Biosimilars: A Comparative Study of Regulatory, Safety and Pharmacovigilance Monograph in the Developed and Developing Economies

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Received, November 23, 2021; Revised, April 2, 2022; Accepted, April 4, 2022; Published, April 6, 2022.

ABSTRACT -- Epitomizing one of the rapidly maturing segments of pharmaceutical industry, biologics gestalt has severely implicated treatment algorithms of many life-threatening diseases especially in oncology, immunology, diabetes, and irresistible infections through integration of biologics in the clinical practice guidelines. As of 2021, the impact is expected to gain resilience as more patents on new biological drugs (such as Erbitux, Avastin, Orencis) are going off. Growing acceptance, trusting on stringent risk-benefits assessment, cost-effectiveness, and potential for return on investment, drive the global market of biosimilars is expected to remain steadfast in the following years; hence knowing about regulatory requirements for approval, opportunities, and barriers to biosimilars uptake in the biggest markets of USA, European Union, Canada, and Asia-Pacific (India and Pakistan) is warranted for development of effective biosimilars marketing strategies. This article reviews the biosimilars development from the beginning (historic) to the end (development & marketing approval perspectives) and then tries to present a clear picture on areas that are still uncertain concerning the biosimilars landscape especially the biologics effect on immunogenicity, the provocative issue of interchangeability, and extrapolation of indications.

INTRODUCTION

Partaking different designations – 'Biosimilars' (EU/EMA); 'Follow-on-Biologics' (US-FDA, Japan, Brazil); "Similar Biotherapeutic Product" (WHO and Pakistan); Similar Biologics (India), and Subsequent Entry Biologics (Canada) - by different regulatory authorities, a biosimilar is "a biological drug product that has demonstrated similar quality attributes, safety/immunogenicity, and efficacy to that of an already licensed biological drug product" (1). In legal terminology, different statutes (2,3) have defined the term 'biosimilars' discretely but without departing from the fundamental conception that a biosimilar drug product is a formally regulated and approved copy of an originator (innovative) biological drug product (the so-called 'reference product') that has demonstrated similarity throughout the various stages of a rigorous similarity assessment procedure.

Sustaining the inherent attributes of large size, complexity in manufacturing, heterogeneity of molecular structure, variability, instability, immunogenicity, difficulty-to-characterization, and impossibility to full replication, biologics represent products that are produced by cutting-edge technology (such as recombinant DNA technology) in living systems (4). In this sense, biosimilars (also referred to as bio-generics) stands apart from classical "generic drugs" (or 'chemo-generics' for the sake of distinction) that are small-molecule chemical drug products with active ingredients *identical* to the innovative drug product. In another sense, biosimilars lead competition into marketplace for biological products the same way as chemo-generics does for new chemical compounds. The ultimate goal in both cases is to cut prices and increase market competition to increase access for patients to affordable medications that are equivalent in safety and efficacy to the originator drugs (5).

Globally, the market for biologics stands exorbitant in demand but their exorbitant rates make them unaffordable and inaccessible to a great majority of patients in developing countries (6). Notwithstanding that three of the top-selling off-patent biologics: trastuzumab, rituximab and bevacizumab are in the WHO list of essential drugs for their potential to treat chronic diseases including cancers and autoimmune disorders more effectively, the road to biosimilars uptake is getting

narrow and tightly curved with stringent regulatory requirements (7) and hold-ups. Contrasting originator biologics, the seemingly abbreviated biosimilar development pathway is restricted by several chokepoints. Starting with the selection of a suitable reference biologic followed by characterizing the key molecular attributes of that reference biologic to create the originator fingerprint, the biosimilar developers are set to engineer a new process to match these attributes of the reference biologic (8). As a rule of law, manufacturing information about reference biologic must be available to biosimilar developers from the patent or other public disclosures; but the originator companies' patent strategy to keep the technical know-how secret at one end while the Patent Offices failure to enforce disclosure obligations at the other, access to manufacturing knowledge and platforms is denied (9).

The practice of maintaining manufacturing secrecy is undisputedly against the provisions of patent law; but staying unchallenged for long impliedly suggests its acceptance by the biosimilar stakeholders. Consequently, to get access to the originator manufacturing process, 'reverse engineering' remains the ultimate option with its associated adverse consequences, particularly, with an increase in development costs and substantial delays in market entry (9). This way, the need for abbreviated clinical trials in biosimilar development pathway has been tactically counterbalanced by rigorous biosimilarity exercise and increasing challenges to the biosimilars clinical safety and effectiveness due to different manufacturing processes and platforms used. US FDA in its guidance on "scientific considerations in demonstrating biosimilarity to a reference product" has clearly suggested that different manufacturing processes (such as using different biological systems) may cause different post-translational modifications, which in turn may affect the clinical safety and efficacy of the reference biologic; thus necessitating a preclinical and clinical re-evaluation of the product to assess whether the change could have any adverse effect on the identity, strength, quality, purity, or potency of the product (10,11).

Several published literature on biosimilars and biosimilarity ecosystem have repeatedly endorsed the need for maintaining consistency in the production and quality controls for increasing biosimilar global acceptance; but failed to justify how meeting this end if the originator manufacturing process and other platforms (specific cell lines, culture conditions, purifications and optimizing conditions to scale-up manufacturing etc.) are kept secret (1,8,12). Access to affordable biosimilars is further compromised by the WHO Guidelines 2009 of a mandatory requirement of placing 50% of the trial patients on reference product; and consequent financial implications typically constituting 50% of the development costs in sourcing originator drugs (13,8). A convincing mandatory demonstration that switching from reference biologic to biosimilar shall not pose any greater risks of immunogenicity or adverse effects is another insurmountable regulatory hurdle in the way to acceptance and increasing uptake of low-cost and effective biosimilars (14).

Whilst amongst thousands of published research articles, there is no established data or scientific evidence available, supporting any greater risk involved in switching a patient from an originator product to a biosimilar, (13) linking switching with increasing risks of immunogenicity is seen as another strategy to obstruct market acceptance of biosimilars that have greatly transformed the healthcare systems worldwide. Bridging extrapolation across indications (i.e., use of biosimilar for indications that stand approved for reference products but are not clinically studied for the candidate biosimilar) with comparable efficacy demonstration with the reference product is still an overwhelming and cost-intensive regulatory requirement entailing substantial costs for the biosimilar manufacturers. Above all, by leaving decision on interchangeability designation on national regulatory authorities (NRAs), WHO has reinforced doubts in biosimilars rapid global acceptance (13).

This article reviews the historic evolution of biosimilars with a mindset to show how biosimilarity conception has progressed and deciphered a virtual plan into a commercial reality. It contrasts biosimilars with generic drugs to clarify various misconceptions including prohibited use of the term 'generic' for biosimilars. The authors take the position that 'biosimilars are also generic drugs (i.e., drugs on which corresponding patents or data protection have expired); (15,16,17) but based on their method of preparation (biosynthesis), the suitable term for biosimilar is 'bio-generics' as distinct from small molecule drugs synthesized in the laboratory through chemical reaction - the 'chemo-generics'. The degree technological advancements have gained momentum in the last three decades, it may not be surprising to get another "generic" in the market with the name "electro-generic", "radio-generic", or nucleo-generic"; and based on their methods of development (electrical, radiological, nuclear etc.) to let EMA/FDA/WHO thinking about setting new standards for similarity assessment of already

approved radio-pharmaceuticals or nuclear medicines.

The article further discusses and contrasts regulatory frameworks of some of the large markets for biologics and biosimilars (such as USA, EU, Canada, India, and Pakistan; Table 1). While crossing the road to biosimilar development and transitioning, a comprehensive account of key scientific considerations in demonstrating biosimilarity, and general scientific principles and approaches apply in assessing demonstration of biosimilarity is given to increase sponsors understanding about the data and information they actually need to collate for their application dossier. Apart from discussions on some of the chronic issues on the biosimilars landscape (such as biologics impact on immunogenicity when manufacturing process altered, interchangeability, extrapolation of indications, and labeling) have been made to clear certain obvious confusions and misunderstandings on the subjects. Given the significance of Pakistani and Indian markets for biosimilars, identification of barriers for market access, meager uptake, and incentives for stimulating uptake also falls within the scope of this study.

HISTORIC TRACK OF BIOSIMILARS REGULATORY FRAMEWORK: EUROPEAN UNION STANDS AHEAD OF UNITED STATES

Whilst history speaks that US takes lead in virtually every new technological advancement or conception; but concerning biosimilars regulatory framework, European Union (EU) pioneered while Asia-pacific succeeded. The idea about biosimilar regulation was first ever floated in June 1998 when the EU Agency for the Evaluation of Medicinal Products published its first concept paper pressing the need to develop a guideline to address the issue of demonstration of comparability for biotechnology-derived products (18).

The fueling power behind developing new comparability standards for biosimilars was the European Commission (EC) understanding about the non-identical character of biosimilars to the originator biologic (19). The 1998 idea was subsequently redefined in 2001 when EU published its first Directive 2001/83/EC referring "biotechnology-derived products" as "similar biological medicinal products" (20). To add further clarity and conciseness in the process of marketing authorization and development of biosimilars, the Directive was revised in 2003 (21). This revision had tightened up biosimilarity demonstration standards by requiring the biosimilars developers or sponsors to provide bioequivalence and bioavailability data, in addition to pharmaceutical, chemical, and biological data to demonstrate biosimilarity (22). More so, need for additional data (toxicological, non-clinical and clinical) was left to be decided on a case-by-case basis depending on the specific attributes of each individual product. Another revision in the Directive was made in 2004 (23) that set biosimilars developers at liberty to fully develop biosimilars during the validity term of the reference biologic patent. The latest revision harmonizing rules on pharmacovigilance in the Directive was made in 2012 (24). Revised guidelines allowing clinical trials conducted off-EEC to support EU application for regulatory approval; and reassessing issues including design, amount, and level of non-clinical and clinical studies; immunogenicity and probability to extrapolate to other indications of the reference medicine came into force in 2015 (22).

European Union: a big market with strong competition sets judicious standards for biosimilarity assessment

To ensure development of high-quality biosimilars and assist sponsors in getting marketing approval, in 2005 European Medicines Agency (EMA) issued its first guidelines concerning biosimilars regulatory approval pathways, followed by a series of product class-specific guidelines (25). These guidelines have set forth demonstration of biosimilarity to the reference biologic in term of quality, safety/immunogenicity, and efficacy following a 'head-to-head comparability' exercise. The target of comparability is to collect evidence whether the candidate biosimilar is 'highly comparable' in quality attributes (physicochemical and functional properties) to the reference product; and if differences are observed whether they have any adverse impact on the clinical outcomes (such as safety/immunogenicity and efficacy) (22). Using this evidence, justification for need and extent of non-clinical (in vitro and animal testing) and clinical studies is warranted. Current advances in analytical techniques and evidence acquired through biosimilarity comparability exercises over the last decade led to the suggestion that a mix of analytical similarity assessment, comparative pharmacokinetic and post-marketing surveillance may provide more compelling evidence of comparative similarity besides saving time and cost-intensive preapproval non-clinical and clinical studies (26). The principles introduced in the EU guidelines often serve as a standard for biosimilar licensing pathways and have been adopted *mutatis*

Table 1. Comparative analysis of biosimilars regulatory approval pathways in European Union (EU), US, Canada, India, and Pakistan.

Domain	EU-EMA*1	US-FDA*2	Canada*3	INDIA-CDSCO*4	PAKISTAN-DRAP*5
Legal framework	▪ Directive 2001/83/EC, as amended ▪ Guideline on similar biological medicinal products. Issued October 2005 (CHMP/437/04 Rev 1) ▪ Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/ 2012) ▪ Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/4283 2/2005 Rev1) ▪ Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/1432 7/2006 Rev 1) ▪ Other product-specific guidelines are available from the EMA website at; www.ema.europa.eu	▪ The Patient Protection and Affordable Care Act of 2010 [Public Law 111–148] ▪ The Biologics Price Competition and Innovation Act of 2009 - a component of PPACA- [Pub. L. 111-148, Sect. 7001-7003, 124 Stat. 119. Mar. 23, 2010] ▪ Guidance for Industry: scientific considerations in demonstrating biosimilarity to a reference product (April 2015) ▪ Guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product. ▪ Guidance for industry: biosimilars – questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009 ▪ Guidance on Considerations in Demonstrating Interchangeability with a Reference Product (2019) ▪ Guidance for Industry: Labeling for Biosimilar Products (July 2018)	▪ Food and Drugs Act and the Food and Drug Regulations ▪ Guidance for sponsors: information and submission requirements for Subsequent Entry Biologics (SEBs). (Ministry of Health: Health Products and Food Branch). (2010). ▪ *Revised Guidance Document: Information and Submission Requirements for Subsequent Entry Biologics (SEBs). (2016)* ▪ Government of Canada. *Guidance document: information and submission requirements for biosimilar biologic drugs*. Ottawa (ON): CADTH; 2017. ▪ *Patented Medicines (Notice of Compliance) Regulations*, SOR/93–133 *("Regulations")*	▪ The Drugs & Cosmetics Act, 1940 ▪ The Drugs & Cosmetics Rules, 1945 ▪ New Drugs and Clinical Trials Rules 2019 ▪ The Rules for the manufacture, use, import, export and storage of hazardous microorganisms/ genetically engineered organisms or cells, 1989 (Rules, 1989) notified under the Environment (Protection) Act, 1986 ▪ 'Guidelines on Similar Biologics (2012)' by CDSCO and DBT ▪ Recombinant DNA safety guidelines 2017 ▪ CDSCO Guidance for Industry, 2008 ▪ Guidance on Good Distribution Practice for Biological Products ▪ Guidance on Pharmacovigilance Requirements for Biological Products	▪ The Drugs Act of 1976 ▪ The Drug Regulatory Authority of Pakistan (DRAP) Act of 2012 ▪ Bio-Study Rules 2017 ▪ Guidelines concerning regulatory requirements for registration of various categories of biological drugs (rDNA therapeutic proteins in Finished Form, Ready-to-fill form, concentrated form, and naked vials) in January 2018 ▪ Guidelines providing a basic framework for implementation of Pharmacovigilance programme of Pakistan October 2019 ▪ Guidelines on Pakistan Good Clinical Practice, Good Laboratory Practice and bio-equivalence and bioavailability studies
Biosimilar definition	"A biosimilar is a biological medicine highly similar to another already approved biological medicine."	"A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product."	"A biosimilar biologic drug, or biosimilar, is a biologic drug that is highly similar to a biologic drug that was already authorized for sale (known as the reference biologic drug)"	"A biological product/ drug produced by genetic engineering techniques and claimed to be "similar" in terms of safety, efficacy, and quality to a reference biologic."	"Similar Biotherapeutic Product (SBP) is that which is similar in terms of quality, safety, and efficacy to an already-licensed reference biotherapeutic product."

Table 1. continues…

Domain	EU-EMA*1	US-FDA*2	Canada*3	INDIA-CDSCO*4	PAKISTAN-DRAP*5
Biosimilarity assessment threshold	▪ High similarity to another already approved biological medicine in the EU ▪ Strict controls during manufacturing & production processes ▪ Minor clinically insignificant differences with the reference medicine –acceptable ▪ Minor variability be kept within strict limits ▪ Step-wise scientifically-tailored comparative approach to support demonstration of biosimilarity – followed ▪ Determinants for high similarity demonstration includes analytical/structural characterization, biological activity and efficacy, safety and immunogenicity studies ▪ No regulatory requirement to re-demonstrate biosimilarity once marketing approval is granted.	▪ High similarity to the reference product ▪ Minor differences in the clinically inactive components – acceptable ▪ No clinically meaningful differences between the PB and the RP in terms of safety, purity, and potency – the guiding rule ▪ Similarity evaluation includes: - Extensive analytical characterization and very less clinical testing - Phase 2 trials – not required - At least 2 randomized CTs are critical –one to compare PK of the RP and PB and the other to demonstrate clinical equivalence - Assessment of residual uncertainty at each step of data generation – required ▪ Totality-of-the-evidence-approach – followed ▪ When assessing manufacturing changes, FDA is empowered under BPCIA to waive preclinical and clinical studies ▪ Post-approval changes in manufacturing process warrant preclinical and clinical reevaluation	▪ Subsequent entry and high similarity to the reference biologic product ▪ No clinically meaningful differences in terms of safety, efficacy and immunogenicity contrasting the reference product ▪ Any differences in quality attributes (i.e., molecular characteristics acceptable if these do not affect safety, efficacy, and immunogenicity ▪ Overall "totality-of-the-evidence" approach follows to demonstrate biosimilarity ▪ Authorization pathway applicable to the new drug submissions but abridged non-clinical and clinical comparative studies for approval- follows ▪ Studies conducted for establishing safety and efficacy of a reference biologic can be relied upon if analytical similarity to reference product is satisfactorily established ▪ Scientific approach to assess demonstration of biosimilarity – follows ▪ Determinants for high similarity includes physicochemical properties and biological activity through analytical testing, biological assays, non-clinical and head-to-head clinical data ▪ High analytical similarity, reduced number of non-clinical and clinical studies and vice versa- rules	▪ Comparable similarity to an already approved reference biologic ▪ Sequential approach to biosimilar development –followed ▪ Similarity assessment includes: - Extensive analytical and quality characterization studies - Abridged preclinical (animal toxicity) and clinical (Phase I and Phase III) data package - Foregoing phase III trials if phase I trials established high PK-PD profile - Foregoing confirmatory safety and efficacy studies based on comparable quality and competent PK-PD data	▪ Similarity in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic following a stepwise approach for similarity evaluation ▪ Similarity evaluation includes: - Analytical characterization (comparative structural and in vitro functional assessments), study of MOA, and any PK, PD, safety and/or immunogenicity assessment in animals - Abbreviated clinical evaluation if analytical characterization and in vitro functional evaluation yields significant similarity - Assessment of residual uncertainty at each step of data generation - Post-approval changes in manufacturing process warrant comparability study

Table 1. continues…

Domain	EU-EMA*1	US-FDA*2	Canada*3	INDIA-CDSCO*4	PAKISTAN-DRAP*5
Interchangeability	Not regulated by EMA; falls within the remit of individual Member States	Regulated by FDA for automatic substitution at the pharmacy-level	Not regulated by the Federal Government; falls under the control of each province according to its own respective regulations	So far, the concept is absent from the guidelines on similar biologics	Guidelines for regulatory requirements for biological drugs are silent on the subject; but the CTD (Form-5) recognizes the concept of product interchangeability. This impliedly suggests automatic substitution of the biosimilar at the pharmacy-level
Naming	INN is the same for related biosimilars; but distinguished by trade name and batch number at all levels especially in case of ADRs.	INN of the reference product is succeeded by a distinguishing four-letter suffix, devoid of meaning, separated from the core name by a hyphen (e.g., trastuzumab-dkst or adalimumab-atto).	SEBs and RBDs have same INN but unique brand names and other Drug Identification Number (DIN) for identifying pharmacovigilance activities without the addition of a product-specific suffix	INN of the biologics should be succeeded by brand names and where brand-name is not known, active substance name is given.	Following WHO guidance, INN of the biologics should be succeeded by a unique brand name. Other important indicators such as proprietary (brand) name, manufacturer's name, lot number and the country of origin may be used for distinction.
Pharmacovigilance	Mandatory - RMP is critical to submit	Mandatory	RMP is mandatory for regulatory approval	Mandatory for 4 years with 6 months PSURs (Periodic Safety Update Reports) for first 2 yrs.	Mandatory – RMP must be submitted with MAA
Extrapolation	Possible if supported by all the scientific data generated from the comparability studies (analytical, non-clinical, and clinical).	Acceptable if the MOA, drug pharmacokinetics across patient populations, and target receptors of the PP are identical across all range of conditions treated by the RP.	Allowed in cases where scientific data adequately supports	May be possible if same MOA/receptors for further indications.	Can only be approved if similar MOA and target receptors across all targeted indications.
Barriers in uptake	▪ Prescribers' concerns on safety, efficacy, pharmacovigilance and extrapolation of data to further indications ▪ Physicians-Patients' loyalties to brand-name drugs ▪ Insufficient marketing strategies by biosimilar companies	▪ Prescribers' uncertainty over product safety, interchangeability and extrapolation of indications ▪ CMS complex and dynamic reimbursement models/rules ▪ Payers' preferences in innovator products ▪ Prescribers'' treatment goals (palliative rather than curing)	▪ Equal treatment to the biosimilars and originators on the formulary ▪ Historic comfort with using the innovator brands ▪ Physicians-Patients' loyalties to brand-name drugs ▪ Absence of policies on interchangeability Switching to biosimilars counts depressing Slow regulatory system	▪ Burden of establishing similarity with the originator drug ▪ Non-availability of manufacturing process of the reference biologics ▪ Complexities and challenges involved in biosimilars development pathways ▪ Low affordability due to non-availability of health insurance	▪ Physicians-patients insufficient awareness about biosimilars ▪ Lack of knowledge about regulatory policies ▪ Uncertainty over safety and efficacy of biosimilars ▪ Non-inclusion of biosimilars in the hospital formulary

Table 1. continues…

Domain	EU-EMA*1	US-FDA*2	Canada*3	INDIA-CDSCO*4	PAKISTAN-DRAP*5
	▪ Insufficient information provided by regulatory authority on public websites ▪ Distrust on free market competition ▪ Concerns on price & reimbursement policies	▪ Patients' reluctance to biosimilar acceptance ▪ Patent litigation ▪ Non-recognition of Patent-linkage scheme (tying-in marketing approval to the patent term) ▪ Non-availability of quality data for the RP ▪ Burden of designing a rigorous package of analytical characterization on biosimilars developers	▪ Originator's intervention ▪ Switching to biosimilars counts depressing ▪ Reimbursement offers for biosimilars from payers do not render them preferred products ▪ Healthcare perception and knowledge about biosimilars ▪ Lack of confidence in the biosimilars approval process ▪ Lack of enough knowledge about biosimilars to counsel with patients ▪ Stringent pricing and reimbursement policies ▪ IP laws standing in conflict with international standards ▪ Slow regulatory system	▪ Prescribers' reluctance to prescribe biosimilar for safety reasons ▪ Manufacturing differences pose safety threats and risks of immunogenicity	▪ Wealthy Patients' loyalty with brand quality, and "low-costs begets low-quality" approach-to-selection ▪ Physicians' loyalty with originator biologics for they receive fringe benefits from innovator companies (financing for clinical research and funding for physicians' training) ▪ Insufficient capacity, infrastructure, and capability to manufacturing of local pharmaceutical companies ▪ Illiteracy, poverty, economic insecurity
Actions to remove barrier/approach to offset challenges	▪ Designing of rigorous education program on EMA approval process (e.g., comparability evaluation) and post-marketing surveillance studies to confirm safety and efficacy ▪ Economic policies incentivizing prescribing biosimilars (e.g., 15%-40% discount in biosimilars price compared to RP) ▪ Standardizing the reimbursement policies ▪ Mandatory inclusion of biosimilars in hospitals formulary ▪ A minimum pre-defined %age (Quotas) on biosimilars use at hospital and prescribers' level ▪ Public tendering ▪	▪ Designing rigorous manufacturer-sponsored educational programs on FDA approval process and how PMS programs works to assure biosimilars safety ▪ Simplifying CMS biosimilars coding and reimbursement processes ▪ Reshaping payers' policies ▪ Close working with payers and prescribers to manage behavioral economics ▪ Designing and development of an early R&D Quality Management System (QMS) ▪ Designing biosimilar analytical development program based on the framework of approved biosimilars ▪ Outsourcing biosimilar manufacturing development projects to CDMOs	▪ Educating healthcare providers, pharmacists, and patients about biosimilars, their manufacturing and rigorous approval processes ▪ Termination of select bio-originators coverage in favor of biosimilars counterparts ▪ Subjecting biosimilars to common drug review process on case-by-case basis ▪ CADTH cessation to reviewing biosimilars submissions ▪ Introduction of enhanced biosimilar access programs (such as PharmaCare biosimilar funding program) ▪ Increasing certainty through collecting data/evidence on the safety aspects of biosimilars transitioning ▪ Placing biosimilars in hospitals formulary as preferential drugs	▪ Stakeholders (physicians, patients, and payers) education programs on biosimilars safety, and efficacy; role in reducing healthcare costs and increasing access to new and differentiated treatment options Robust policymaking to expand biosimilar volume and patients' greater access to life-saving drugs	▪ Making education system effective and national economy stable (invariability in prices and sustainable growth) ▪ Designing patient-physicians' rigorous education program on DRAP approval process and pharmacovigilance studies to assure safety, efficacy, and immunogenicity profile of the biosimilar ▪ Diluting the conception that biosimilr are inferior to the originator drugs ▪ Mandatory inclusion of biosimilars in hospital formulary ▪ Standardizing reimbursement policies on medical allowances

Table 1. continues…

Domain	EU-EMA*1	US-FDA*2	Canada*3	INDIA-CDSCO*4	PAKISTAN-DRAP*5
	▪ Integrating ML and AI in the healthcare system	▪ Use of deuterium-hydrogen exchange technique for designing quality analytic data package ▪ Use of state-of-the-art cGMP facility ▪ Integrating ML and AI in the healthcare system	▪ Providing clinical support (such as sharing in copayments, laboratory testing, and nursing) by the manufacturers of biosimilars		▪ Integrating ML and AI in the healthcare system
Inducements for biosimilars development	▪ Low-cost in development ▪ Abbreviated approval process ▪ Increase in market competition ▪ Increase in patients' access and affordability to biologics therapy ▪ Economic policies incentivizing prescribing biosimilars ▪ Lower priced biosimilar may extend the scope of reimbursement policies to other patient groups ▪ Cost savings from biosimilars may increase the possibility to work on gain-sharing arrangements (i.e., distribution of cost savings amongst stakeholders such as payers, hospitals, and physicians) ▪ Cost savings may increase the possibility to employ more healthcare professionals	▪ Decreased business risks ▪ Potential to break monopolies and drive price competition ▪ Global biologics market sales are expected to exceed $390bn in 2020 from $46bn in 2002 ▪ Low-costs in development ▪ Abbreviated approval pathway ▪ Reduction in time to market through designing and development of Quality Management System (QMS) ▪ Releasing funds for future R&D	▪ High quality framework for manufacturing and distribution ▪ Policies giving preferential treatment to biosimilars ▪ Friendly environment for research and development clinical trials ▪ Abridged regulatory requirements and speedy review process ▪ Low development cost ▪ Flexible approach to biosimilar approval	▪ Established pathway for regulatory approval ▪ Abbreviated development pathway ▪ With 20% share in global market, great opportunities for investment ▪ Partnership opportunities with industry leaders ▪ Export opportunities to unregulated and semi-regulated countries ▪ Wider treatment options for patients and physicians ▪ Ineffective patent enforcement, poor monitoring of laws, and low R&D costs pave the ground for domestic biologic manufacturers	▪ Lesser time-to and costs in development ▪ Abbreviated approval pathway ▪ Cost savings in healthcare system ▪ Increase in market competition Global biosimilar market is expected to reach $25bn to $35bn in 2020, providing unfolding growth opportunities for biosimilar manufacturers ▪ Getting on the essential drugs list ▪ Patients access to low –cost but effective new treatment options

Sources: *1 European Medicines Agency; available at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar; https://www.ema.europa.eu; *2 Biosimilar Guidance | FDA; available at: https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances; https://www.fda.gov; *3: Biosimilar Drugs | CADTH; available at: https://www.cadth.ca; Allison Inserro. Health Canada Updates Its Biosimilar Fact Sheet. The center for Biosimilars dated: September 4 2019; available at: https://www.centerforbiosimilars.com *4 Biosimilar Guidelines 2016-Revised,cdr – Birac; https://birac.nic.in; Guidelines On Similar Biologics – IBKP – Department of ; available at: https://ibkp.dbindia.gov.in *5 The Drug Regulatory Authority of Pakistan Act, 2012; Common Technical Document (CTD) for Registration of Human Drugs (S.R.O. 713(I)/2018); available at: www.dra.gov.pk

mutandis by many countries including Australia, Canada, Japan, Korea, and Singapore.

In EU, market authorization of biosimilars is granted through a centralized procedure established in accordance with Article 10(4) of 2001 Directive at the EMA (20). Under this system, a new market authorization application (MAA) for biosimilars can be filed before and after the expiry of data exclusivity; but a biosimilar is approved for marketing only post-patent and -data exclusivity expiry of the reference product (27). Akin to MAA for a new biologics, MAA for biosimilars is required to accompany full modules 1,2 ,3 of the dossier called common technical document (CTD), however, for Module 3, 4, 5 if there are differences in the manufacturing process or other product-related materials (such as cell culture, expression system, culture medium etc.) then sufficient data (nonclinical or clinical) addressing only the specific conditions or detected differences must be provided (27). The dossier (CTD) contains; i) administrative data (Module 1); ii) summary on the quality/analytical, non-clinical and clinical data (Module 2); iii) information about the chemical, pharmaceutical and biological characteristics (Module 3); iv) non-clinical study reports (Module 4); and v) clinical study reports (Module 5). MAA for biosimilars is also accompanied by a two-part risk management plan (commonly EU-RMP) containing: i) safety specification and pharmacovigilance plan [Regulation (EC) No. 726/2004 substituted by Regulation (EC) No.1235/2010) and ii) risk minimization plan. [Article 8(3) (ia) of Directive 2001/83/EC substituted by Directive 2010/84/EU)].The EMA Biosimilar Medicinal Products Working Party (BMWP) evaluates MAA and makes recommendations to the Committee for Medicinal Products for Human Use (CHMP) on the non-clinical and clinical aspects of the biosimilars medicine. MAA assessment is published in the form of European Public Assessment Reports (EPAR) and public can have access to it (28). EMA makes opinion about the safety of medicines in question and based on this opinion European Commission grants marketing authorization. Post-approval, EMA performs pharmacovigilance so as to continue monitoring safety of biologics once they are on the market. As of July 2012, akin to all biologics, biosimilars are also subjected to EMA's new guidelines on pharmacovigilance (29). Contrasting chemo-generics, biosimilar regulatory procedure for biosimilars is not abridged rather 'tailored' in the form of a robust head-to-head comparability exercise to the reference product. EMA has published legally non-binding guidelines on comparability assessment and as such evaluates each application on its own merit (30).

Comparability at EMA is a 3-step exercise: i) quality comparability (physicochemical and biological/functional characterization; ii) non-clinical comparability trials (comparative *In vitro* & *In vivo studies*); iii) clinical comparability trials (comparative clinical trials involving PK, PD, safety including immunogenicity, and efficacy studies). At each step, depending on the residual uncertainty about the similarity of two product or specific differences the extent and design of the next study may be defined. Of note, differences having no adverse impact on the quality, safety, and effectiveness of the final product may be discounted for new or full clinical trials; but where differences exist in the manufacturing process and resulting product attributes, these entail relatively higher data package for biosimilars comparability exercise.

From practice viewpoint, the starting point in the biosimilar development is the procurement of several batches of the reference product over an extended period of time, followed by a rigorous characterization (physicochemical and biological) of the reference product, using state-of-the art technologies/assays to create a 'fingerprint' profile of the product (27). This profile sets a criteria/target range to which the biosimilar should adhere. However, target range may be extended if any changes in the manufacturing process affect the quality attributes of the product. Comparability demonstration in any case is not suggestive of 'identical' quality attributes, but rather, "highly comparable" quality profile and absence of any clinically relevant differences is the ultimate threshold for biosimilars marketing approval. Perhaps with this mindset, the biosimilar – Tevagrastim was approved after conducting a full phase-III trial on 384 breast cancer patients while Zarzio was allowed market authorization relying simply on phase I PD study on 146 healthy volunteers. No clinical tests/trials on patients were conducted (27).

The first biosimilar (Omnitrope-rhGH) by Sandoz was approved for marketing in 2006. Right now (2019), there are over 45 EC-approved biosimilar products across 15 product categories including Roche's Herceptin (trastuzumab) and Abbvie's Humira (adalimumab) available on the European markets (31). Owing to stringent science-based regulatory security of biosimilars for marketing approval, no safety issues concerning use of biosimilars have been reported in EU. In a joint-study conducted by the 'Analytical method development team and 'Bioanalysis team of Samsung Bioepis Co., Ltd., South Korea over assessment of similar quality attribute

characteristics in a biosimilar SB5 and a reference product of adalimumab (Humira) sourced from US and EU, the results has revealed the absence of "no clinically meaningful differences in terms of safety, purity, and potency between the two products" (32). By increasing the likelihood of competition, disrupting monopolies (dominant positions), avoiding 'duplicative' clinical studies, and speeding-up regulatory process, biosimilar development program is expected to positively influence the management of healthcare systems in the European countries.

UNITED STATES: A "LAND OF OPPORTUNITY" FOR EVERY BIOSIMILAR DEVELOPER MEETING FDA'S MINIMUM LEVEL OF SIMILARITY – "FINGERPRINT-LIKE SIMILAR" – FOR REGULATORY APPROVAL

In USA, prior to the enactment of the Patient Protection and Affordable Care Act, 2010 (PPAC Act), (33) a legislative framework to allow competitors to develop and get similar versions of FDA-licensed reference biological products approved – post loss-of-patent & data exclusivity – was lacking. PPAC Act amended the Public Health Service Act, 1944 and other statutes to create *"an abbreviated licensure pathway in section 351(k) of the PHS Act for development of biological drug products that proved to be similar to, or interchangeable with an FDA-licensed reference product".* These new legal provisions in the PPAC Act were formally referred to as the Biologics Price Competition and Innovation Act 2009 (BPCI Act) (34). BPCI Act further directed US Food and Drug Administration (FDA) to regulate a pathway for approval of biosimilars. In response, FDA prepared its first Draft Guidance for Industry in 2012, floating the initial concept of "follow-on-biologics". The final guidance providing an overview of important scientific considerations for demonstrating biosimilarity was sanctioned in April 2015 (35) In the succeeding years, FDA developed a series of further guidance documents to facilitate implementation of BPCI Act (See Table 1).

Whilst FDA specific criterion for biosimilars approval is quite stringent; yet the underlying principle for approval is based on the so-called "as a whole" consideration (36). US-FDA approved the first ever biologic – human insulin (brand name: Humulin), developed by Genentech and licensed to Lilly, in 1982 and the first bio-similar product named Zarxio [filgrastim-sndz] by Sandoz, Inc. in 2015. Zarxio was a biosimilar to Neupogen. Biosimilars market in USA gained momentum over 2017. FDA approved a total of five biosimilars in 2017, seven in 2018 and ten in 2019. Uptil now there are 28 FDA-approved biosimilars on the US market. The most recent are: Nyvepria (pegfilgrastim-apgf)- the 4th biosimilar to Neulasta-approved on June 10, 2020; and Hulio (adalimumab-fkjp) – the 6th biosimilar to Humira-approved on July 6, 2020. More applications for biosimilar approval will be in pipeline as more originator products have passed patent and data exclusivity periods (37).

Notwithstanding the relatively low-cost of development, low business risks, and consequently greater opportunities for biopharmaceutical companies to invest in biosimilar development programs; biosimilars still counts a small fraction of the US market.

CANADA: AN ESTATE OF PROVINCIAL INDEPENDENCE IN MANDATING POLICIES ON BIOSIMILARS

In Canada, the first biosimilar product (Omnitrope) was approved in 2009 as a new drug under the Food and Drug Act and the Food and Drug Regulations but the Canadian market is still experiencing a low uptake of biosimilars despite a substantial costs savings to its manufacturers and sponsors and consistency in introduction of new policies to stay tuned to the international standards and practices (38).

The Canadian Agency for Drugs and Technologies in Health (CADTH) and the Governments of British Columbia and Alberta have taken drastic steps as part of their strategy to expand biosimilar drug products access and use across Canada. To facilitate achieving the said objectives, the Canadian government has substantially increased its annual spending on biologics. Out of the total expenditures of $12.5 billion on drugs in 2021, $1.4 billion was anticipated for biologics (39). In June 2019, subject to certain exceptions, CADTH and the pan Canadian Oncology Drug Review (cCODR) stopped reviewing applications submitted for biosimilars regulatory approval. This action has speed-up the biosimilars approval process in Canada. Until 2019, Health Canada approved at least 9 biosimilars based on the data demonstrating "high similarity' and "no clinically meaningful differences in terms of safety and efficacy" between the reference drug product and the biosimilars (38).

Health Canada released its regulatory framework governing approval of biosimilars in 2010, which was subsequently revised in 2016 and 2017 to bring the guideline in harmony with EMA

guidelines (40). On the difficult question of interchangeability (i.e., shifting from one drug to another equivalent drug), the Federal Government of Canada has given authority to each provincial government to decide and declare as per their respective regulations whether the two products (innovator and biosimilar) are interchangeable (or substitutable) (41). In this assessment, biosimilars that are produced using a different manufacturing process and/or starting material under different process conditions are taken as leading to a product which is non-equivalent in therapeutic effects to the innovator drug product (42). Determination of therapeutic equivalence through clinical trials in the backdrop of EPREX (alpha-branded Eprex) frequent recalls incidents (43) and safety compromises by the Indian bio-generic manufacturers (the second-largest exporter to Canada) (44) have set new challenges and demands careful consideration of manufacturing process and control of quality for biosimilars post-approval marketing in Canada (45).

For a change in routine use of one specific product to another specific product (i.e., switching) the Health Canada's revised fact sheets states: "*No differences are expected in efficacy and safety following a change in routine use between a biosimilar and its reference biologic drug in an authorized indication*". For monitoring and managing safety risks post marketing authorization, Health Canada requires all biologics, including biosimilars manufacturers to submit and maintain a Risk Management Plan in line with those of reference product.

INDIA: TOUGH COMPETITION FROM LOCAL PHARMACEUTICAL INDUSTRY MAY HARDLY ALLOW INNOVATOR COMPANIES TO GET SUPERIORITY IN BIOSIMILARS MARKET

Contrasting the position in other parts of Asia, biosimilars uptake in the Indian market is increasing robustly. There are more than 100 biopharmaceutical companies engaged in developing similar biologics to meet the needs of its increasing population. India has been ranked second worldwide in the global supply of vaccines. The domestic sale is increasing at a compound annual growth rate (CAGR) of 14% while exports stand at a flabbergasting figure of US$51 million (46). Expected to command 20% share in the global market, Indian biosimilar market may reach $40 bn by 2030 (47). First biosimilar relating to hepatitis B vaccine was approved in India in 2000. Uptil now more than 50 biopharmaceuticals that include predominantly biosimilars have obtained marketing authorization (48). Indian biopharmaceutical companies are also thriving to get marketing authorization of their novel and similar biological products outside the Indian border. In 2019 an Indian Company got FDA approval for first biosimilar herceptin (active: trastuzumab) to market in the United States.

The governing legal framework for biosimilars in India is the Drug and Cosmetic Act (1940), Drug and Cosmetic Rules 1945, and Rules for Manufacture, Use, Import, Export, and Storage of Hazardous Microorganisms / Genetically Engineered Organisms or Cells, 1989 (rules, 1989) notified under Environmental (Protection) Act, 1986. In 2012, the Department of Biotechnology (DBT) working under the Ministry of Science and Technology, released the first "Guidelines on Similar Biologics: Regulatory requirement for marketing authorization in India". This guideline was subsequently revised in August 2016 (49). There are various other guidelines helping in the development and assessment of similar biologics in India (6).

Akin to EU-EMA and US-FDA, India has adopted a stringent comparability exercise at the level of quality, safety, and efficacy for biosimilar approval. India regulatory framework further requires the reference biologic must be an innovative product and be licensed in India. Failing this, the product must be licensed and marketed for four years in a country with well-established regulatory framework. (e.g., European Union, Japan, United States, Canada, and Switzerland). In case of national healthcare emergency, this formality may be relaxed or renounced (50).

PAKISTAN: WITH A RELATIVELY SMALL-SIZED AND TECHNOLOGICALLY LESS-ADVANCED PHARMA INDUSTRY IS A GOLD MINE FOR INNOVATOR AND GENERIC COMPANIES

In Pakistan, biosimilar development is taken as the economic rights of the generic drug manufacturers after the patent and data exclusivity over a new biological drug has been lost. Associated with this right is automatic increase in market competition and consequent increase in availability of low-costs drugs that are equivalent in quality, safety, and efficacy to their originator's counterpart. High costs of innovative biological drugs and challenges of developing new products to sustain sturdy flow of drugs for public good may not be viewed as generic companies' business objectives in Pakistan, but a by-product of the economic activity.

With strong patent system, well-organized regulatory landscape governing the pharmaceutical

industry, and resolution to maintain steady, continuous run of new technologies in the country, the current national policy is to effectively protect rights of the innovator companies until the term of their respective patents and data exclusivity has expired. Post loss-of-exclusivity; pharmaceutical and/or generic companies may enter the market with competing drugs (generics/biosimilars) for investment returns.

Contrasting small molecule drugs, good clinical outcome, large market size, and increasing probability for return on investment (ROI) have made the market for biosimilar products equally attractive for innovator and generic companies. Many big pharmaceutical companies such a Amgen, Boehringer, Sanofi, Pfizer and Merck have entered in the biosimilars products development race (51). Adding to the list of factors fueling ROI is the population size. Several studies demonstrate that medicines are inelastic goods in that their demand remains change constant and is not influenced by shift in price (52). A country with big population size therefore provides big market and ROI opportunities for pharmaceutical and generic companies.

As per the World Population Review 2019, Pakistan's population is 216,565,318. It is ranked 4th amongst the Asia-Pacific Countries (APAC) and as such following China (1,433,783,686), India (1,366,417,754), and Indonesia (270,625,568) is another big market for biotherapeutics and biosimilars. The pharmaceutical industry of Pakistan is ranked 10th in the region and until 2019, the number of registered companies operating in Pakistan was 650 approx. (53). The number of prescription drugs sold at licensed pharmacies is more than 9,000 while over-the-counter drugs also covers a sizeable segment (54). Notwithstanding the fact that compared to position in 1990s, currently MNCs has little representation in Pakistan [less than 30]; but still with technologically less advanced and GMP compromising local pharmaceutical industry, Pakistan is still a gold mine for innovator companies and prospective biosimilar developers.

Development of biosimilars regulatory framework in Pakistan

The principal legislation governing regulatory requirements for approval of all types of drugs/therapeutic goods in Pakistan is the Drugs Act of 1976 (55). However, with the passage of the DRAP Act, DRAP working under the Ministry of National Health Services, Regulations and Coordination, Government of Pakistan, has become the principal authority to administer, and monitor the enforcement of the Drugs Act of 1976 and Rules made under the Act of 1976. DRAP has integrated all offices including the Federal Drugs Control Administration and the sub-offices set up in all provinces and laboratories called the Central Drugs Laboratory, Karachi; the National Control Laboratory for Biologicals, Islamabad; and the Federal Drug Surveillance Laboratory, Islamabad, previously established under the Drugs Act of 1976 (56).

For evaluation, assessment, registration, and licensing of biological drugs for human beings, and animals; and performance of all other functions as required for the prequalification by WHO of locally manufactured human biological drugs, the Federal Government with the recommendation of the Policy Board has constituted a Division of Biological Evaluation and Research, headed by the Director Biological Drugs. For determination of specific pathway for approval of biological drugs, DRAP has introduced changes in the regulations made under the Drugs Act 1976.

To help sponsors in providing data for getting marketing approval of biological drugs, DRAP released its first guidelines concerning regulatory requirements for registration of various categories of biological drugs (rDNA therapeutic proteins in finished form, ready-to-fill form, concentrated form, and naked vials) in January 2018, followed by product specific guidelines for registration of imported enoxaparin in April 2018. These guidelines are however generalized and set *mutatis mutandis* internationally recognized standards for biosimilars approval.

DRAP's biosimilar regulatory pathway: Horizontal and abbreviated

Akin to legislations in other parts of the world, DRAP-Act has created a statutory pathway for marketing authorization of biological drugs. As part of application dossier, DRAP requires applicants to submit all technical data derived from the analytical/quality characterization studies, non-clinical and clinical (PK, PD, safety, and efficacy) studies including reports on post-marketing experience on the prescribed Form 5F titled: "Common Technical Document (CTD) for Registration of Human Drugs" (57). Except some differences in the contents of module 1 (administrative part) and sub-headings of other modules 2-5 created under national requirements, this is the same document as was originally developed by the European Medicines Agency (EMA) of the European Union, the Food and Drug Administration, USA (US-FDA) and the Ministry of Health, Labour and Welfare (Japan) for use across Europe, Japan and the United States (58). The five-parts CTD (Figure 1) is a standard

document for registration of all pharmaceuticals and biological products including biosimilars however the required details may be subject to explanations and exemptions by the Registration Board.

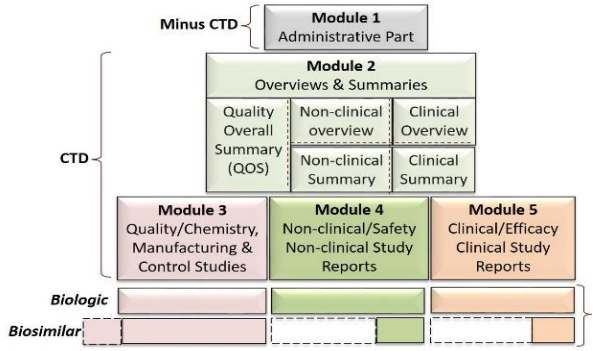


Figure 1. The CTD modules. Comparison of regulatory requirements for a reference product (RP) and proposed biosimilar (PB). For RP, CTD modules 3 (CMC studies), 4 (non-clinical studies) and 5 (clinical studies) are required in full while for PB, module 3 study is extended and modules 4 and 5 are abridged. [Source: Bui et al. (2015) (8); http://www.ich.org/page/etd]

When an applicant files Form-5F (CTD), DRAP enters the application in the database of received applications. Application Form 5F together with a pharmaceutical dossier that includes a set of documents as specified in Schedule I of the DRAP Act (section 2(xxviii) of the DRAP Act) is scrutinized and evaluated on first-in, first-out basis by the Registration Board. Incomplete applications are issued observations requiring rectification of shortcomings. After that Biological Evaluation & Research Division of DRAP prepares the summary for consideration of Registration Board. For locally manufactured drugs, Registration Board may cause the premises of drug manufacturer to be inspected by a panel of experts and detailed report is presented before the Registration Board. For imported drugs, GMP inspection of foreign manufacturer is carried out prior to grant of registration. However, pharmaceutical / biological products approved by United States Food and Drug Administration (USFDA), World Health Organization (WHO), European Medicine Agency (EMA) or regulatory bodies of Japan, Australia, Canada, or any of regulatory authority of erstwhile Western Europe (United Kingdom, Germany, France, Switzerland, Netherlands, Austria, Belgium, Denmark, Finland, Sweden, Italy, Ireland, Luxemburg, Norway, Scotland and Spain) or three stringent regulatory bodies of erstwhile Eastern Europe are exempted from inspection. Registration Board takes the final decision. Issuance of registration certificate is subject to fixation of MRP by the Federal Government under the Drug Pricing Policy-2018. The registration process is completed within 3-18 months (59).

Under the DRAP Act, sale and use of human biological drugs is not sanctioned until prior approval ("Lot Release Certificate" issued under the WHO's Lot Release system of evaluation) from the Federal Government Analyst of the National Control Laboratory for Biologicals, Islamabad has been obtained (60).

Exemptions in CTD data package/pharmaceutical dossier requirements

For biological drugs including biosimilars approved for marketing by FDA, EMA and other regulatory authorities that have set stringent biosimilarity assessment criteria for registration, DRAP has provided various exemptions to let the biosimilar regulatory process strikingly smooth and swift. Below are various exemptions in data required in the CTD (Module 2-5) for new drug product and generics/biosimilars (Table 2).

The exemptions in modules 2-5 reflect that for registration and/or marketing authorization of biological products including biosimilars, DRAP principal reliance is on the international standards set by the regulatory authorities such as FDA/EMA/WHO/ICH; hence a new drug or biosimilar approved elsewhere is earnestly required less data/evidence to establish similarity in the 'therapeutic trilogy" (quality, safety, and efficacy) contrasting a drug that has been locally manufactured.

BIOSIMILARITY ASSESSMENT THRESHOLD: PROBING 'HIGHLY SIMILAR' AMONGST SAME, SIMILAR & VIRTUALLY IDENTICAL

Inherent variability in structure and consequent quality attributes is one of the causative agents for regulatory authorities to set standards for similarity assessment between a proposed biosimilar and its reference biologic. These standards generally go beyond mere "average bioequivalence" consideration. Various criteria for biosimilarity assessment are provided in the industry guidelines of various regulatory authorities especially FDA and EMA (Table 3). Though abbreviated relative to the dossier requirements for new drug molecules; but still burdensome when compared with chemo-generics. Chow and Ju (2013) (61) had classified biosimilarity assessment criteria into three categories, particularly:

Table 2. Exemptions in CTD Modules 2-5

Module	Section	Sub-section	New Drug Product	Generic Drug Product/biosimilars
2	2.4	Non-Clinical Overview	Not Exempted	Exempted
	2.5	Clinical Overview	Not Exempted	Exempted
	2.6	Non-Clinical Written and Tabulated Summaries	Not Exempted	Exempted
	2.7	Clinical Summary	Not Exempted	Exempted
3 (3.2.S)	3.2.S.2 Drug Substance	3.2.S.2.3 Brief Description of Manufacturing Process and Process Controls	Not Exempted	Exempted
		3.2.S.3.4 Control of critical steps and Intermediates (Closed Part)	Exempted	Exempted
		3.2.S.3.5 Summary of Process Validation and/or Evaluation	Not Exempted	Exempted
		3.2.S.3.6 Brief Manufacturing Process Development	Exempted	Exempted
3 (3.2.P)	Drug Product	3.2.P .2.2.1 Pharmaceutical Equivalence through Comparative Dissolution Profile	Not Exempted	Not Exempted
	3.2.R	3.3.R.3 Product Interchangeability (Bioequivalence Study Reports)	Exempted	Exempted
		Bioequivalence	Exempted	Exempted
4	4.2.3	4.2.3.3 Genotoxicity	Exempted	Exempted
		4.2.3.4 Carcinogenicity	Exempted	Exempted
		4.2.3.5 Reproductive and Developmental Toxicity	Exempted	Exempted
		4.2.3.6 Local Tolerance	Exempted	Exempted
		4.2.3.7 Other toxicity studies	Exempted	Exempted
5	Clinical Studies	Innovator (In-house and Published data)	Not Exempted	Not Applicable
		New Drug Generic version (Published data)	Not Applicable	Not Exempted

Source : [www.dra.gov.pk]

i) absolute change versus relative change,
ii) aggregated versus disaggregated, and
iii) moment-based versus probability-based.

Amongst these, they regarded probability-based criteria not only much more stringent for biosimilarity assessment between follow-on biologics but also sensitive to minor variability. They further indicated the suitability of aggregated criteria based on individual bioequivalence criterion for drug switchability and population bioequivalence criterion for drug prescribability (61). Zhang et al. (2013) urged the need for a universal approach, which they named "biosimilarity Index" for assessment of biosimilarity (62). This approach was originally derived from 'reproducibility probability' approach, presented by Shao and Chow in 2002 (63), followed by development of an Index based on the approach by Chow et al in 2013 (64). The biosimilarity index approach was based on selected study endpoints, average biosimilarity criterion and standard 2x2 crossover study design. The proposers claimed the advantage of using this approach for quantifying the level of similarity against any selected criteria (64). Statistical approach to evaluate analytical similarity was however withdrawn by US FDA in June 2018. According to EMA, because of the availability of ultra-high-resolution and throughput analytical techniques and their sensitivity to quantify differences in molecules at the level of parts per trillion over the past three decades (65) similarity between second-generation biosimilars (such as monoclonal antibodies) and the reference biologics is best demonstrated at the analytical level (8).

Contrasting new biologics, the biosimilar development objective is to produce a biologic that is "highly similar" to, and exhibits "no clinically meaningful differences" to the reference biologic at the level of safety, purity, and potency (66). For this reason, the preclinical evaluation phase of the biosimilar development pathway encompassing analytical characterization (comparative structural and functional assessments); study of mechanism-of-action; pharmacokinetic (PK), pharmacodynamics (PD) and/or safety and immunogenicity assessments in animals (animal toxicity), is more extensive compared to the clinical evaluation phase that is more comprehensive in new biologics (8) (Figure 2).

Table 3. Standard data package required by regulatory agencies to support a demonstration of biosimilarity.

Domain	Goal of study	Aim of study	Element/Critical quality attributes	Analytical methods/biological assays
Analytical/quality characterization studies	1. To demonstrate that proposed biologic (PB) is 'highly similar' to the reference product (RP) and exhibits no clinically meaningful differences from the reference biologic product in terms of safety, purity, and potency.	▪ To support a demonstration of biosimilarity ▪ To characterize RP and PB quality attributes ▪ To analyze batch-to-batch variability ▪ To assess whether minor differences such as N- or C-terminal truncations in the molecular structure impact the molecule function; and if not justify it scientifically. ▪ To ensure that PB have high quality attributes similar to those of the RP ▪ To make an assessment about the nature and extent of non-clinical and clinical data required for approval.	1. i) <u>Physicochemical / structural characterization</u> ▪ Molecular mass ▪ Primary structure (amino acid sequence) ▪ Higher-order structures [secondary, tertiary, quaternary (including monomer, low molecular weight (LMW) and high-molecular weight (HMW) variants, aggregates] ▪ Free thiols (-SH) group ▪ Disulfide bridges ii) <u>Post-translational modifications</u> ▪ Glycosylation ▪ Phosphorylation ▪ Deamidation ▪ Methionine oxidation ▪ PEGylation ▪ N- or C-terminal variants iii) <u>Quantity/contents</u> ▪ Protein concentration ▪ Interfering excipients (e.g., HSA) iv) <u>Purity profile</u> a) Product-related impurities ▪ Oxidation ▪ Deamidation ▪ Aggregation b) Process-related impurities ▪ Host cell proteins ▪ Endotoxins ▪ Yeast mannans ▪ Reagents ▪ Downstream impurities v) <u>Stability</u>	<u>For primary structure (amino acid sequence):</u> ▪ Peptide mapping (LC-ESI-MS/MS) ▪ Peptide mass fingerprint (MALDI-MS) ▪ MALDI TOF ▪ MS amino acid sequencing <u>For higher-order-structure (conformation)</u> ▪ Far- and near-UV CD spectroscopy ▪ 2D-NMR fingerprinting ▪ SPR ▪ ELISA ▪ FTIR spectroscopy ▪ Intrinsic and extrinsic FL spectroscopy ▪ HDX-MS, ▪ Multiplex-based ACA ▪ DSC ▪ X-ray crystallography <u>For Size heterogeneity (LMW/HMW)</u> ▪ SE-HPLC, SEC/MALLS, SV-AUC ▪ SDS-PAGE ▪ HP-SEC ▪ AF4 ▪ AUC ▪ CE-SDS (non-reducing/reducing) DLS and MFI ▪ RP-HPLC-UV/MS peptide mapping <u>For Post-translational modifications</u> ▪ Mass spectrometry ▪ NP-HPLC-(MS) ▪ GC-MS ▪ HPAEC-PAD ▪ CZE ▪ UV/VIS at A280
	2. To demonstrate that the established safety and efficacy data package for the RP also applies to the PB	▪ To support a demonstration of biosimilarity ▪ To determine pharmacologic activity (protein mechanism-of-action) and specific assays based on the product attributes	2. <u>*In vitro* functional/biological characterization</u> Assessment includes measurement of: i) <u>Antigen binding (Fab) functions</u> ▪ Ligand neutralization ▪ Receptor activation and/or blockade ▪ Apoptosis	<u>*In vitro* biochemical assays</u> ▪ Ligand or receptor binding assays ▪ Enzymatic assays ▪ Cell-based assays (binding, CDC, ADCC, apoptosis)

Table 3. continues…

Domain	Goal of study	Aim of study	Element/Critical quality attributes	Analytical methods/biological assays
		▪ To evaluate functional effects on pharmacodynamics markers or efficacy measures. ▪ To justify a more selective and targeted approach to animal and/or clinical testing.	ii) Fc-associated effector functions ▪ Binding affinity of the Fc to relevant receptors (e.g., FcγR, C1q, FcRn) ▪ Complement-dependent cytotoxicity (CDC) ▪ Antibody-dependent cell-mediated cytotoxicity (ADCC)	▪ Functional assays (FRET, SPR, FACS, ELISA) ▪ Alpha Screen
Non-clinical studies (Animal toxicity)	1. To support biosimilar marketing authorization application 2. To support biosimilarity assessment made in step 1 (analytical/quality characterization)	▪ To address residual uncertainty or slight differences observed at step 1 to confirm comparable clinical performance of the PP and the RP ▪ To assess clinical relevance of the observed differences in quality attributes of the PP and the RP in step 1.	a) *In vitro* studies ▪ Pharmacological studies ▪ Toxicological studies b) Determination of the need for *in vivo* studies Factors to be considered include: ▪ Presence of potentially relevant quality attributes not detected in the RP ▪ Presence of potentially relevant quantitative differences in quality attributes between the PP and the RP ▪ Relevant differences in the formulation (e.g., use of excipients not normally used in biotech-derived products) c) *In vivo* animal studies (if necessary) ▪ Comparative PK and/or PD and/or safety in animal model ▪ Animal toxicity studies ▪ In vivo study design should observe principle of 3Rs (animal replacement, refinement, reduction)	*In vitro* assays (data already available from biological assays in quality characterization step 1): ▪ Ligand or receptor binding assays ▪ Enzymatic assays ▪ Cell-based assays *In vivo* functional assays include: Animal models exhibiting disease state or symptoms
Clinical data / studies	1. To support a demonstration of biosimilarity 2. To demonstrate safety, purity, and potency in one or more conditions-of-use	▪ To make an assessment of immunogenicity, PK, and PD ▪ To detect potential differences in the molecular attributes and the safety and efficacy ▪ To address unresolved questions based of PK/PD study data ▪ To confirm comparable clinical performance of the RF and PB	Nature and scope of clinical studies: ▪ Comparative PK/PD studies (bioequivalence studies) using surrogate PD/biomarkers, or ▪ Comparative PK/PD studies (bioequivalence studies) in human using single-dose cross-over/parallel design, and homogenous study population ▪ Confirmatory PK/PD studies ▪ Safety and efficacy ▪ Immunogenicity	Magnetic resonance imaging

Table 3. continues…

Domain	Goal of study	Aim of study	Element/Critical quality attributes	Analytical methods/biological assays
Additional data / studies	To establish comparability of the PB manufactured by the old and new manufacturing process	To detect differences in response between the PB and RP, the nature and extent of changes in the product attributes and then need for further studies	Comparative multiple-dose PK studies to confirm similar PK profile at steady-state	---------
Pharmacovigilance (Phase IV studies)	Close monitoring of safety and continued risk-benefit assessment	To address identified and potential risks associated with the concerned product in post-marketing follow-up	▪ Description of pharmacovigilance system ▪ Risk management plan ▪ ADR reporting ▪ Post-marketing studies (Phase IV)	---------

[Source: Adapted from Schiestl et al. (2017) (22) and Kirchhoff et al. (2017) (122)] Abbreviations: LC–MS, liquid chromatography–mass spectroscopy; ESI, electrospray ionization; MALDI, matrix- assisted laser desorption/ionization; TOF, time of flight; MS, mass spectroscopy; UV CD, ultraviolet circular dichroism; NMR, nuclear magnetic resonance; SPR, surface plasmon resonance spectroscopy; ELISA, enzyme-linked immunosorbent assay; FTIR, Fourier transform infrared; FL, fluorescence; HDX, hydrogen deuterium exchange; ACA, antibody conformational array; DSC, differential scanning calorimetry; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; HP- SEC, high-performance-size-exclusion chromatography; AF4, asymmetric flow-field fractionation; AUC, analytical ultracentrifugation; CE-SDS, capillary electrophoresis with sodium dodecyl sulfate; RP-HPLC, reverse-phase high-performance liquid chromatography; NP-HPLC (MS), normal phase high-performance liquid chromatography with optional mass spectrometry; GC–MS, gas chromatography–mass spectroscopy; HPAEC- PAD, high performance anion-exchange chromatography with pulsed amperometric detection; CZE, capillary zonal electrophoresis; HAS, human serum albumin; NP, normal phase; RP, reverse phase; CDC, complement dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; FACS, fluorescence activated cell sorting; FRET, fluorescence resonance energy transfer

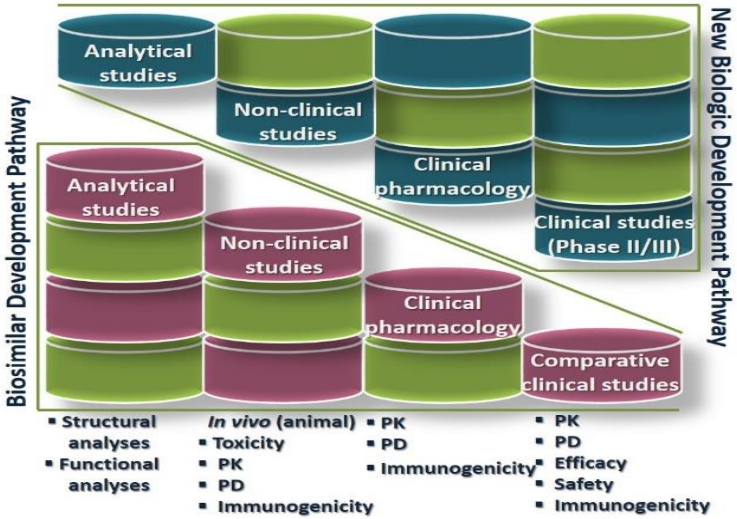


Figure 2. Step-wise approach to generate data in support of biosimilarity demonstration. [Source: Christl et al. (2018) (36)]

Subject to demonstrating high similarity between the proposed biosimilar and its reference biologics at the analytical and preclinical evaluation phase, less or abbreviated data package may be required for the clinical evaluation phase of the biosimilar development pathway (3). Though all-embracing but once similarity threshold for each attribute characterized through sensitive in vitro testing has been set out, demonstration of similarity gets relatively easy for biosimilar sponsors. For instance, barring some minor and clinically insignificant differences ensuing from N- or C-terminus modifications, a comparison of primary amino acid sequence of biosimilar and its reference biological product sourced from USA and EU had shown similarity between the two products. Following structural characterization, data collected from probing and monitoring of post-translational modifications (e.g., glycosylation, PEGylation) and assays conducted for functional assessments may justify the extent of more directed and selective approach to subsequent nonclinical and clinical biosimilarity assessment studies. Appreciating the need for industry, EMA has issued specific guidance for similarity assessment of biosimilars (e.g., mAb-based biosimilars) (66). In addition, the EMA and WHO regulatory guidelines also consider conducting "one repeat-dose" toxicity study in the biosimilarity assessment exercise. Apart, deliberation of factors influencing immunogenicity in animal studies may help assessing even minute differences in immunogenic probability between a biosimilar and the reference biologic (2). Simply lacing reliance on animal studies for immunogenicity assessment in humans is not astute. Conducting clinical trials on humans and post-marketing pharmacovigilance is mandatory (67). Extending reliance on their assessment and the fact that preclinical evaluation phase is the foci where doubts about similarity between two iotas are best cleared; EMA- relying on analytical characterization results - has considered two versions of the reference biologics as highly similar (68).

Akin to complex data analytics used by FDA, EMA, and other regulatory authorities for assessing biosimilarity, DRAP takes the biosimilarity assessment task as a frontier beyond which a drug product may be ranked as 'highly similar' as against the various levels of similarity: not similar, similar, highly similar and fingerprint-like similar. Though to facilitate sponsors in biosimilars approval process, DRAP's principal reliance is on assessment made by the ICH adherent countries (as FDA-EMA accepted the use of a foreign comparator) (69), nonetheless for drugs that are manufactured locally, DRAP (as FDA-EMA do) takes biosimilarity assessment as an investigation based on two comparative studies: i) mandatory comparative analytical/quality characterization of the biosimilar to the reference product; and ii) if differences are observed, try to link the noted difference(s) and the clinical outcomes (human PK, PD, safety including immunogenicity, and efficacy) through some sensitive assays/analytical tools, to establish which amongst the physical, chemical, and functional attributes have or have no substantial impact on clinical outcomes (70).

In practice, if biosimilarity studies data reveals that there is high analytical similarity between the candidate biosimilar and the reference product at the molecular level, the product may be deemed to have high similarity and low residual uncertainty. DRAP may then be content on more specific or pointed clinical studies. If structure and function studies data analysis lead to higher uncertainty, additional clinical studies (such as comparative PK and PD followed by safety/immunogenicity and efficacy studies) may be required for the biosimilar product to get DRAP's approval. The ultra-high-resolution and, state-of-the-art analytical techniques are sensitive to spot differences between closely related molecules and characterizing all critical and non-critical attributes to make-up a fingerprint of the originator drug that provides a framework against which a biosimilar manufacturing process is developed to match this fingerprint.

Statistically, if 50% similarity in critical quality attributes is taken as average then 60% is above average; 70% is fairly similar; 80% is similar, 90% is highly similar and 99% is excellent or fingerprint-like similar. Fingerprint-like similarity thus represents a level touching superlative similarity and high similarity is ranked below it. This means that if there is high structure and function similarity, the biosimilar contains the same active ingredient as the reference product. In addition, the biosimilar has the same performance and quality as the reference. Biosimilars that do not closely match to the originator's fingerprint at the molecular level needs to submit additional preclinical and clinical data to demonstrate similarity convincingly.

Strategically, at each step of the biosimilarity demonstration, the biosimilar applicant should carry out a residual uncertainty risk assessment and endeavor to identify next step to address it so as to let DRAP withdraw requesting new data to support biosimilarity. To achieve this, there is need to ensure that all known risks have been offset, calculated, or accounted, or evaded (71). 'High

similarity' notion may thus be counter-balanced by a low residual uncertainty and low similarity with a follow-up pharmacovigilence studies making an assessment that high adverse safety events, if there is any, are product-specific or molecule-specific (5). A single study design to screen all characters or parameters of interests to establish biosimilarity seems unrealistic.

MAINTAINING BATCH-TO-BATCH CONSISTENCY IN BIOSIMILARS QUALITY REQUIRES DEVELOPMENT OF RESILIENT MANUFACTURING PROCESS

Contrasting small molecule drugs, higher-order structures, post-translational heterogeneity, and potential immunogenicity do not allow stability in the manufacturing process conditions of biologics, and eventually to final product attributes (commonly: critical quality attributes) including physicochemical characteristics, biological activity, bioavailability, safety, and efficacy (72). Even if the manufacturing conditions are unwavering, over time change in biologic's characteristics may result in consequent variability in product quality in follow-up lots or batches (commonly: the drift) (8). Preclinical and clinical re-evaluation of the biologic to rule out any adverse impact of the pre- and post-changes in the manufacturing process conditions; cell lines; culturing conditions; expression system; purification process etc. on product quality, safety, efficacy, and immunogenicity seems mandatory (8). Development of a resilient manufacturing process based on quality-by-design (QbD) approach may obviate the need for undertaking comparability exercise for every next batch of product for quality assurance. To compare batches of biologics for quality consistency, the International Conference on Harmonization (ICH) has provided Q5E guidelines (73). The manufacturing process of a biosimilar must stand in congruity with the ICH guidance for biologics development.

In a scientific context, this is a proven fact that structural variability in biological products either manufactured by nature's factory (human body) or in the laboratory through rDNA technology is a natural phenomenon, not a defect or imperfection. This is further proven that causative agent for post-translation modifications including different immunogenic response may be both biological processes and/or processes used to produce biotherapeutics (1). For instance, in case of therapeutic proteins, each stage of manufacturing process (including cell culture, purification, and storage) seeds discrete post-translation modifications, directly affecting the clinical properties of the final product and possibly influencing its quality (potency), PK, PD or immunogenicity (74). In a study conducted by Planinc et al. (2016) (75), substantial variability in the level of glycosylation in several batches of reference biologics – infliximab, trastuzumab and bevacizumab had been observed. This envisages that post-translational modifications of biologics are susceptible to changes in the manufacturing process conditions and as such requiring mandatory batch-to-batch consistency (44). Hence, for understanding product and process relationship, it is equally important to understand impact of variability in raw materials specification on process development; understanding correlation between process conditions and critical quality attributes; and impact of any variation on the clinical efficacy of the biosimilar (76). For biosimilar developers, this urged the need for grasping the theory of variability linked with the reference biologic and as such controlling the manufacturing process to control production and quality (clinical safety and efficacy) against manufacturing drifts for each next batch (1). Consequently, to begin with the development of a biosimilar, gentle unfolding of the critical quality attributes (typically physicochemical and functional) of the originator using state-of-the-art techniques/analytical tools to define the originator fingerprint, calculating the extent of variations against each attribute through testing as many batches of the originator as may define the bounds of similarity for each attribute, and close matching to the originator fingerprint thus obtained at the preclinical stage is considered as mandatory to demonstrate similarity between the originator and the biosimilar at the level of quality, safety and efficacy (40). However, development of a new process and use of different host cell lines, expression systems and manufacturing conditions to ensure high similarity with the originator fingerprint for the reasoning that originator manufacturing process is not known to the biosimilar developer due to its proprietary nature (77) is principally not correct as a disclosure of the process in the technical document, enabling a person skilled in the art to practice the invention the same way as the innovator company is a legal requirement to discharge in the patent grant process. In the real-world examples, however, this requirement is not enforced on the part of Patent Offices because companies preferred holding manufacturing processes for competitive advantages (78). Nonetheless, rather than accepting this official slackness, biosimilar manufacturers companies must think of initiating

patent opposition or revocation proceedings against failure to disclose the enabling disclosure in the patent specification (79). Thus, need for developing a new process and calibrating process conditions to fine-tune biosimilar to the originator's fingerprint should be something connected with the availability of advanced analytical tools/methods since the originator was developed and characterized (about 5-8 years back) for improved quality, high-yield or enhanced production of the biosimilar rather than lack of knowledge about the originator process. Moreover, once similarity between the originator and the biosimilar had been established through – i) practicing the originator process or developing new or improved processes; ii) quality assurance at each step of the process development and product makeup (commonly: Quality-by-Design approach); (80) and iii) analytical testing to fully characterize the biosimilar, repeating analytical comparability exercise time and again throughout the life cycle of the biosimilar to demonstrate time and again that biosimilar squarely fits in a pre-defined set of critical quality attributes (including structure/sequence, content, glycosylation profile, biological activities, and process impurities) present in the reference biologic (81) seems not more than a commercial strategy to create barriers in the way to biosimilars uptake and market entry. This may be corroborated from the real-world situations in anti-rheumatic biologics where authorized changes in manufacturing process for therapeutic monoclonal antibodies following their initial approval, had never affected the critical quality attributes of the biologics (69). Experts' findings also support that biosimilars approved by advanced regulatory authorities warrant consistency in their quality, safety, and efficacy profile post-approval (82). This envisages that if biosimilars are biological products in much the same way as the reference biologics, then post-approval changes in process conditions for enhanced yield and improved quality must not affect the critical quality attributes of the biosimilar; hence any requirement to reiterate head-to-head comparability exercise from process development through production scaling-up, and process validation (1) in the absence of any documented evidence to the contrary must be treated as excessive. Taken it otherwise, to put the biosimilar developers under burden to re-establish that process developed for biosimilar manufacturing invariably produce a product meeting its pre-defined characteristics is discriminatory if the same process scheme that was developed for the first batch production, with reasonable process controls at each stage of the manufacturing had been followed.

Since consistency in product quality is principally dependent on the manufacturing process, strict monitoring, and controls at each stage of product manufacturing may ensure a biosimilar molecule with uniform product character and quality even batch-after-batch (1). Strict observance of 'process control guidance' (step-to-step quality checks throughout production) may in parallel evade concerns over safety/immunogenicity and ensure uninterrupted distribution of biosimilars and patient-physician trust (83).

Biologics impact on immunogenicity – does manufacturing process differences warrant the probability of biosimilar producing more ADAs as compared to the originator?

Another feature discriminating biologics, including biosimilars, from small-molecule drugs is immunogenicity. It is marked by the presence of anti-drug antibodies (ADAs) in the treated individual circulations. ADAs, whether neutralizing or non-neutralizing, may affect the biologics therapeutic efficacy either by reducing or inhibiting or sometimes modulating it (84). Also, antibodies cross-reactivity with endogenous proteins can lead to clinically meaningful consequences creating a serious barrier in the way to developing biologics. Consequently, the regulatory authorities urged the need for assessment of immunogenicity during different phases of the biologics development, including post-marketing safety surveillance (85). Immunogenicity is influenced by number of factors. In its "Guideline on Immunogenicity assessment of therapeutic proteins" (25), EMA has classified these factors into three: i) patient-related factors; ii) (a) disease-related factors; ii) (b) treatment-related factors; and iii) product-related factors (Table 4).

When establishing safety profile of the biologics as part of the regulatory approval pathway, in addition to the head-to-head assessment of analytical, non-clinical and clinical data, EMA, US FDA, and WHO recommend head-to-head assessment of clinical immunogenicity in a sufficiently sensitive population as mandatory (86,87). In biosimilars development process, immunogenicity assessment in clinical studies is a stepwise process (Figure 3).

It opens-up with the screening of the test sample to detect the presence of ADAs in treated patients (85). Given the fact that different therapeutics to be tested has different properties, there is no single assay for immunogenicity assessment. The guiding rule for assay selection is

Table 4. Factors influencing immunogenicity

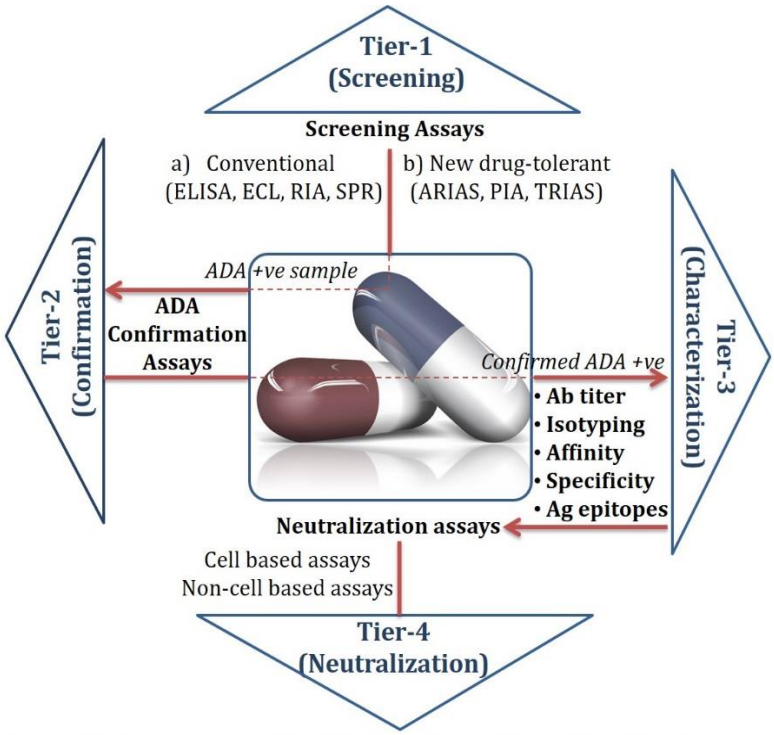
Category	Example
Patient-related	Genetic factors modulating the immune response
	Genetic factors related to a gene defect
	Patient immune system
	Age-related factors
Disease-related	Patient's activated or impaired immune system
	Therapeutic indications
	Disease stage
	Concomitant therapies
	Previous treatment
	Pre-existing antibodies
Treatment-related	Dosage
	Route-of-administration (intravenous vs. subcutaneous vs. intramuscular vs. inhalational vs. intradermal vs. ocular)
	Treatment duration (short-term vs. long-term vs. re-exposure after a long treatment-free interval)
	Pre-existing or endogenous antibodies resulting from previous exposure to similar or related therapies, but also present in treatment-naïve patients)
	Administration frequency
	Mechanism-of-action
Product-related	Nature and origin of active substance
	Protein size and structural complexity
	Post-translational modifications
	Formulation and packaging
	Denaturation or fragmentation
	Aggregation and adduct formation
	Impurities

[Source: Adapted from Pineda et al. (2016) (85)]

It opens-up with the screening of the test sample to detect the presence of ADAs in treated patients (85). Given the fact that different therapeutics to be tested has different properties, there is no single assay for immunogenicity assessment. The guiding rule for assay selection is its specificity, sensitivity, precision, drug-tolerance, and reproducibility with reference to the tested biological product (85). Screening step is followed by confirmatory assays that determine the particular specificity and sensitivity of the ADAs to the biosimilar and disregard wrong results (false positive). Samples that are ADAs positive undergo characterization assays that determine the concentration of antibodies (the titer) and nature of ADAs. For identification of neutralizing antibodies, bioassays or ligand-binding assays are used. ADAs potential impact on clinical outcomes is assessed through evaluating immunogenicity in combination with pharmacokinetic, safety, and efficacy considering the overall data collected during various stages of immunogenicity assessment (86).

It is scientifically and clinically proved that biological products are the safest drugs and generally do not induce any significant immunogenic response; and where it is, this gets as part of their mechanism-of action (or intrinsic property), not as an adverse event (88,89). The most significant adverse effect biologics may induce in treated patients is immunodeficiency that may lead to outcomes such as infections, and autoimmunity. It is generally assumed that even with minor differences when contrasting with reference biologics, biosimilars may induce atypical adverse events and anti-drug antibodies (ADAs); hence undertaking of comprehensive clinical studies throughout the various phases of biosimilars development and constant monitoring during post-marketing surveillance is critical to confirm initial assessment on biosimilars safety and efficacy (90). The concerns over safety of biosimilars got strength when the first-generation biosimilar – erythropoietin alpha – had been reported to cause severe anemia associated with pure red cell aplasia in chronic kidney patients (91). Though the incident eventually found to have been the result of improper changes in the product packaging unlikely to translate into clinically relevant consequences; nonetheless until today it is being ascribed to – i) changes in product characteristics due to variations in the manufacturing process; and ii) presence of neutralizing ADAs in the treated patients' circulations. This misconception has severely affected the physicians-patients' trust on the safety and efficacy of biosimilars; hence meager uptake in the global market since long (91). In keeping with these challenges, EMA, FDA and WHO have made assessing immunogenicity of biological biosimilars in clinical trials as well as during the post-marketing drug safety surveillance phase, a mandatory requirement (90).

The practice of monitoring 'real world' drug safety and efficacy post-approval (Phase IV study) to identify adverse effects that did not get surface at the clinical trial stage no doubt takes the drug safety to another level; but given the uncertainty at each stage of the biosimilar development pathway (Phase I- Phase III) and divergence in opinions what constitutes a clinically meaningful difference in immunogenicity due to lack of uniform standards for immunogenicity assessment, keeping a long-term track of biologics safety post-approval apparently seems to be a mere record-keeping and maintaining exercise. For instance, takes the case of Flixabi (an infliximab (Remicade) biosimilar) that received EMA approval notwithstanding that majority of the members of EMA Committee for Medicinal Products for Human Use had raised concerns over the high ADAs rates in Flixabi



Type	Result	Assays selection threshold	Assays validation studies parameters	Immunogenicity assessment study design
Tier-1	ADA positive sample	For screening assays ▪ Validated ▪ Sensitive ▪ Capacity of detecting all clinically relevant antibodies (including IgM & IgG subclass) ▪ Having sufficient throughput ▪ Automated	▪ Cut-points –(must be determined before commencing clinical trials) ▪ Sensitivity ▪ Selectivity ▪ Precision ▪ Specificity ▪ Robustness ▪ Concentration linearity ▪ Limit of drug tolerance	▪ Careful selection, assessment, and characterization of assays ▪ Identification of appropriate sampling points including baseline samples for determination of pre-existing antibodies ▪ Adequate sample volume ▪ Adequate sample processing/storage ▪ Selection of statistical methods for analysis of data
Tier-2	Confirmed ADA positive	For confirmatory assays ▪ Must take into account the limitations and characteristics of the screening assays		
Tier-3	Correlation of antibodies with clinical response Assays for clinical markers (including PK, PD) Evaluation of clinical impact of induced antibodies	For NAb assays ▪ Validated as per assay specific control signals ▪ Respond well to the biological product ▪ Tolerant to residual therapeutic protein		
Tier-4	Assessment of neutralizing capacity (or identification of neutralizing antibodies)	--		

Figure 3. Multi-tiered approach to immunogenicity assessment in clinical studies [Source: Adapted from Pineda et al. (2016) (85) and EMA Guideline on immunogenicity assessment of therapeutic proteins (25)]

treated patients compared to Remicade (the reference biologics) in Phase I and Phase III clinical equivalence studies (77). According to the committee members, high ADA rates questions the lower efficacy of the Flixabi versus Remicade; the propriety of bioanalytical platforms, and similar immunogenicity threshold (77). Approaching the issue from another perspective, at one end of the scale, it is clinically proved that immunogenicity of biological products is unpredictable and is subject to careful investigation; (92,77) while at the other, researchers and sponsors (pharmaceutical companies) have acknowledged the impropriety of the types of assays/techniques employed in the assessment of immunogenicity in clinical comparative trials and cautioned to exercise great care when comparing the immunogenicity patterns to avoid incorrect results (77,85,93). In parallel, experts have also acknowledged the absence of a universally validated, or calibrated approach for clinical immunogenicity assessment (77). Now the question needing scientific justification is how in the absence of a fully-validated, classified approach for clinical studies or trials, and uniform standards for the quality and quantity evaluation of the evidence, post-approval drug safety surveillance can get perfection. Still from another perspective, it is repeatedly said that even minor changes in the manufacturing process, processing conditions, and media ingredients can alter the molecular shape of a

biological product; hence its solubility, biological function or even immunogenicity; (77,94) but in parallel there is experimental evidence on record that supports the views that post-approval changes in manufacturing processes instigated by the need for producing good quality product in high yield or making use of state-of-the-art technology for scaling-up production for instance, do not question safety and efficacy of the biosimilar (5). For the sake of reference, in the EU market of anti-rheumatic biologics, since initial approval some biologics had more than 50 approved manufacturing changes, mostly having no impact on the CQAs of the product. On this issue, further supports may be taken from the FDA practices that follows the general founding principle on similarity assessment (i.e., "the higher the level of analytical similarity, the less the clinical evidence required to demonstrate clinical similarity") (63). Following this approach, FDA had approved low molecular weight heparin – Levonox- without any clinical trials (82). From FDA perspective, this once again clarifies and accentuates FDA's approach on the relative significance of analytical similarity assessment over clinical comparative trials.

Rationally speaking, if a biosimilar had received regulatory approval based on the integration of different markers and 'totality-of-the-evidence" submitted then what are the additional factors influencing different patterns of immunogenic activity and high risk of producing anti-drug antibodies post-approval (92). If such factors include use of high-throughput techniques developed in recent years for immunogenicity assessment (such as new drug-tolerant assays), then scope of such assessment should indiscriminately extend to new biologics as well. Contrasting immunogenicity data collected using traditional assays; increase in the level of antibodies using high-throughput techniques is associated with the more sensitive and specific nature of the modern immunoassays rather than changes in the manufacturing process or over time changes in the product quality attributes (85). Deliberating over the real-world instances, before sponsor of an already-approved biosimilar is required to submit additional data on immunogenicity to support safety and efficacy, factors including post-approval changes to the formulation, sensitivity and precision level of the modern immunoassays, sampling timings, pre-existing antibodies (natural or previous treatment-related), antibodies developed or likely to develop from parallel treatments, receptors, immune complexes, length of treatment, new patient populations to be treated and clinical relevance of immunogenicity data must be given due consideration (85).

In its 01 December 2017 Guideline on Immunogenicity assessment of therapeutic proteins, (25) EMA has mandatorily required conducting head-to-head comparative immunogenicity studies in biosimilar development; but has made it an optional requirement when there is a change in the manufacturing process of the product. In the latter case, the comparability exercise is a stepwise process (see ICH Q5E) beginning with analytical characterization (physicochemical and biological testing). If this step results indicate a difference between the pre- and post-change versions of the product, EMA requires immunogenicity evaluation integrated with the pharmacokinetic, safety, and efficacy testing. This impliedly suggests that akin to practices followed by FDA, in the absence of clinically meaningful differences in immunogenicity, EMA may relax the requirement for extensive comparative clinical data package on the efficacy and safety of the post-change version of approved biosimilar.

It is indisputable that strict quality control, stringent regulatory requirements for approval, robust post-marketing surveillance programs introduced by FDA, EMA, and WHO, and the clinical experience collected over the past decade for the first-generation biosimilars (such as erythropoietin, somatotropin, and filgrastim) and recently for the second- generation mAbs and antibody-receptor fusion proteins (such as infliximab biosimilars) have significantly restored the physicians-patients trust on biosimilars and consequently improved biosimilars uptake in the global market; (90) nonetheless given the paucity of clinical data on immunogenicity available at the time of biosimilar approval need for additional pharmacovigilance activities shall be remaining there as part of risk management plan. Should getting additional data on ADAs and trough levels be the requirement for assessment of immunogenicity and dealing with adverse events in the post-approval phase then there should be a strong scientific justification for the same before the sponsors take the requirements still another barrier in the ways to biosimilars uptake.

USE OF ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING (ML) IN BIOSIMILARITY ASSESSMENT

As technology advances, use of the most cutting-edge tools/technologies that can transfigure drug discovery and development process more efficiently and more reliably at each development stage up to its use in diagnosis and clinical settings is increasingly desirable for early market entry and improving healthcare system (95). As cost is the key

igniter on this track; reduction in costs and enhanced efficiency are the strategic targets. AI-augmented and cloud-based platforms (such as Augusta, IBM Watson,) offer a robust solution for the scientists and generic drug companies including the biosimilar developers (96). For finding a drug biosimilar, processing of existing drug compounds (or biologics) data and labeling according to their contents, molecular structures (or DNA sequences), shapes of crystals, binding sites, solubility, stability, dissolution rate, affinity etc. is a prerequisite. The processed and labeled data is then run through a machine-learning (ML) algorithm for finding list of brand-name counterparts. Generic drug manufacturers or biosimilar developers can then narrow-down the list of possible candidates until the most effective or good representative is filtered out (96). The company then needs to test only short-listed compounds/molecular entities to test their potential as the closest counterpart to the reference biologic. Integrating ML and AI in the healthcare system can escalate the process of finding workable biosimilars at a significantly low costs and human resources. Many top-ranked pharmaceutical companies such as - Johnson and Johnson in collaboration with IBM's Watson Health are making collaborative efforts for transforming high volumes of patients' data originated from clinical trials (especially cancer, autoimmune diseases and diabetes), private data (lab reports); MRI/CT Scan reports; and other healthcare data into a digital model and are applying ML and AI-based digital models to speed-up new drug discovery and development process, clinical trials, identification of novel drug targets, and finding of robust solution using real-time data to gain better insight on treatment preferences and faster diagnosis (97). Other big pharmaceutical and biotechnology companies (namely Merck, AstraZeneca, Sanofi, Abbvie, BMS, and Roch) are acquiring AI and ML technologies to bring their advantages direct to their businesses (98). Through democratization of real-time medical data, new algorithms can be developed allowing biopharmaceutical companies to get a preview about the clinical efficacy of their new biologic and biosimilars before they think of conducting costly and time-intensive clinical trials (99).

Crashing costs and timelines for new quality drugs to enter the market is not the only benefit ensuing from use of AI, ML, and technologies like blockchain. Other allied benefits from cost-savings for multi-stakeholders (such as payer, physician, patient, pharmacists, hospitals, clinics) evolving from digital technology drivers are: increasing access to biologic treatment; availability of healthcare at an early stage of diagnosis; patient's freedom to treatment options; increase in number of healthcare facilities (hospitals and doctors), spawning of new or improved innovations; improvements in hospital settings; increasing competition – drop in off-patent biologics prices, and consistent supply of low costs biosimilars (100). Strategically designed and scientifically applied, AI and ML can be used to perform extensive analytical characterization and comparative non-clinical evaluation to support similarity searching and demonstration of biosimilarity between the reference biologic and the biosimilar. The technology can put the biosimilar on the comparative clinical safety and efficacy/immunogenicity, PK/PD track more swiftly.

Clinical trial design for biosimilarity assessment

As repeatedly indicated that contrasting chemo-generics, biosimilars are structurally complex and because of the use of different living materials, manufacturing processes do not allow creation of identical or true replicas of originator products (the 'reference biologics'). This is why by far, biosimilars can offer comparable safety and efficacy; and are not truly interchangeable at the pharmacy level. Alongside these differences, clinical trial design in biosimilars drug development requires induction of new and diversifying approaches to address the new research question involving "no clinically meaningful differences" or "not worse than" about two interventions (experimental and controlled) (101).

Contrasting traditional trial design approaches (such as superiority trials and equivalence trials respectively built on "better than the control" or "as good as the standard treatment" hypotheses), non-inferiority trials have been set to demonstrate that the new treatment is 'not worse than' the established one by more than a small pre-specified amount (technically the 'non-inferiority margin' or 'delta (Δ) (102). In non-inferiority analysis, differences between the treatment results of the test drug and the active comparator are indicated in terms of confidence interval (CI). These confidence intervals are then compared to delta to assess whether the test drug is inferior, non-inferior or even better than the active comparator. On completion of the study, the lower 95% CI must not exceed the pre-defined delta limit (102,103) (Figure 4).

Defining delta is thus the most challenging in non-inferiority trials (104). Generally, non-inferiority margin is selected based on statistical and clinical considerations (such as increased safety, better compliance, easy administration, convenient dosing schedule, and low costs); but regulatory authorities

(such as EMA and US-FDA) preference is to set historical evidence of the active control as standard for defining delta (104,105). FDA expects at least two adequate and well-controlled non-inferiority trials to support biosimilarity; but in certain cases, such as where non-inferiority trials show superiority to an active control, a single trial may be taken as sufficient basis to support effectiveness of the test drug (106).

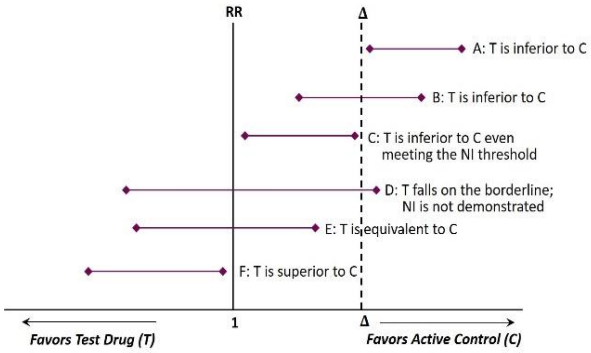


Figure 4. Possible outcomes of non-inferiority study with 95% Confidence Interval (CI). | = Solid vertical line represents relative risk of 1; ¦ = Dotted vertical line represents delta (Δ); Δ = Non-inferiority margin (5%); ─ = Each horizontal line represents a confidence interval (CI, 95%); RR = Relative risk; NI = If the upper bound of 95% CI does not exceed Δ; Superiority = If 95% CI does not exceed 1 [Source: Leung et al. (2020); Dranitsaris et al. (2013), Althunian et al. (2017) (103,105,106)]

Generally, non- inferiority trial outcomes are guided by confidence intervals (CI) which is calculated using the formula (107):

$$\overline{x} \pm z\frac{s}{\sqrt{n}}$$

wherein x̄ is the sample mean, z is the confidence level (e.g., for 95% or 99%CI, z value is respectively 1.960 and 2.576), n is the number of observations and 's' is standard deviation, calculated by the formula (107):

$$SD=\sqrt{\frac{\sum (x-\bar{x})^2}{N-1}}$$

Non-inferiority trials are need of time in that in many conditions such as cancer, myocardial infarction, and atrial fibrillation, use of placebo arm is unethical; hence assessment against an established treatment is robust and provides more effective treatment options. Non-inferiority trials are efficient and conclusive, and the clinical insight they provide facilitate drug manufacturers to decide on future investment plans; nonetheless acceptance of new treatment as standard treatment after non-inferiority trial success may result in entry of lesser treatments in the market; this is why unless the test drug is shown to be non-inferior and in parallel superior its acceptance as standard treatment in follow-up non-inferiority clinical trials must be carefully decided.

INTERCHANGEABILITY: MUST BE CONSIDERED ON A CASE-BY-CASE BASIS– ONE 'FIT-FOR-ALL-PURPOSE' APPROACH IMPRACTICABLE

In medical parlance, interchangeability refers to the possibility of using generic form of drug in lieu of the originator. Two drugs (small molecule drugs) may be said to be "interchangeable", if changing one drug for the other is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber (108). Contrasting chemo-generics, the additional threshold for biosimilars to receive the 'interchangeability' designation is 'alternating'. This is a practice to make certain whether or not a repeated and regular interchanging between a reference product and a biosimilar or replacing one biosimilar with another affect's safety or efficacy of the drugs in any given patient (25,68). If switching the same patient from a reference product to a biosimilar produces the same clinical results, and probability of risks in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch, the biosimilar may be entitled interchangeable biosimilar with the reference product (5,63).

Interchangeability is however not a change or shift during the course of treatment. A physician may take start with either of a reference product or a biosimilar. When starting treatment with a biosimilar rather than reference product is referred as 'primary substitution'. After the treatment has been started, a change from the reference product to a biosimilar (or vice versa) with the physician approval is a 'secondary substitution or switching'. Exchange between a reference product and biosimilar at the recommendation of the pharmacist, without explicit approval of the prescriber, is designated as 'automatic substitution' (109). This suggests that notwithstanding a biosimilar is 'highly similar" or "comparable" to a reference product, decision on substitution (at the pharmacy level) or interchangeability (by physicians) with the reference product is not automatic[110]. Depending on the untoward immune response induced by the biologic, affecting treatment efficacy and creating adverse event or causing neutralization of the therapeutic product, treatment prescriber shall decide on switching. For non-medical reasoning

(such as costs and availability), substitution decision may be taken at the pharmacy level (72). For the sake of illustration, biosimilar epoetin is an effective, well tolerated, and less-expensive option for the treatment of renal anemia, as such reasoning for switching from the reference biologic to the biosimilar is apparently non-medical (72). However, as manufacturing process can change the glycosylation site occupancy pattern that affects EPO glycoforms activity, decision on switching is then prompted on medical reasoning. Need for increasing dose of biosimilars insulin post-switch, inefficacy, intolerability, mode- and route-of-administration do fall within the domain of medical perceptive, shifting the burden of switching decision on the treatment prescriber (72).

For alternating or switching studies of biosimilars, several designs moving back and forth from single switch to multiple switch have been suggested; but the ultimate threshold for interchangeability has been set to be - the state-of-the art demonstration of biosimilarity together with expansive post-marketing surveillance plan to dispel any disquiets over immunogenicity (111) (Figure 5).

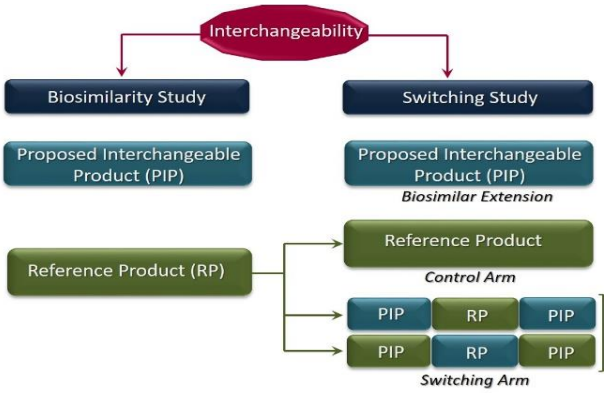


Figure 5. Possible switching study design for interchangeability demonstration. To support a designation of interchangeability, the clinical pharmacokinetics (PK) is the most sensitive endpoint. Apart, other endpoints such as assessment of immunogenicity and safety are clinically important. [Source: Adapted from 'FDA guidance for industry on considerations in demonstrating interchangeability with a reference product' (112), and Laura et al. (2019) (121)].

In EU, EMA in coordination with EC had published a guide to biosimilar medicine in 2017. This guide has created a distinction between interchangeability, switching and automatic substitution. According to the guide, "exchanging one medicinal product for another that is expected to produce the same clinical effect" is interchangeability (110). On interchangeability of biosimilars, the current EMA position is that it has not provided any regulation on the issue; and has left the practice for regulation by the national regulatory authorities under their respective legal frameworks. Independently, national regulatory authorities favor physician's involvement on interchangeability decision provided patients' prior informed consent and adequate clinical monitoring is fixed (110). Given the stringent regulatory approval pathways for biosimilars, regulatory authorities from some EU states like Norway, Netherlands, and Germany have unanimously declared that "EMA-licensed biosimilars are interchangeable" (72). A biosimilar that is developed in line with the EMA standards may however be substituted with the reference product as a therapeutic alternative.

On May 13, 2019, FDA issued a legally non-binding guidance to assist sponsors in demonstrating that a proposed biosimilar product is interchangeable with a reference product. The guidance focuses only on therapeutic protein products – one class of biologics. The guidance is evocative of the FDA's mindset on the subject of interchangeability and implicates *"s*omething is suggested or recommended, but not required". Avosla (infliximab-axxq; Amgen) – the fourth biosimilar to Remicade (infliximab; Janssen Biotech, Inc.) approved in 2019 – is approved for all eligible indications of the reference product; but not approved as an interchangeable biosimilar (112).

On interchangeability, Indian guideline for similar biologic approval is silent. Pakistan however follows the same approaches as EMA, FDA, WHO developed on interchangeability. The above implies that in the highly regulated markets of USA, EU, Canada, and Australia interchangeability remain a clinical decision and is considered on a case-by-case basis based on the totality-of-the-evidence (72). In the less regulated markets of Asia-pacific, where legal frameworks on biosimilarity and interchangeability are still evolving, a biosimilar that is designated 'interchangeable' elsewhere is considered as safe and effective as the reference drug.

Notwithstanding that in legal terms, biosimilars and interchangeable biological products have distinctive targets to achieve nonetheless once similarity between the candidate biosimilar and the reference biologic has been established through rigorous head-to-head comparability exercise at the level of molecular structure, content, glycosylation profile, biological activity, process impurities (typical critical quality attributes (CQAs) for a mAb)[1], pharmacodynamics and pharmacokinetic parameters, as well as safety, efficacy, and immunogenicity; and production of full "body-of-

evidence" relating to all phases I-IV of drug development, (25) concerns over safety of switching or diminished efficacy of alternating or switching and need for further studies/clinical trials evaluating two or more alternating switches to ensure that *such alternation or switches between the reference drug and the biosimilar or another biological product do not affect the therapeutic safety and efficacy* seem to be imaginary and an insurmountable barrier in the biosimilar uptake in the market and substitution decision at the pharmacy level (14). Safety and efficacy of switching to biosimilar may be evidenced from the results of clinical trials conducted as part of the regulatory requirements or to secure interchangeability designation, such as short-term, phase III EGALITY trial involving switching from reference etanercept to biosimilar GP2015 conducted on 200 patients; phase IV non-inferiority, randomized NOR-SWITCH trial contrasting effect of switching from reference infliximab to biosimilar infliximab (CT-P13); post-approval, randomized, double-blind PIONEER study probing the safety and efficacy of filgrastim biosimilar EP2006 for the prevention of severe neutropenia in patients with breast cancer; multicenter, randomized, confirmatory studies of the biosimilar infliximab CT-P13 (PLANETRA and PLANETAS), having 1-year open-label extension phase; multicenter, randomized, double-blind phase III study contrasting the safety of switching from the reference adalimumab to the biosimilar ABP501; Dutch multicenter prospective BIO-SWITCH study in patients with RA, PsA, and AS analyzing the impact of switching from originator infliximab to the biosimilar on the treatment results, and several others studies conducted during the last 15 years. And in cases of adverse events, the degree of risk involved in switching to biosimilar is not greater than continuing treatment with the originator (110).

Given the above, and the facts that risk-benefit profile of the originator drug has already been demonstrated by the innovator company, (65) while "high- or fingerprint-like similarity threshold for the biosimilar has been discharged by the biosimilar manufacturer through demonstrating close analytical similarity and similarity at the level of biological CQAs to the reference biologic, (1) regulatory authorities requirement for conducting extensive clinical studies to evidence safety of switching to get "interchangeable designation", provides no other logical explanation except to creating another barrier in the way to biosimilar market entry. In the public interest, the said requirement needs to be relaxed to allow the low-cost biosimilars to enter the market swiftly.

EXTRAPOLATION OF DATA TO OTHER INDICATIONS IS POSSIBLE IF THE PRESENTED SCIENTIFIC EVIDENCE ADDRESSES ALL POSSIBLE FACETS OF THE 'EXTRAPOLATED' INDICATION (MECHANISMS-OF-ACTION, SAFETY, AND IMMUNOGENICITY)

Another matter of debate in biosimilarity consideration is extrapolation of data to other indications of the reference product. For instance, use of first-generation filgrastim biosimilars is extensively studied only in cancer patients or patients with depressed immune response as such its use in mobilizing and collecting stem cells in healthy donors may lead to seriously biased estimates as the different medical indications apparently do not hold the region of extrapolation (27). Likewise, in case of second-generation infliximab biosimilar CT-P13, be supposed to clinical evaluation in aortic regurgitation and ankylosing spondylitis, granting of marketing authorization for inflammatory bowel diseases by the major regulatory authorities has sparked strong debate questioning scientific reasoning supporting such decision (113). Concerns over use of biosimilar anti-inflammatory mAbs in rheumatoid arthritis, gastroenteritis, and dermatitis indications are also growing with increasing intensity.

Contrasting first-generation biosimilars with one active site and capacity to bind the same receptor and as such the same mechanism-of-action across all therapeutic indications; the second-generation biosimilars (mAbs and antibody-receptors fusion proteins) with complex mechanism-of-action and multiple receptors or binding sites [primary antigen-binding regions (Fab) and potential effector function regions (Fc)] have the capacity to provoke different auxiliary effects that may contribute at different degree to the efficacy (or tolerability) of mAbs across different therapeutic indications (90). If difference in mechanism-of-action are taken as relevant, additional studies (nonclinical or clinical) may be needed. Considerations for extrapolation of data therefore cannot be justified on statistical grounds solely; it needs to be justified scientifically by some objective studies.

In European Union, EMA has tried to resolve the controversy by setting below standards for extrapolation considerations:

i) Demonstration of similarity with the reference based on the totality of evidence gathered from systematic comparability exercise at the level of structure, function, PK and PD.

ii) In case of different or unknown

mechanism-of-action, submission of additional corroborating evidence (non-clinical or clinical) on biosimilars similar impact on the studied indication as the originator product.

iii) Characterization of biosimilar safety profile with reasonability and elimination of intolerable immunogenicity (25,27).

Of note, scope of extrapolation of data is not restricted to new biosimilars but extends to comparison of changes in the already-licensed product attributes, approved for variety of therapeutic indications, due to post-approval manufacturing changes. According to the KCE Report-2013 (27) experts had not come across even with a single instance where new clinical data was required for every indication. The scientific justification behind this was the overall data collected from the comparability exercise that had convincingly established that changes in manufacturing process have no adverse bearing on the product safety and efficacy; hence absence of clinical trials did not suggest compromised safety in case of biosimilars (114).

Relying on the scientific justification threshold, EMA approved infliximab biosimilar (Remsima) for all indications for reference product upon submission of data supporting lead indications - rheumatoid arthritis and ankylosing spondylitis.

In the USA, on the question of extrapolation, sufficient scientific justification may let the candidate biosimilar to be approved for more conditions of use for which the reference product is licensed. In extrapolation considerations, FDA guidance has outlined mechanism-of-action in each condition of use; PK, bio-distribution, and immunogenicity in different patient populations as sufficient to support extending the safety data to other indications.

LABELING BIOSIMILAR – EFFECTIVE POST-MARKETING SAFETY SURVEILLANCE REQUIRES DISTINCTIVE LABELING

One of the prerequisites for effective management of post-marketing safety surveillance of biologics is its one-off, confusion-free labeling or identification. This requisite is further fortified by the physicians' need to correctly report and ascribes the adverse drug reactions to the correct biologic (77). While regulators have evenly recognized the need for labeling; but whether a biosimilar should have exactly the same non-proprietary name as the reference product or this should be a distinctive of the reference product or a mixing of the two, the regulators opinions diverge. For the sake of reference, in its Draft Proposal on 'the International Non-Proprietary Names (INN)' dated July 2015 (115), WHO has suggested adding a voluntary but independent, unique but non-promotional, devoid of meaning but capable to trace the source or origin of product, a four-character biological qualifier at the end of the biosimilar (5). EMA, at the other end of the scale, favors using the same INN naming for biosimilar as for the originator but at the same time require indicating the brand name and batch number during ADR reporting to let the two products correctly differentiated (77,90). EMA sees comparability of two biologicals as a sufficient ground for common INN naming (27).

FDA approaches biosimilars designation issue from another perspective. According to FDA, the issue should not be interlocked with regulatory approval process, interchangeability considerations or INN name usage in pharmacovigilance studies (27). FDA holds the view that originator companies assign INN name to new chemical entities or new biologics far ahead of the drug regulatory process is finalized and as such any nexus between interchangeability and INN resulting in inappropriate substitution of the products with similar INN is disavowed (27). FDA argues that similar INN validates that active in both biosimilars and the reference product is comparable.

Following WHO proposal, FDA released its draft guidance 2015 and invited suggestions whether four characters should be devoid of meaning or meaningful as filgrastim-sndz (filgrastim-sandoz) the placeholder's name given to the first FDA-approved biosimilar. Whether interchangeable biosimilar shall follow the same nomenclature is yet to be decided (5). FDA however does not sanction incorporation of comparative data supporting demonstration of biosimilarity in the biosimilar product labeling. This can be accessed from the FDA website (Drugs@FDA).

To let the pharmacovigilance effective in its fundamental objectives, physicians, pharmacists, dispensaries, and hospitals must have correct information about ADR reporting obligations (77). In a survey of Dutch Hospital conducted in 2016, only 76% of the ADR reports contained the brand names of the biologics while that reporting needs to be fully consistent and must indicate the batch number to make the post-marketing surveillance effective (116). Secondly, though clinical switching studies is not mandatory for regulatory approval nonetheless submission of switching-related immunogenicity data in the post-marketing surveillance phase should be made obligatory to avoid physician's meeting with residual uncertainty when assessing the potential impact of switching in their patient populations. Apart, the condition of use and route-of-administration (subcutaneous,

intramuscular, or intravenous) must be included in the labeling to let the physicians make suitable treatment plan for their patients.

PHARMACISTS' FREEDOM-TO-SUBSTITUTION – A MATTER OF STATES PREROGATIVE IN EU, REGULATED BY FDA IN USA, NOT OF CONCERN IN INDIA, BUT ACKNOWLEDGED BY DRAP IN PAKISTAN

Chemo-generics role in reducing healthcare costs is well recognized but the credit equally goes to pharmacists' ability and independence over generic drugs substitution decision with branded drug (or substituting prescribed medicine with an alternative medicine). For biosimilars however, pharmacists' freedom-to-substitution meets with two restrictions: firstly, they are required to receive sufficient authority for substitution independence from their respective state pharmacy practice laws; and secondly, they need to give due consideration to the additional standards set by FDA before they could make a substitution-decision (5).

With the publication of FDA's Purple Book providing details/list of all biological products (including biosimilars) and prospects of products interchangeability with another product (117), pharmacists are now in better position to make substitution-decision provided state pharmacy practice laws equally support such decision[5]. A product designated 'interchangeable' means that the product meets the FDA's high standards of interchangeability and may be substituted with the reference product at the pharmacy-level foregoing prescriber's consultation. Switching between non-interchangeable and the reference product is, however, still a matter of careful consideration in patients for immunogenicity reasons. For patient's safety reasons, treatment should be continued with either of the two first administered[5].

Countries that do not allow automatic substitution of biosimilars at the pharmacy-level may avail alternative "therapeutic interchange" mechanism to get the drugs including biologics prices lowered (118).

In the EU, "automatic substitution" at the pharmacy-level is not normally practiced. The matter is left at the state's prerogative.

CONCLUSION

Loss-of-exclusivity (patent and/or data) over new biologics opens up a mechanically-gated opportunity for generic drug companies to go-to-market with competing biosimilars. This apparently seems promising; but indeed, entrapped with so many competition-discouraging strategies prevailing "the survival of the fittest". Stringent regulatory requirements, demand for additional clinical studies to rule out manufacturing differences post-approval, constraints over pharmacy-level substitution, and mandatory switching studies/non-inferiority trials for interchangeable designation are some of the key factors compromising the low-cost and enhanced accessibility mandate for biosimilars. Though current advances in science and digital technologies such as the cloud-based platforms, AI, ML algorithms, and Internet of Medical Things (IoMT) collectively offer the potential for creating a new digital healthcare ecosystem that can be more centralized and speedy, accelerate drug development and regulatory approval process, reduce clinical trial costs, improve clinical R&D productivity, and increase the opportunity to ROI (119); nonetheless until a suitable framework for their integration into healthcare system is developed, pharmaceutical companies must be careful as too much reliance on the skills and knowledge of contract research organizations (CROs) and clinical trial experts may direct them towards a great void. In conflict cases, these CROs can deny access to the real-time data and use it in parallel to run their own line of business activities, turning the healthcare system once again towards its embryonic condition (120). Being the market of future with sales estimate around $15bn by 2020, global harmonization and perfection in biosimilar development approaches and regulatory pathways is increasingly wanting. Until this is achieved, access to the originator manufacturing process including technical information and all associated platforms are the real-world approaches to reduce biosimilar development costs, enhance uptake and increase acceptance in the global market.

CONFLICT OF INTEREST. None.

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