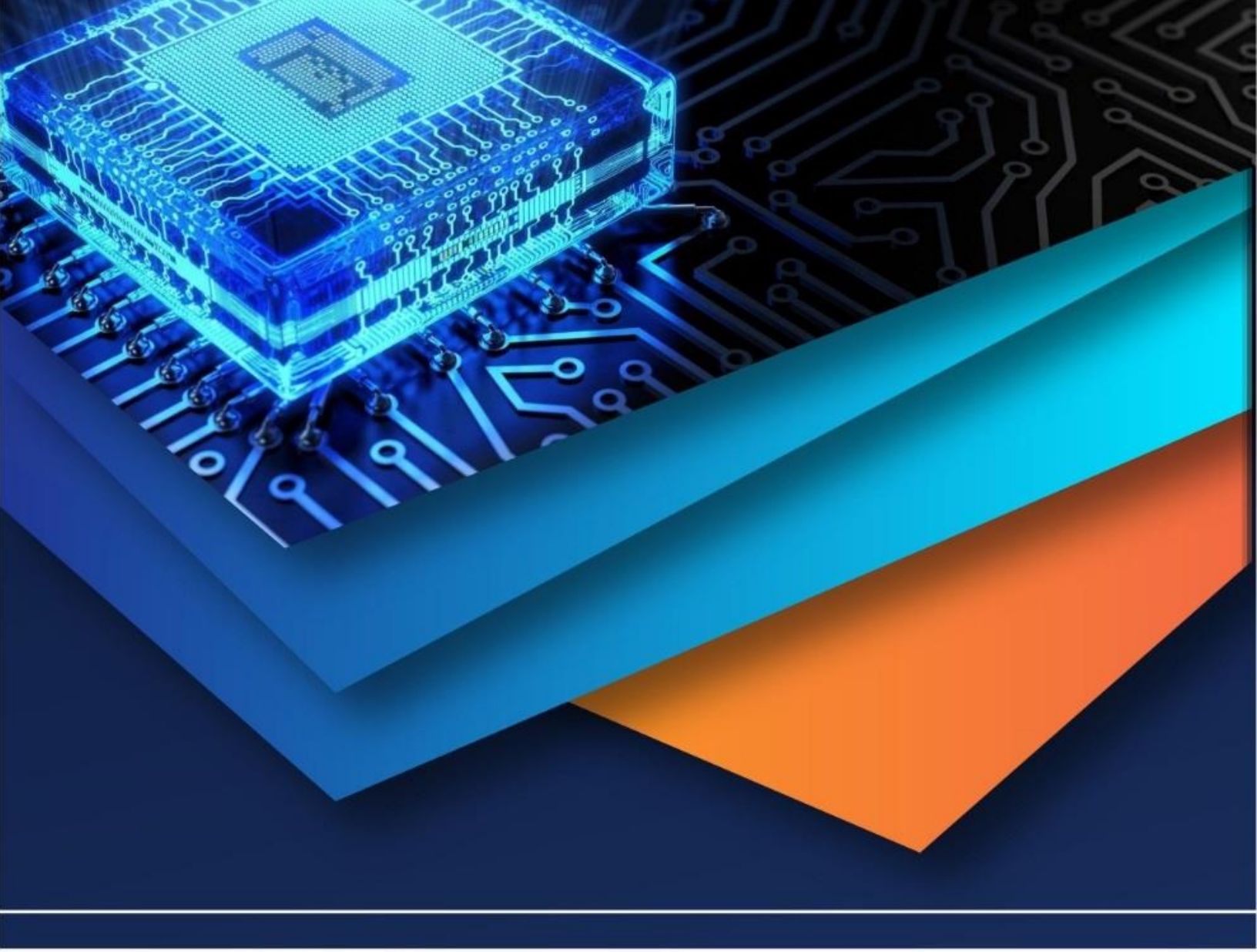

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