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PERSPECTIVE

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Biosimilars and interchangeable biosimilars: facts every prescriber, payor, and patient should know. Insulins perspective

Shashank R Joshi[a], Shivani Mittra [b], Praveen Raj[b], Viraj Ramesh Suvarna[b] and Sandeep N Athalye[b]

[a]Department of Diabetology and Endocrinology, Lilavati Hospital and Research Center, Mumbai, India; [b]Clinical Development and Medical Affairs, Biocon Biologics Ltd, Bengaluru, India

ABSTRACT

Introduction: For many of the 537 million adults living now with diabetes, the cost of insulin is becoming prohibitive as the insulin prices have tripled between 2002–2013. Globally, the direct annual cost of healthcare expenditure due to diabetes will soon be US$1 Trillion. Biosimilars provide access to high-quality, affordable biologic therapy that is otherwise inaccessible due to the high costs of original biologics.

Areas covered: A primer to the development of biosimilars shows comparable structural and analytical characterization to the original biologics (e.g. insulins), with no clinically significant or meaningful differences in efficacy and safety. 'Interchangeability' status, a regulatory designation by the US FDA, bestowed to some biosimilars, enables confidence in high-quality, bio-equivalent biosimilar of insulin with key global approvals. This can allow rapid uptake of biosimilars by the prescribers, formulary decision-makers, and payors. Biocon-Viatris's biosimilar Insulin Glargine (Semglee®) is the first interchangeable biosimilar insulin approved by the US FDA.

Expert opinion: The 'interchangeable' status can prompt faster and wider uptake of insulin biosimilars and keep the insulin expenditure under control, especially for patients who otherwise practice non-adherence or rationing of life-saving insulin. Education, support, and awareness can ensure that interchangeable biosimilars gain wider acceptance.

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biologics; biosimilars; interchangeable; regulatory; substitution; switching

1. Introduction: a primer on biosimilars

Biosimilars are lower-cost biological treatments for diseases such as autoimmune disorders, cancers, genetic disorders, and diabetes and are intended to increase patients' access to biologics as they are priced lower than the original biologic and may further lead to the competitive pricing of the original biologic. Taking diabetes as an example, with the direct annual cost of treatment soon reaching US$1000 billion globally [1], biosimilars come across as an innovative solution to bring down and keep insulin expenditure in control, especially for the under- or un-insured patients, who, in certain cases, start rationing their life-saving insulin, leading to potentially fatal complications. Of the uninsured in the US, nearly 70% are paying the full price of insulin, which can be as high as US$900 for a month's supply [2].

Biologics are generally large, complex structures manufactured from living organisms through complicated biotechnological processes and, as a result, display inherent variability and structural differences even between batches of the same product [3]. Hence, batch-to-batch consistency is vital for both the original biologic and its biosimilar, which is also a biological product similar in all respects to the original reference biologic. In contrast, generic drugs are small molecules that have simpler structures and are relatively easier to characterize and be manufactured reproducibly, resulting in lesser time and cost of development. Despite sharing a similar commercial basis for development, generic drugs and biosimilars differ in terms of structure, development, regulatory requirements, and authorization [4] (Table 1). The innovator never reveals the proprietary information; therefore, the biosimilar manufacturer uses a different source and a different process, and the process, in turn, defines and becomes the product. Biosimilars are not bio-identicals because, during the process, post-translational biochemical modifications such as glycosylation, sialylation, phosphorylation, acetylation, or amidation may occur. These are also not bio-betters, which are improved versions of the biologics and are regarded as new biologic entities in themselves. However, since they have to demonstrate therapeutic equivalence, for all practical purposes, biosimilars are identical to the original biologics as there are no clinically significant or meaningful differences in efficacy and safety, including immunogenicity. The basic amino acid sequence is identical for the biologic and its biosimilar; thus, the orthogonal analytical techniques used to establish bio-similarity become a unique fingerprint identifier (Figure 1). A biosimilar manufacturer may measure up to 100 critical quality attributes (CQAs) across 40 or more biochemical, analytical, pharmacological, or functional assays to ensure bio-similarity [5].

CONTACT Shivani Mittra shivani.mittra@biocon.com Biocon Biologics Ltd, Biocon House, Tower 3, Semicon Park, Electronic City - Phase II, Bangalore – 560 100, India

Article highlights

- Biosimilars have comparable structural and analytical characterization to the original biologics with no clinically significant or meaningful differences in efficacy or safety.
- Biosimilars provide access to high-quality, affordable biologic therapy that is otherwise inaccessible due to high cost.
- The biosimilar denoted with an 'interchangeable product status' by the US FDA may be substituted for the reference/originator product after following stringent requirements to be deemed 'interchangeable'.
- This substitution can be an 'auto-substitution' at the pharmacy level as is clinically practiced in the US, Canada, and Australia.
  OR It can be a physician-guided substitution, also called 'switching,' as is clinically practiced in some member states of the EU, India, Japan, and the rest of the world.
- Biocon-Viatris's biosimilar Insulin Glargine is the first 'interchangeable' biosimilar insulin approved by the US FDA.
- Patient and HCP's education and support programs play an important role in the faster and wider uptake of biosimilars.
- Insulin biosimilars with key global approvals provide value to patients and payors who are paying for expensive therapies.

Table 1. Comparison of biologics, biosimilar, and generics.

	Relative Comparison		
Attribute	Biologic	Biosimilar	Generic
Complexity of manufacturing	++++	+++++ (relatively more complex as needs to be matched to specifications established by reference product)	++
CMC characterization complexity and burden	+++	++++	++
Clinical development complexity/burden	++++	+++	+
Cost of development	++++	++	+
Time from start of development to approval (in years)	8–10	5–7	1–2
Interchangeability and/or substitution [7]	No	Yes (approval may need additional studies)	Yes

CMC, chemistry, manufacturing, and controls.
All comparisons are based on authors' experience working on generics, biologics, and biosimilars.

2. Regulatory requirements for biosimilar approvals: comprehensive and evolving

Biosimilars are designed to match the structure, function, and clinical effects of an already licensed reference biological product. A head-to-head comparison with the reference/originator biologic's CQAs and other quality attributes is required to demonstrate the bio-similarity of the proposed biosimilar. Also, once demonstrated, the comparable analytical characterization and similarity of the biosimilar with its reference biologic help in seeking approval for all originator indications without the need for large clinical trials [6]. The FDA has established extensive biosimilar guidelines to evaluate and establish bio-similarity. It defines a biosimilar as: 'a biological product highly similar to the reference product notwithstanding minor differences in clinically inactive components' and 'with no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product' [7–9]. The approval pathway for biosimilars was instituted in the EU in 2006 [10], and these guidelines were revised in 2015 [11]. According to the EMA, a biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). Similarity must be established in terms of quality characteristics, biological activity, safety, and efficacy [12].

There has been a rapid evolution of guidelines, with most countries adopting the general framework of the US FDA, EMA, or WHO, whereas others established their individual guidelines based on these principles. Through the rigor of the guidelines, the regulatory authorities ensure that biosimilars meet high standards of quality, safety, and efficacy, as well as exhibit bio-similarity to the reference product [10,13].

The regulatory requirement for biosimilars development is to test it under the paradigm of 'totality of the evidence' criteria, which can be defined as the sum of data from analytical chemistry, manufacturing, and controls (CMC); functional assays; animal studies; clinical pharmacology [pharmacokinetic (PK),

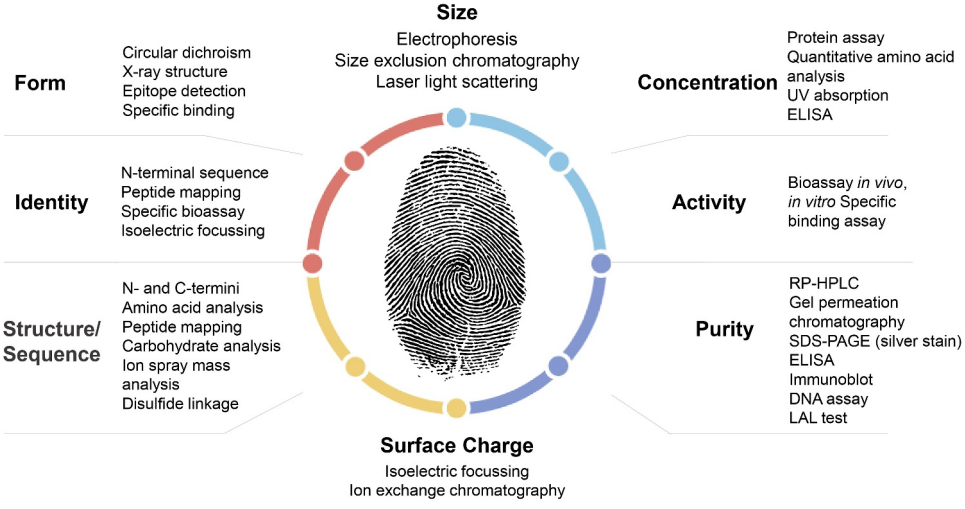

Figure 1. Orthogonal analytical techniques used to ensure bio-similarity.

pharmacodynamic (PD)]; and clinical Phase 3 studies on efficacy and safety, including immunogenicity studies [8,14]. Upon a case-by-case evaluation, the FDA can mandate a few studies in order to prove high similarity to the originator biologic, or even waive off a few studies, while establishing its efficacy [8]. The 'totality of the evidence' accepted by the US FDA, EMA, and WHO denotes that 'the patients can expect the same clinical performance when using the biosimilar as when using the reference biologic' and that 'there will be no clinically meaningful differences with respect to safety or effectiveness' [15,16].

2.1. Biosimilar development process

Development requirements of biosimilars are different from the original biologic, with a higher focus on the analytical characterization and demonstration of clinical equivalence with the reference biologic (Figure 2(a); Figure 3). The development process may vary between countries keeping in mind the country-specific regulatory requirements and understanding different countries' regulatory nuances can be complex (Figure 2(b)). It is challenging for biosimilar developers to develop a clinical development package that satisfies the requirements of all key regulatory agencies. Harmonization in the requirements will be needed for optimizing and reducing the development costs for biosimilars in the future, which will spur more competition and further benefit patients and payors. The following section talks about the development requirements of a biosimilar, taking insulin as an example.

2.1.1. Pre-clinical studies

The pre-clinical phase for biosimilar insulin includes the following studies for comparison of the biosimilar to the reference biological as described in the FDA and EMA guidelines. It encompasses comprehensive structural and analytical characterization, *in vitro* functional assessments, and PK/PD and immunogenicity assessments in animals [17]. It is worth mentioning here that the FDA's Center for Drug Evaluation and Research is encouraging the use of new approach methodologies to improve regulatory efficiency and potentially expedite drug development of new biotechnology-derived products [18]. The US Congress has begun an amendment to the Biologic Price Competition and Innovation Act (BPCIA) to remove animal testing of biosimilars [19].

2.1.1.1. Analytical characterization.

We cannot underscore enough the importance of the analytical and functional data to establish molecular similarity and hence the 'totality of the evidence' for the development of biosimilars. If any residual

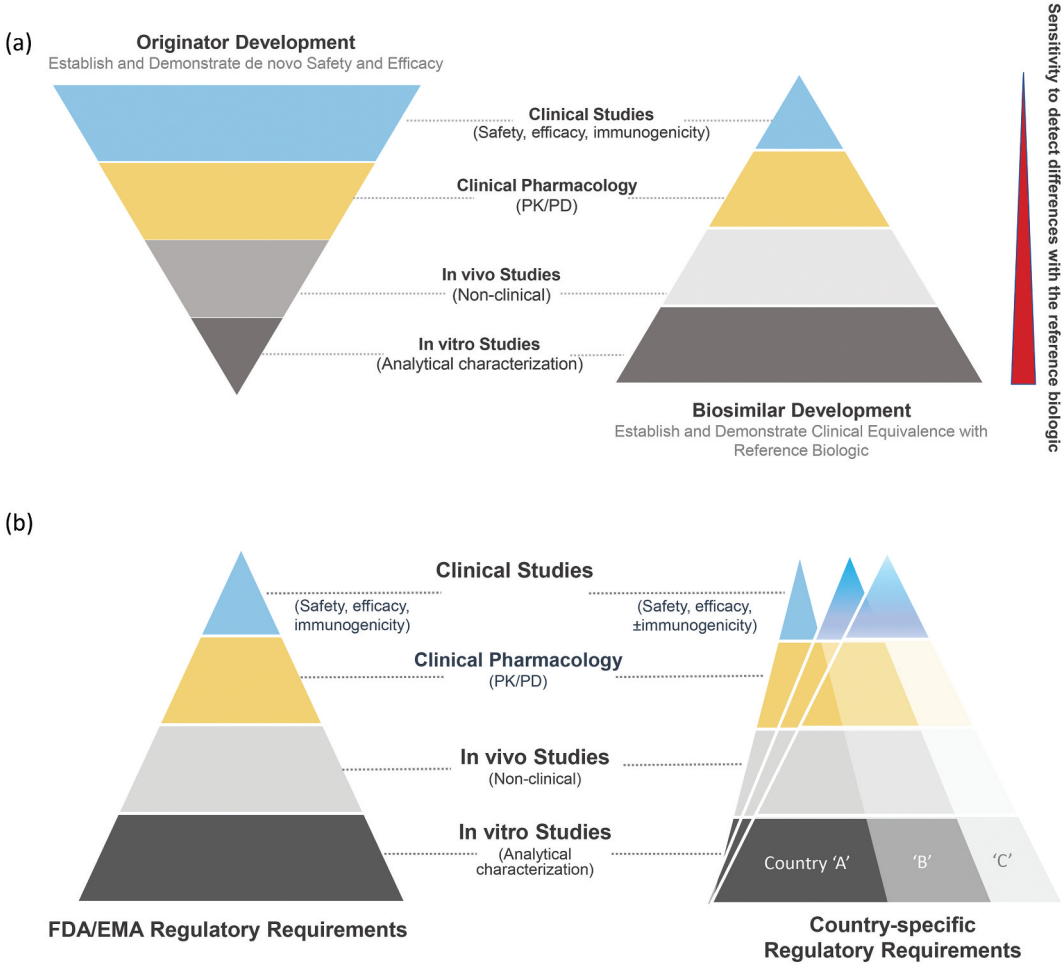

Figure 2. (a) Development pathway of biosimilars vs innovators. (b) Understanding different regulatory nuances of different countries are complex.

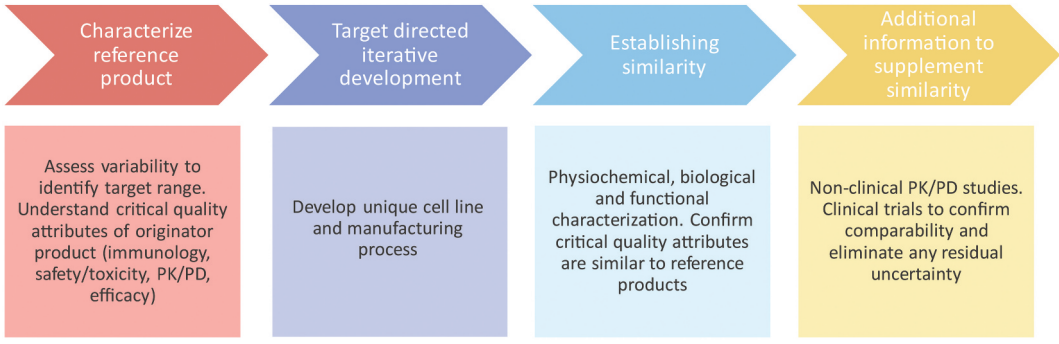

Figure 3. Schematic of biosimilar development.

uncertainty is observed after the analytical similarity assessment, human PK and PD studies and (if required) safety and efficacy trials are carried out to ascertain potential clinical relevance [8,15,16,20].

The biologics subchapter of the FDA 21 CFR 601.2 recommends that a 351(k) Biologics License Application (BLA) should have adequate CMC information, including validated manufacturing processes and quality control aspects [21]. The primary amino acid sequence of a biosimilar is kept sacrosanct; however, other features of the biologic protein such as three-dimensional folding, glycosylation, charge, and impurities are variable based on the manufacturing processes followed [22]. These other features can affect the antigen-binding and the immunogenicity of a drug, and in turn its efficacy and safety.

Modern analytical methods such as ultra-high-resolution mass spectrometry can provide an in-depth comparative analysis of the proposed biosimilar to its reference biological product. Liquid chromatography-mass spectrometry peptide mapping with Edman sequencing confirms the primary sequence of the amino acids. Accurate analytical characterization can be done to assess bio-similarity between the biosimilar and the reference product by analyzing higher-order structures, including secondary, tertiary, and quaternary structures (including aggregation), enzymatic post-translational modifications (such as glycosylation, phosphorylation, sialylation, acetylation), protein deamidation and oxidation, and directed chemical modifications such as PEGylation sites and characteristics.

The advancement in protein structure characterization has led to many improvements in the manufacturing processes and product testing. Extensive clinical experience and better scientific understanding of insulin, which in comparison to other biologics is a well-understood and well-characterized, structurally uncomplicated protein, has come up with no meaningful clinical impact of immunogenicity on its safety or efficacy [21]. The real-world evidence also validates diminished concerns about the immunogenicity risk affecting the safety and efficacy of insulin.

2.1.1.2. In vitro functional assays. Binding assays to insulin receptors (IR-A and IR-B), on/off cellular kinetics, *in vitro* biological activity such as receptor auto-phosphorylation, metabolic activity (glycogen formation, lipogenesis, inhibition of simulated lipolysis, and glucose transport), and mitogenic activity are some functional assays undertaken to ensure biosimilarity [8,11,23].

2.1.1.3. Animal studies. Animal toxicity studies or studies using human cells and tissues, single-dose animal PK/PD studies, and immunogenicity studies involving measurement of anti-therapeutic protein antibody responses are undertaken [14]. Pre-clinical *in vivo* studies are conducted in relevant animal species in which the reference biological product has an established toxicological or PD profile. If a biologic is cross-reactive with humans and one or more non-clinical species, the animal species are expected to be reflective of results in the humans. Most agencies do not require non-human primate studies for ethical reasons.

The EMA [10] and WHO [24] regulatory guidelines suggest consideration of at least one repeat-dose toxicity study, including PK and immunogenicity measurements, in relevant species [10,13,16,24].

The US Congress is potentially suggesting amendments to BPCIA to remove animal testing, and it is hoped that the EMA will also come up with a definitive statement on this, although this is already an assumed status with the EMA [25].

2.1.2. Clinical studies

2.1.2.1. Phase 1: pharmacokinetic/pharmacodynamic studies [11]. PK and PD bioequivalence are essential to prove similar efficacy between the biosimilar and the reference biological insulin. EMA guidelines for biosimilar insulin analogs recommend PK/PD studies to be carried out in normal healthy volunteers or patients with T1DM in a crossover design wherein insulin action is measured by the extremely stringent euglycemic hyperinsulinemic clamp technique.

2.1.2.2. Phase 3: efficacy and safety studies [26]. The phase 3 trials are designed to establish equivalence or non-inferiority. Euglycemic glucose clamp studies in healthy volunteers are used as surrogate markers for the PD effects of glucose-lowering drugs and waive the need for comparative phase 3 clinical studies in the EU. Safety studies are focused more on comparative clinical immunogenicity as immune response can affect the safety and effectiveness of the product. As per the US FDA's Guidance on Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin products (November 2019), 'if a comparative analytical assessment based on state-of-the-art technology supports a demonstration of "highly similar" for a proposed biosimilar or interchangeable insulin product,

there would be little or no residual uncertainty regarding immunogenicity; in such instances, the proposed biosimilar or interchangeable insulin product, like the reference product, would be expected to have minimal or no risk of clinical impact from immunogenicity' [21]. Hence, in these cases, a comparative clinical immunogenicity study generally is not deemed necessary to support a demonstration of biosimilarity and/or interchangeability.

2.1.2.3. Immunogenicity studies. Immunogenicity refers to the development of antibodies against the drug [i.e. anti-drug antibodies (ADAs)]. Therapeutic insulins and their biosimilars, derived from a living organism through recombinant DNA or controlled gene expression methods, are immunogenic, with nearly 90% of patients developing antibodies to insulin, regardless of their purity and origin. Unlike small molecules and their generics, biologics and their biosimilars are large, high-molecular-weight, three-dimensional structures that may contain modified forms of the basic structure. As these are complex biopharmaceuticals, batch-to-batch heterogeneity while manufacturing and processing proteins even under stringent conditions is unavoidable.

There may be several factors that can induce immunogenicity with insulin use, and these may include the protein structure and characterization, glycosylation, manufacturing and downstream process impurities, formulations, aggregates, dosage, treatment duration, and route of administration [13]. The other important aspect is that T1DM patients are more immunogenic than T2DM patients. To assess the immunogenicity considerations between the biosimilar and the reference biologic, the following are observed: changes in ADA incidence, relative antibody levels, the incidence of ADA cross-reactivity to human insulin, and drug-specific ADAs. This assessment covers the nature of the immune responses, the incidence of the immune responses, any loss of efficacy, or any new safety concerns, and with ADAs developing early, a 6-month study is sufficient to observe the incidence and titers of the antibodies. There is, however, little evidence both through longer-term clinical trials and through real-world data to suggest that the insulin antibodies developed as a result of the insulin treatment affect glucose homeostasis, dose requirements, or incidences of hypoglycemia [27,28].

The US FDA and the EMA guidance on clinical immunogenicity considerations for biosimilars and the US FDA guidance on interchangeable insulin products, for the same, do not specifically recommend comparative clinical immunogenicity studies provided that analytical assessment supports the demonstration of a 'highly similar' biosimilar product. The EMA has a specific requirement that studies should always include a reasonable number of people with T1DM, underscoring the propensity of this population toward immunological responses. For mixed populations, the type of diabetes and pre-existing anti-insulin antibodies should be stratified. As blinding of study participants is likely unfeasible, at the minimum, the ADAs are to be determined in a blinded fashion [11,13].

More on immunogenicity is discussed in the next section in the context of immunogenicity being regarded as one of the risks of switching between biosimilars and reference products.

3. Biosimilars and international guidelines on interchangeability

The term 'interchangeability' is a regulatory term, and the US FDA approves an interchangeable designation to a biosimilar when additional criteria for interchangeability are met. All biosimilars are not interchangeable. According to the US FDA, an interchangeable product, in addition to being a biosimilar, should meet additional requirements based on a specific 'switch trial design' evaluation of the product. Interchangeability standards are described under section 351(k) of the BLA. The regulations state that in addition to showing bio-similarity to the reference product, the risk of safety (including immunogenicity) or diminished efficacy of alternating or switching between the biosimilar and the reference product should not be greater than the risk of using the reference product alone [17]. Also, the biological product 'is to be biosimilar to the reference product' and 'is expected to produce the same clinical result as the reference product in any given patient' [17].

The biosimilar 'interchangeable' product may be substituted for the reference product. This substitution is an 'auto-substitution' at the pharmacy level (clinically practiced in the US, Canada, Australia; Table 2 [11,17,29–33]). In some member states of the EU, Japan, India, and the rest of the world, a physician-guided substitution, also called 'switching,' is practiced (Table 2).

It should be noted that 3-switch studies to establish interchangeability are only required for automatic substitution, at the pharmacy level, in the US. The interchangeability status requires extensive studies with multiple switches, as well as switches between biosimilars of the same reference product, requiring hundreds of patients per study, which makes the development of biosimilars slow and expensive. In addition, the results have not provided any definitive answer as the sample size is too small [34]. Thus far, the 'interchangeable' status has been granted to only two products by the FDA: biosimilar Insulin Glargine (Semglee®, insulin glargine-yfgn) in July 2021 and Cyltezo® (adalimumab-adbm) in November 2021 [34]. The regulatory requirements for biosimilars must see a natural evolution and a paradigm change toward removing inefficiencies in clinical designs for the development to become cost-effective as sky-rocketing cost of developing biosimilars is becoming a shared deterrent for biosimilar developers [27,35].

To do so, efforts should be underway to press upon the revision of several biosimilar guidelines to move stepwise in the direction of reducing the clinical requirements for biosimilars to aid switching from reference biologic to biosimilar or switch from one biosimilar to another. For the US, it may mean finally doing away with the switch studies to claim the interchangeability status. A review based on 178 clinical switch studies has found no evidence of switch-related adverse effects, including an increased risk of immunogenicity [28]. Post-marketing surveillance of biosimilar monoclonal antibodies up to 7 years post-approval has not revealed any biosimilar-specific concerns on safety or immunogenicity despite exposure of >1 million patient-treatment years [27]. From the EU perspective, interchangeability of EU-licensed biosimilars

Table 2. Guideline recommendations for interchangeability to biosimilars.

Place	Authority	Statement	Statutory/legal definition of interchangeability	Responsibility for implementation	Outcome	References
USA	FDA	FDA determines a biological product to be interchangeable with a reference product if (1) the biological product 'is biosimilar to the reference product' and 'can be expected to produce the same clinical result as the reference product in any given patient' and (2) 'for a biological product that is administered more than once to an individual, the risk 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'	Yes, through BPCIA 2019	Individual states	Auto substitution	[17]
European Union*	EMA	'Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect .... Replacement can be done by: Switching, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent Substitution (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber'	No	Member states	Physician-directed switching or auto substitution	[11]
Australia	TGA	No formal definition of interchangeability. However, 'brands that can be substituted by the pharmacist are indicated in the Schedule of Pharmaceutical Benefits by an "a-flag" (a small "a"). Only a-flagged medicines can be substituted by the pharmacist'	No	PBAC	Auto substitution	[29]
Canada	Health Canada	' ... the term "interchangeability" often refers to the ability for a patient to be changed from one drug to another equivalent drug, by a pharmacist, without the intervention of the prescriber who wrote the prescription. Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug'	No	Individual provinces and territories	Auto substitution	[30]
Brazil	ANVISA	Not defined. Interchangeability considered to be a matter of clinical practice	No	Physicians	Physician-directed switching	[31]
Japan	PMDA	Not defined. Interchangeability considered to be a matter of clinical practice	No	Physicians	Physician-directed switching	[32]
India	DCGI	Not defined. Interchangeability considered to be a matter of clinical practice	No	Physicians	Physician-directed switching	[33]

*For the United Kingdom (UK), Diabetes UK has released a position statement on the use of biosimilar insulin in 2019. It is recommended that decisions regarding biosimilar insulins should be made on a case-by-case basis and the health care providers and patients should jointly agree on the appropriate use of biosimilar insulin after weighing the risks and benefits [6].

ANVISA, Agência Nacional de Vigilância Sanitária; BPCIA, Biologics Price Competition and Innovation Act; DCGI, Drugs Controller General of India; EMA, European Medicines (Evaluation) Agency; FDA, Food and Drug Administration; PBAC, Pharmaceutical Benefits Advisory Committee; PMDA, The Pharmaceuticals and Medical Devices Agency; TGA, Therapeutic Goods Administration; USA, United States of America.

already happens as a substitution guided by the prescriber. Based on the data above, an automatic substitution at the pharmacy level can also be a possibility for EU-licensed biosimilars in the near future [27].

The next section describes the current requirements by the US FDA to provide the label of interchangeability to a biosimilar.

3.1. Interchangeability studies

The US FDA recommendations to demonstrate interchangeability include a specific randomized two-arm study design that includes a switching arm ($\geq$ 3 switches between the reference and the interchangeable product) and a non-switching arm that receives only the reference product in a clinically representative patient population [8,23]. The objective of this study focuses on demonstrating no clinically meaningful change in immunogenicity and its effect on PK, efficacy, or safety after 'multiple switches' compared to the non-switching reference drug arm.

Thus far, biosimilar Insulin Glargine (insulin glargine-yfgn) is the only biosimilar insulin that has been granted the interchangeability label in July 2021 [36]. Results of the INSTRIDE-3 Phase-3 Switch study, completed in 2017, showed that switching participants between biosimilar Insulin Glargine [co-developed by Biocon Biologics and Viatris (erstwhile, Mylan)] and reference Insulin Glargine (Lantus; Sanofi Aventis) demonstrated equivalent efficacy and similar safety and immunogenicity, indicating that people taking reference insulin glargine can safely switch to the biosimilar insulin glargine [26]. Since 2019, the regulatory requirements for insulins have been further changed. Insulins are regarded as simpler molecules, compared to other biologics, and hence will be approved now as interchangeable biosimilars under the 351(k) BLA pathway [17,21]. As per the 2019 US FDA guidance, a comparative clinical immunogenicity study is generally not deemed necessary to support a demonstration of bio-similarity and/or interchangeability if the comparative analytical

assessment based on state-of-the-art technology supports the demonstration of 'highly similar' for a proposed biosimilar or interchangeable insulin product and there is little or no residual uncertainty regarding immunogenicity [17,21].

4. Switching to a biosimilar interchangeable insulin

4.1. Improved access to insulin

Access to life-saving insulin is most vital to prevent significant comorbidities leading to blindness, amputations, and premature death, and the resultant healthcare expenditure. At the growing prevalence rate of diabetes, the global insulin market valued US $24 billion in 2018 is growing at a compounded rate of 4.9% [37]. Cumulatively, over 150 million people with diabetes now need insulin worldwide [1,38], and it is estimated that half of these people do not have access to affordable and good-quality medicine despite the rising demand [39,40]. A quarter of the US population having diabetes requires insulin, which makes it more than 10 million insulin users [16]. The International Diabetes Federation (IDF) launched its theme for 2021–2023 on 14 November 2021 (World Diabetes Day) as *Access to Diabetes Care, if not now, when?* Lack of global access to insulin and its high cost is a big cause of patient non-compliance and under-treatment and significantly contributes to non-sustainable economic development goals. This problem magnifies further in low-income and middle-income countries where medicines are mostly bought out-of-pocket, especially in the private sector [41]. In India, for example, 62.6% of healthcare spending is out-of-pocket and because a large percentage of the population is rural, insulin use acceptance and accessibility are limited by its non-affordability [42].

Availability, affordability, and quality of medicines are the three key factors that impact not only the clinical parameters but also adherence to the treatment. Globally, between 2002 and 2013, the average price of insulins has nearly tripled, and this has made the drug out of reach of many patients. In 2018, it was estimated that about 33 million people with T2DM did not have access to insulin. However, this number is projected to reach 41 million by 2030 [42,43]. Current levels of insulin requirement are highly inadequate compared to the projected need, particularly in Africa and Asia.

The introduction of biosimilar insulins is expected to increase the market competition and enable access to insulins, with an expected 20–40% price reduction in the US [43]. A recent cost-savings analysis in the US suggests a potential cost savings of 15% with long-acting insulin analogs upon introduction of biosimilars of insulin analogs [44,45]. A similar market correction may be observed in India and in other Asian countries with the advent of biosimilars of insulin analogs, especially those with the 'interchangeability' status, which promises both high affordability and high quality [46].

4.2. What does it mean for different stakeholders?

Increased options, patient access to quality insulin, and competitive pricing are the major benefits of using biosimilar insulins. In countries where most of the pharmaceutical spend is out-of-pocket, the introduction of biosimilars can result in a competitive marketplace, drive down the cost of reference products, and allow patients access to life-saving insulin [47]. Patient adherence is also likely to increase with decreased costs of biosimilar insulin.

4.2.1. Health care professionals (HCPs)

Physicians are the key decision-makers for patients' health and often make prescription decisions based on the perceived ability of the patient to pay [48]. Hence, the availability of biosimilar insulins will allow the HCPs to make better clinical decisions for the treatment of diabetes for individual patients. The potential for individualized patient care is possible with the introduction of biosimilars.

To make the patient an inclusive partner in decision-making, the HCPs have an important role to play [48]. They can support the patients with the following points to adopt an insulin biosimilar:

- *Potential benefits in terms of affordability and cost savings*
- *Robust scientific evidence in terms of clinical trials with the switch design*
- *Rationale for the switch/substitution explained through the patient information leaflets*
- *Use of medical education in making informed patient-centered decisions, dose calibration (convert unit-per-unit, similar monitoring, etc)*
- *Consideration of personal preferences of the patients for the choice of biosimilar insulins in terms of the type of the product and the pen/device to be used* [49].

4.2.2. Patients

Patients may be more willing to use biosimilar insulin, which is equally effective, safe, and more affordable. Patients treated with insulins should be made aware of the relevant aspects of using biosimilar insulin to help them make informed decisions along with their HCPs if a change is required in the current therapy [50]. Patients should be educated on cost savings and also assured that biosimilar insulin will be equally safe and effective as the reference insulin product. The impact on their out-of-pocket costs will be variable based on the insurance coverage, and manufacturer coupons for patient assistance yet can offer a big advantage to those with inadequate or no insurance. In certain countries, interchangeable insulins will allow speedy access as the pharmacists are able to auto-substitute immediately.

4.2.3. Policymakers

Appropriate market introduction of biosimilars is a high priority because of the prospect of reduced medical costs according to policymakers [49,50]. Policymakers, to encourage faster uptake of biosimilars, can become more inclusive of biosimilars by addressing the following:

- *Encouraging competition and innovation*
- *Drafting policies to encourage the practice of high-quality biosimilars insulins, more so, states should implement interchangeability policy to allow rapid update of biosimilars*

- *Addressing over-patenting by brand manufacturers to block biosimilar competition by strengthening the IPR, increasing patent transparency, and speeding up the patent dance to help biosimilars get to market* [51,52].

4.2.4. Payors and formulary decision-makers

Table 3 provides guidance to decision-makers for choosing the right biosimilar for inclusion in their formulary or for prescribing to the appropriate patient population. In addition to the safety and efficacy, the extensive checklist also includes manufacturing and product considerations, an important aspect, for example, can be a change in the delivery system or device between the biologic and the biosimilar [52]. When switching between products with different administration devices, training may be required for the newer device and it is important to check whether the patient or HCP has been educated on its usage. Post-marketing safety surveillance has shown no device-related challenges and it has been observed that self-administration of biosimilar products with different administration devices is doable and does not lead to any increase in adverse effects [27].

5. Conclusions

Despite developmental and commercial hurdles, biosimilars are likely to majorly impact diabetes care. HCP and patient education on biosimilars can ensure that biosimilar insulins gain wider acceptance. Several important questions around switching patients from older affordable insulins to newer expensive formulations or concentrations, interchangeability in clinical practice, and clinical outcomes of the same need to be studied from the real-world evidence generated from electronic healthcare databases. Demonstration of better prescription coverage with direct health outcomes and correlating it with pharmaco-economic advantages to healthcare systems and payors will eventually benefit patients through controlling the cost of insurance coverage and/or out-of-pocket costs. The fact that one in four patients with diabetes rations their insulin dose in the US is not good news for the rest of the world.

After 100 years of its discovery, it is important to ensure that every patient that requires insulin for their health has access to it. Accessibility to high-quality, affordable insulins will be a joint responsibility of regulators, payors, HCPs, and manufacturers.

6. Expert opinion

Till June 2020, >90% of the global insulin supply and ~100% of the US insulin supply was provided by three large manufacturers [52]. In June 2020, a biosimilar Insulin Glargine, co-developed by Biocon Biologics and Viatris (erstwhile, Mylan), was approved by the US FDA under the 505(b)(2) NDA pathway and, in accordance with the new legislation, is now considered a biologic under section 351(a) [53]. In 2021, biosimilar Insulin Glargine was designated as the world's first 'Interchangeable Biosimilar Insulin' [36,54–57]. Biosimilars are sweeping the landscape in a manner that generics did four decades back, and interchangeable biosimilars are notching this even higher. Biosimilars and interchangeable biosimilars should have the same status of being the standard-of-care for biologic therapy as generics have for small molecules.

It is to be noted that a product approved as a biosimilar does not automatically become 'interchangeable' with the reference biologic. As per the US FDA, 'Availability of biosimilar and Interchangeable products that meet the FDA's robust approval standards will improve access to biological products through lower treatment costs' [57,58]. The interchangeability designation by FDA, hence, takes the biosimilar concept to the next level. Edwards et al. [59], in their Perspective Review on switching to biosimilars, opined that although the EU and few other countries support prescriber-led switching, due to paucity of data on multiple switches, the prescriber and patients are wary of substitution at the pharmacy level as is the case for interchangeable biosimilars. In the recent past, data on multiple switches studies have been generated for biosimilars. Interchangeable products are studied with multiple switches versus the reference product to demonstrate that in addition to showing bio-similarity, there is no greater risk in terms of safety or diminished efficacy compared to the reference product and is expected to produce the same clinical result as the reference product in any given patient. Therefore, the interchangeable biosimilars can be 'auto-substituted' at the pharmacy level in countries like the US, Canada, and Australia; elsewhere, it can be a physician-guided substitution. An 'interchangeable' designation gives prescribers, patients, formulary decision-makers, and payors enough confidence to ascribe to faster and wider uptake of biosimilars.

While acknowledging the recent advancements in the US FDA regulations on phase 3 waivers for biosimilar approvals, it is interesting to note that the option of a waiver for phase 3 studies also exists in the EMA guideline. More recently, the EMA also is making use of this option, and now, with good pre-clinical and PK/PD data, and little or no residual uncertainty regarding immunogenicity, neither FDA nor EMA may require phase 3 studies in the future. This regulatory reform and harmonization in FDA and EMA should spread across other regions to ease the development and deployment of global trials based on scientific justification.

Going forward, more biosimilars will be approved as interchangeable with the original reference biologic. When a patent expires, the product does not, and the innovator tries to move prescribers toward their next innovation, even if just incremental, priced at a premium. Biosimilar review and approval guidelines should spur the conduct of comparative effectiveness research and head-to-head meta-analyses to substantiate whether the incremental improvements also lead to improved patient outcomes. Much awareness and education efforts are required on the part of regulators and biosimilar manufacturers to ensure the successful uptake of biosimilars and interchangeable biosimilars.

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Table 3. Checklist for evaluation of biosimilars by payors/committees for formulary inclusion. Adapted with permission from [53], © 2014 SAGE publications.

Safety and Efficacy	
Product characteristics	• Are there any differences in the formulation of the biosimilar under consideration versus the reference product?• Are there any differences in incompatibility (e.g. injection pain, interference with laboratory assays) between the biosimilar under consideration and the reference product?
Clinical data	Typically, FDA and EMA approval guarantees adequacy and quality of data; however, additional data from other regions may be reviewed
Immunogenicity	Are there any clinically significant differences in the immunogenic profiles between the biosimilar under consideration and the reference product with respect to the incidence of- Infusion reactions- Neutralizing antibodies
Manufacturer Considerations	
Medication availability	• Does the manufacturer ensure a reliable and uninterrupted supply of the product? • Does the manufacturer have the capability to increase production in another location, if necessary, to meet demand?
History of shortages and recalls	• Has the manufacturer experienced shortages of this product or other products? • Has the product ever been recalled because of quality concerns? • Has the manufacturer had other products recalled as a result of quality concerns?
Handling practices	• Does the manufacturer adequately document and maintain controlled temperature during the distribution of the product? • Does the manufacturer take the necessary steps to prevent exterior contamination of vials?
Supply chain security	• Does the manufacturer have adequate security technologies for product authentication, warehouse/cargo security, and market surveillance to detect potential product diversion or counterfeits?
Anti-counterfeit protection	• Does the manufacturer have a program in place to guard against counterfeiting?
Hospital and Patient Considerations	
Packaging and labeling	• Are the containers, packaging, and labeling well designed and easy to read? • Are there any differences in packaging between the biosimilar under consideration and the reference product? • Are there any differences in warnings on the label regarding handling between the biosimilar under consideration and the reference product?
Product storage	• Are there differences in shelf-life or storage requirements between the biosimilar under consideration and the reference product? • Are there any differences in light sensitivity between the biosimilar under consideration and the reference product? • Do any differences in storage conditions offer an advantage or disadvantage in terms of patient care? • Will both the biosimilar under consideration and the reference product be stocked based on indications between the products or for patients admitted on the reference product?
Product administration	• Are there any differences in the delivery system or device between the biosimilar under consideration and the reference product (e.g. auto-injector)? - Does the labeling for the biosimilar under consideration include information on delivery? - Is there a plan for educating patients receiving a biosimilar with a different delivery system/device from the reference product? • Does the biosimilar under consideration have fewer approved routes of administration than the reference product? • If provided in vials, are there any differences in the amount of excess product between the biosimilar under consideration and the reference product? • Are there any differences in pharmacy technician time and techniques for compounding between the biosimilar under consideration and the reference product? • Are there any differences in the timing of administration or patient experience that may affect patient and nurse preference between the biosimilar under consideration and the reference product?
Interchangeability/ substitution	• Does the biosimilar under consideration meet clinical and regulatory criteria to be freely substituted for the reference product (and vice-versa)?
Variety of indications	• Is the reference product currently being used for multiple indications? - If so, is the biosimilar under consideration being evaluated for all those same indications, including FDA/EMA-approved indications and those considered standard of care?
Product naming	• Will the selected name ensure traceability of adverse events to the specific product?
Information technology support	• Does the hospital have a robust information technology infrastructure to support - Distinguishing the biosimilar under consideration from the reference product during order entry? - Tracking which product was administered (biosimilar under consideration versus the reference product? • Is the labeling of the biosimilar under consideration compatible with the facility's current technology (e.g. bedside barcode scanning)?
Economic considerations	• Is reimbursement support available for patients receiving the biosimilar under consideration? • Will all government and commercial payor policies apply equally to both the reference product and the biosimilar under consideration? • Are there any differences between the biosimilar under consideration and the reference product with respect to ease of access to the product (e.g. based on payor requirements)? • Are there financial and/or legal risks of using the biosimilar under consideration for an unapproved indication for which the reference product has approval? • Does the difference in cost for the biosimilar under consideration versus the reference product support a full formulary conversion?
Patient education	• Does the manufacturer provide patient education materials at a 6th-grade reading level? - Do materials appropriately distinguish biosimilars and generics? • Is it necessary to develop materials for educating patients on the interchangeability of biosimilars?

EMA, European Medicines (Evaluation) Agency; FDA, Food and Drug Administration.

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ORCID

Shivani Mittra http://orcid.org/0000-0002-5488-7140

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