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Similar biologics in India: A story of access or potential for compromise?

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Biosimilars or similar biotherapeutic products are the biological products approved by regulatory agencies based on the demonstration of similarity in quality, safety and efficacy with reference biologics (or original biologics). Though biosimilars could be considered as interchangeable therapeutic alternatives over original biologics, there are concerns regarding their similarity in effectiveness and safety with reference product along with the level of evidence of similarity required for approval. The biosimilars, particularly, monoclonal antibodies that are developed based on the complex manufacturing processes, require stringent comparative evaluations. The Indian Regulatory Authorities in July 2012 developed the first guidelines for approval of similar biologics, which comprised requirements for the manufacturing process, quality evaluation, preclinical and clinical studies, as well as post-marketing studies. The 2016 guidelines, an update to previous guidelines, were released with the intent to provide a well-defined pathway at par with international regulations for the approval of similar biologics in India. This article highlights the key attributes of the 2016 Regulatory Guidelines and also describes the aspects such as interchangeability, nomenclature and labelling of similar biologics in India. Rigorous consideration is imperative for highly complex similar biologics of monoclonal antibodies on a case-to-case basis.

Key words Biopharmaceuticals - biosimilars - immunogenicity - India - large molecules - pharmacovigilance - potency - regulatory guidelines - similar biologics

Biologics are biotechnology-derived medicinal products manufactured from living organisms or contain components of living organisms, and these products are specifically designed to resemble the body proteins or modulate the immune system. Biological products have made a major transformation in the therapeutics of many diseases, particularly for chronic diseases involving overactive immune system or impaired immune surveillance[1,2]. A plethora of biological agents are currently available in the market, including insulins, vaccines, human growth hormone, erythropoietin, interleukins, interferon, clotting factors and monoclonal antibodies[3,4]. Biologic agents have shown greater clinical benefits as compared to conventional drugs[1]; however, the affordability of these medications is beyond many, which limits access especially in resource-limited countries. The increase in demand for cost-effective treatment, expiry of patents

and marketing exclusivities of biologics have led to the development of biosimilars - biological agents that are similar to the innovator or previously licensed biologics (also known as reference product or reference biotherapeutic product; Fig. 1). The biosimilars are approved by the regulatory authorities based on rigorous comparative analytical, immunogenicity, non-clinical and clinical evaluations[5,6]. This article provides an overview of the approval process and the key attributes of the 2016 Indian Regulatory Guidelines for the approval of similar biologics. It also describes the unaddressed aspects such as interchangeability, nomenclature and labelling of similar biologics in India.

Definition of biosimilars

In India, biosimilars are known as similar biologics. According to the Central Drugs Standard Control Organization (CDSCO) and Department of Biotechnology (DBT) guidelines released in 2016, a similar biologic product is that which is similar in terms of quality, safety and efficacy to an approved reference biological product based on comparability[7]. Various countries and agencies follow different definition and terminology for biosimilars (Table)[8-10].

Intended copies

Intended copies (otherwise called as biomimics, me-too biologics, non-comparable biologics; Fig. 1), although claimed to be similar to original biologics, should be distinguished from biosimilars to avoid confusion. These biocopies do not undergo demonstration of similarity or lack comparative studies with appropriate reference product or did not achieve regulatory approval as per the regulatory requirement for biosimilars[11]. These biologics are often developed and marketed in various middle- and low-income countries having less robust regulatory requirements[12]. Patients administered with such biological agents face a greater risk of therapeutic failure and side effects. A study showed that the use of intended copies of etanercept and rituximab marketed in Columbia and Mexico resulted in failure to treatment and increased adverse events[13]. In Mexico, the intended copy of rituximab was withdrawn by Comisión Federal para la Protección Contra Riesgos Sanitarios due to the development of anaphylactic reactions in several patients who switched from the original product[14].

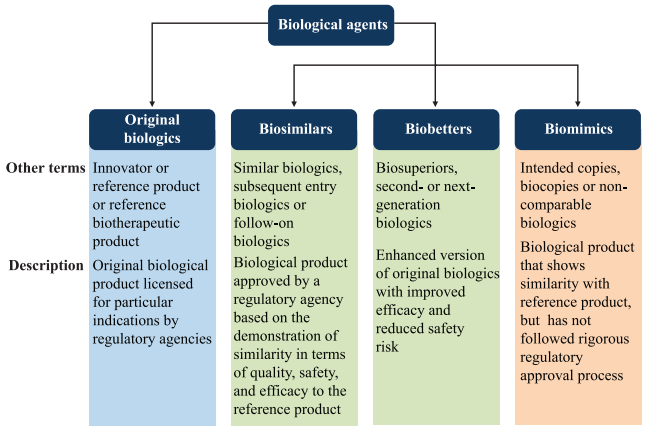

Fig. 1. Classification of biopharmaceutical agents.

Biobetters

Biobetters (also referred as biosuperiors, second- or next-generation biologics; Fig. 1) are different from biosimilars and are enhanced over the original product[15]. The original biologics are modified by either chemical (polyethylene glycol) or molecular (using recombinant DNA technology) method to develop these biobetters. These biologics may result in improved efficacy and reduced dosing frequency as well as safety risks such as immunogenicity, toxicity and adverse effects[16]. The regulatory approval of biobetters requires supporting evidence of efficacy and safety and is mostly eligible for patent protection[17].

Biosimilars are not biogenerics

Unlike chemical generics, the development of biosimilars is unique and more complex in nature[18]. The chemical drugs are small molecule products that can be easily reproduced using chemical synthesis, as these have well-defined structure and formula. However, biosimilars are large molecules with multi-dimensional structure and are developed from cell lines or living organisms using recombinant DNA technology, which is more complicated compared to chemical synthesis[19,20]. Further, manufacturing biosimilars such as monoclonal antibodies (molecular weight between 145,000 and 160,000 Da) is more intricate than biologics such as insulins and hormones (molecular weight of nearly 6000 Da; Fig. 2)[21-23].

The entire manufacturing process is performed under strictly controlled conditions, and it includes selection of the DNA sequence, cloning, transfection, amplification, purification, formulation and validation[24] (Fig. 3). It remains a big challenge for a biosimilar manufacturing company to develop a similar product, as detailed information on the process of manufacturing of the original drug is patent protected and also because the same cell line is not available to the biosimilar manufacturer. Any changes in the manufacturing

Table. Comparison of different regulatory guidelines for the approval of biosimilars

Specification	India - Department of Biotechnology and Central Drugs Standard Control Organization[7]	United States - Food Drug Administration[8]	Europe - European Medical Agency[9]	World Health Organization[10]
Definition of biosimilars	"A similar biologic product is that which is similar in terms of quality, safety and efficacy to an approved reference biological product based on comparability".	"A biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components".	"A biosimilar medicine ('biosimilar') is a medicine highly similar to another biological medicine already marketed in the EU (reference medicine)".	"SBP is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product".
Reference product	Innovator product approved in India or ICH countries based on a full safety, efficacy and quality data.	Innovator product approved by the FDA. For comparison with a non-US approved product, the requirements under section 351(k)(2)(A) of the PHS Act need to be addressed.	Original product approved in EU based on a complete dossier.	Originator product that was approved based on a full registration dossier.
Pre-clinical studies	Comparative PD (*in vitro* and *in vivo*) and toxicological studies should be conducted before clinical studies and designed to identify if there any significant differences between the similar biologics and the reference product.	Demonstration of similarity based on evidence from pre-clinical studies (including the assessment of toxicity) is required.	Non-clinical studies should be performed in a step-wise manner before initiating clinical studies. *In vitro* studies should be conducted first, followed by *in vivo*, if deemed necessary. These studies should be comparative in design to detect differences between the similar biological product and the reference product.	Non-clinical evaluation of a new biotherapeutic normally encompasses a broad spectrum of PD, PK and toxicological studies to validate the efficacy and safety of an SBP and should be comparative in nature.
Clinical studies	Clinical studies (PK, PD studies, and confirmatory safety and efficacy studies) are required. Phase 3 should include appropriate primary endpoints and the patient population needs to be sensitive and homogenous. Studies should be conducted as per the Indian GCP guidelines, generally in ≥100 evaluable patients in the test group.	Comparative human PK, PD, clinical immunogenicity, or clinical safety and effectiveness are required. At least one study with equivalence design and adequate power is required to evaluate any clinically meaningful difference between the proposed biosimilars product and reference product.	PK/PD studies, followed by clinical efficacy and safety studies, confirmatory studies for demonstrating clinical biosimilars comparability are required. At least one study with adequate power and equivalence design in a sensitive population to detect potential differences with regard to efficacy and safety is required.	Clinical studies should be designed with testing strategies to detect differences between the SBP and the reference product. At least one study with equivalence design in a sensitive population is preferred.
Immunogenicity	Both pre-approval (comparative) and post-approval (non-comparative) of safety assessments including immunogenicity are required.	Safety studies including immunogenicity assessments are required.	Safety studies, including immunogenicity assessments, are required. A head-to-head comparative study of 12-month duration is recommended in the sensitive population to detect any potential difference in immunogenicity between proposed biosimilar and reference product.	Data on immunogenicity are obtained from the comparative efficacy studies. In case of chronic administration, a one-year pre-approval data are usually required.

Contd...

Specification	India - Department of Biotechnology and Central Drugs Standard Control Organization[7]	United States - Food Drug Administration[8]	Europe - European Medical Agency[9]	World Health Organization[10]
Pharmacovigilance	Comprehensive pharmacovigilance plan should be prepared by the manufacturer to further evaluate the clinical safety. Post-marketing phase 4 study may be required, preferably within two years of approval.	Post-marketing safety monitoring and mitigation strategy for biosimilars are required. In addition, a post-marketing study or a clinical trial may be required to evaluate certain safety risks.	Pharmacovigilance and risk management plan should be submitted according to current EU legislation and pharmacovigilance guidelines. Potential risks, including immunogenicity, should be closely monitored.	Submission of safety specifications and pharmacovigilance plan is required during the submission of the marketing authorization application. All information on product tolerability should be included in post-marketing safety report. Such safety information must be evaluated along with the evaluation of the frequency and causality of adverse events.
Extrapolation	Extrapolation of indication is possible if there is a similarity in quality and pre-clinical assessments between similar biologics and reference product or if MoA or involved receptor is same for other indication or if clinical efficacy/safety is proven in one indication.	Extrapolation of indication needs sufficient scientific justification and is considered on case-by-case basis.	Extrapolation to other clinical indications of the reference product is possible, but needs scientific justification and could be considered on a case-by-case basis.	Extrapolation may be possible if sufficient scientific evidence is provided along with the benefit/ risk information of that indication.
Interchangeability	Not addressed Usually made randomly by the prescriber or pharmacist based on the product cost and assumed patient affordability	Interchangeable product (approved based on the demonstration of interchangeability), may be substituted with the reference product by a pharmacist without the involvement of the clinician who prescribed the reference product.	The decision is delegated to the Member States in the EU.	Not addressed.
Nomenclature	Not addressed	INN, followed by a four-letter suffix that is unique and 'devoid of meaning'.	Same INN as the original product for biosimilars. Trade name, packaging and appearance should be different.	BQ scheme, consisting of a unique 4 letter identification code is used along with INN.

EU, European Union; ICH, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; FDA, Food and Drug Administration; GCP, Good Clinical Practice; INN, International Nonproprietary Names; MoA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics; PSURs, periodic safety update reports; SBP, similar biotherapeutic product; PHS, public health service; EU, European Union; BQ, biological qualifier

process such as use of different cell lines, growth medium and protein purification processes can also result in variations in the final product[25]. In addition, there are chances of batch-to-batch variations occurring for the same biosimilars and even for originator manufacturing the same biologic. These minor variations in biosimilars can be acceptable, but it is imperative to demonstrate that the variation due to the development process does not affect the products' physiochemical properties, effectiveness and quality[26].

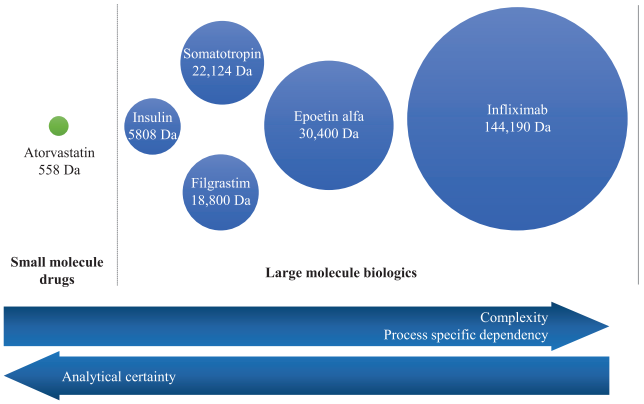

Fig. 2. Comparison of small chemical drugs versus biologics.

Biosimilars: A potential for compromise

India, being one of the leading countries in manufacturing affordable, efficacious and safe generic medicines, has also emerged as a key player in biopharmaceuticals, especially in the manufacturing of biosimilars[27]. There are nearly 60 biological agents that have been approved in India and almost half of these are similar biologics[28]. The cost of biosimilars marketed in India is approximately half the cost of innovator products, and this difference is attributable to lower manufacturing and development cost. In addition, there are patient assistant programmes by manufacturing companies, which address the issues of affordability and access[29]. Although biosimilars have gained acceptance from both physicians and patients because of its affordable price, but there have been questions regarding their adequately similar efficacy and safety as compared with the reference product[30]. In controlled clinical studies of biologics, particularly biosimilars, safety concerns may occur beyond the study completion. Long-term evaluations such as post-marketing studies of biological agents are required as there are only limited patient experiences available during approval in terms of safety and immunogenicity.

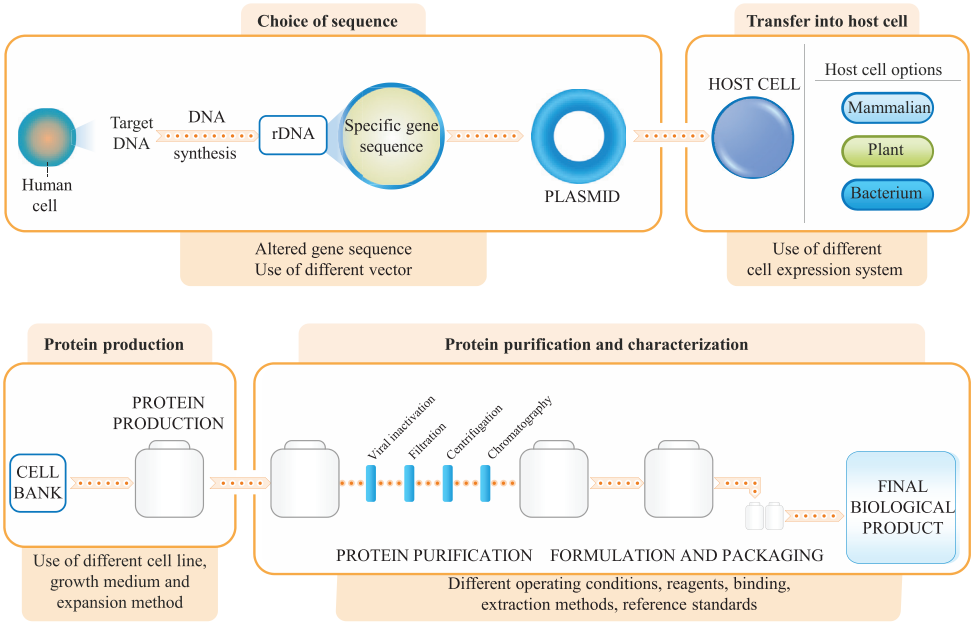

Fig. 3. Variation between manufacturing of biologics and similar biologics. The manufacturing process to produce biologics and similar biologics, include complex and controlled procedures. The process involves cloning of the relevant gene into a DNA vector and transferring it into a host cell. After the protein expression, appropriate cell line is selected and expanded in a growth medium using suitable expansion method. Complex purification and validation procedures are followed to obtain the purified final biological product. The characteristics of the final product may differ based on variation in selection of the DNA sequence, cloning, transfection, amplification, purification, formulation and validation procedure followed. rDNA, recombinant DNA.

Side effects related to the long-term use, off-label use, drug-drug interactions or use in comorbid conditions can only be identified on exposure to the drug after its approval. Above all, as biological agents could lead to deviation in quality characteristics due to unknown variations (also known as drift) and known variations (evolution) in manufacturing process, it is important to establish long-term surveillance to prevent risk to patients[31]. It is also essential to improve the identifiability of the biologics after market approval with easily distinguishable product names[32] and establish robust standards of interchangeability between two biological products to further improve the safety assessment[31].

The assessment of toxicity and safety of monoclonal antibodies, in particular, is a cause of concern because of its increased complexity. The manufacturing of biosimilar monoclonal antibodies can cause disparities in glycosylation pattern, which could result in micro-heterogeneity. Development of guidance documents and assurance of similarity are daunting tasks with biologics such as monoclonal antibodies compared with other biologics. The World Health Organization (WHO) has drafted separate guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products[33].

Guidelines for similar biologics in India

In India, until July 2012, similar biologics were approved by Review Committee on Genetic Manipulation (RCGM) and CDSCO on a case-by-case basis using abbreviated pathway for new drugs[34]. The biological products launched in India until 2012 followed an *ad hoc* abbreviated procedure on a case-to-case basis, and these products underwent a necessary procedure as per the Indian guidelines to be categorized as true biosimilars[34]. As there was a growing trend in the development of biosimilars, and to improve the standards of the approval requirement at par with the established regulatory bodies such as European Medicines Agency (EMA) or the United States Food and Drug Administration (US FDA), the Indian regulatory agency considered providing a clear pathway enunciating the requirements to substantiate equivalence in safety, efficacy and quality of a similar biologic to an authorized reference biologic. The first 'Guidelines on Similar Biologics' framed by the CDSCO and DBT came into effect from September 2012[35]. On August 15, 2016, the Indian Regulatory Authority released updated guidelines with several inputs from the WHO and expert consensus opinion[7]. The approval of biosimilars follows a sequential process and involves various authorities such as Institutional Biosafety Committees, Institutional Animal Ethics Committee, RCGM, Genetic Engineering Advisory Committee, Drug Controller General of India Office, and the Food and Drugs Control Administration[3,36]. These guidelines for similar biologics provide the regulatory requirements regarding manufacturing processes and quality aspects and comparative exercise for preclinical studies, clinical studies and post-marketing requirements. The guidance document recommends the use of reference biologic in all the comparability activity related to quality, preclinical and clinical considerations. The attributes of 2016 Indian Guidelines[7] are compared with those of guidelines from established regulatory authorities, particularly US FDA[8], EMA[9], and WHO[10] (Table).

Reference biologic

The rationale for selecting the reference product should be provided to regulatory authorities and the reference product selected for the comparability exercise should be approved in India based on the complete data set[7]. The reference biologics that are not marketed in India ought to be licensed in any of the member countries of International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. The formulation, route of administration, dose and strength of similar biologics have to be similar to that of the reference product[7].

Manufacturing process and quality considerations

The requirement of providing a complete description of the manufacturing process including biological raw materials used (such as host cell cultures, vectors and gene sequence) and post-translational modifications (*e.g.*, glycosylation, oxidation, deamidation and phosphorylation) has been re-emphasized in the 2016 guidelines[7]. The description should include the comparability of product developed at clinical scale over reference biologic. Overall, the manufacturing process is required to be consistent and reproducible and should be in accordance with good manufacturing practices. The characterization studies for similar biologics should be performed to evaluate physicochemical properties, purity, content, strength, biological activity and immunogenicity. Stability studies along with accelerated studies and stress studies

are required to be conducted for similar biologics for the evaluation of shelf life, storage conditions and degradation profile. Variances between the similar biologic and the reference product and their potential impact on the efficacy and safety of similar biologic should be investigated. For example, two candidate biosimilars of etanercept produced in China showed a difference in molecular mass, amino acid sequence and glycosylation pattern and therefore, did not meet the requirements of EMA to qualify as a biosimilar, although they exhibited affinity and biological activity analogous to those of the original product. This emphasizes the importance of exhibiting the similarity in the manufacturing process and the need for conducting preclinical and clinical studies to ensure standard efficacy and safety of the biosimilars[37,38].

Demonstration of similarity

In India, extensive characterization studies are recommended to determine the qualitative and quantitative difference between the candidate similar biologic and reference product[7]. The documentation should contain comprehensive information regarding the differences observed during analytical characterization, quality aspects and detection and estimation of relative levels of protein variants[7]. The pharmacokinetics (PK) study should be adequately powered to demonstrate equivalence in PK of similar biologic versus the reference product. The guidelines also recommend that PK and pharmacodynamic (PD) studies are to be conducted before the large-scale phase 3 studies. Thus, a sequential format for conducting these studies is important.

Preclinical and clinical studies

After the analytical evaluation that characterizes the similarity of similar biologic and reference biologic, preclinical and clinical studies are conducted to further evaluate the efficacy and safety aspects[7]. Evaluation of PD activity *in vivo* should be performed in case the *in vitro* studies (*e.g.*, cell proliferation or receptor binding assays) do not reflect clinically relevant PD activity. A minimum of one repeat dose toxicity study (*in vitro*) in the relevant species should be performed[7].

The guidelines require comparative PK and PD studies to establish the similarities in PK/PD characteristics between similar biologic and reference biologic on a case-to-case basis[7]. Both PD and PK studies may be combined, or PD study can also be conducted along with phase 3 studies wherever applicable. At least one randomized phase 3 study that is desirable to establish the similarity in efficacy and safety between the purported similar biologic and reference product, except recombinant human-soluble insulin products, where only comparison of safety is needed. Clinical studies having non-comparative safety and efficacy outcomes are generally not preferred, and it is desirable for all similar biologics to conduct equivalence (with predefined margins) or non-inferiority studies with adequate sample size (statistically determined based on the data from earlier PK/PD studies) and duration for demonstrating comparable safety, efficacy and immunogenicity with the reference biologic. If equivalence, non-inferiority or comparability studies are performed, the manufacturer must provides a clear justification and consult the CDSCO before initiating the study. Sample size estimation and its rationale and comparability limits have to be defined clearly and justified before initiating the study. The comparability phase 3 studies intended for seeking market approval should be conducted in more than 100 evaluable patients and phase 4 studies in more than 200 patients[7].

Waiver of safety and efficacy study

Based on the 2012 CDSCO guidelines[34], nearly 20 biosimilars, including biosimilars of infliximab, etanercept, adalimumab and rituximab, received approval/license to market in India. However, clinical studies conducted for the approval or data published were limited. The present guidelines suggest that a waiver can be provided to confirmatory efficacy and safety study if there is a high similarity with the reference biologic with respect to structural and functional characteristics, preclinical and PK/PD outcomes. The European Regulatory Authorities mandate at least one well-powered equivalence study, with the relevant patient population having at least one relevant endpoint for an appropriate duration to determine the difference in efficacy and safety between biosimilar and reference product[9]. In Europe, biosimilar of infliximab (Remsima) gained approval based on extensive comparability programme mainly comprising characterization, preclinical and clinical studies. Predominantly, two clinical trials (a pivotal and a PK/PD/immunogenicity trial) were conducted in accordance with international standards to compare efficacy (based on pre-specified equivalence margin), PK and safety profiles between the infliximab biosimilar (Remsima) and original product[39,40]. The Indian Regulatory Authorities[7] have made stringent regulations

ensuring that there is no waiver for confirmatory phase 3 clinical studies as far as possible, especially when dealing with biologics such as monoclonal antibodies.

Immunogenicity

The immunogenicity of a biopharmaceutical agent is considered to be critical as it may affect the efficacy by cross-reacting with the active fragments, accelerating drug clearance and lowering circulating levels of the active drug and may also have the potential to compromise the safety by causing reactions such as allergy, anaphylaxis and infusion reactions[41]. An example is epoetin alpha, where the treatment resulted in producing a life-threatening antibody reaction (pure red cell aplasia) due to variations in the manufacturing process[42,43]. As analytical testing or animal (preclinical) studies cannot predict the biological response in humans, clinical studies are mandatory to identify the potential risk of immunogenicity and adverse events[44]. The immunogenicity potential should be evaluated in comparison to the reference biologic. The present guidelines recommend providing pre-approval comparative safety data based on adequate patient exposure (sample size and duration) along with published data on the reference biologic to provide evidence that there are no unexpected safety concerns[7]. These considerations would be particularly important to biologics such as monoclonal antibodies and fusion proteins compared with other biologics as there is a potential for variations in manufacturing and clinical aspects.

Post-marketing requirements

According to the Indian Guidelines[7], as the clinical studies performed on similar biologic before the approval are usually limited, rare adverse events are likely to occur beyond the study time period and hence may not be captured adequately. Thus, a complete pharmacovigilance plan should be put in to place by the manufacturer to further evaluate the safety. The pharmacovigilance plan should consider periodic safety update reports submission. After the market approval, safety data in addition to the previously submitted data may be required to further determine if there is any remnant risk associated with similar biologic. A pre-defined study with a single arm is required to be conducted in at least 200 patients and compared with previous data from the studies of the reference product[7]. The number of post-marketing studies to be conducted should be described in the pharmacovigilance plan and status of the studies has to be updated to the CDSCO. With regard to post-marketing safety and immunogenicity study, the present guidelines[7] recommend (on a case-to-case basis) to perform at least one study of non-comparative design to evaluate safety and immunogenicity and to validate that the similar biologic does not pose any safety concerns and undesirable immunogenicity. A strategy for the assessment of immunogenicity with appropriate rationale has to be provided. Head-to-head comparison studies are generally recommended, and it is imperative in evaluating the safety and immunogenicity even after the product enters the market.

Extrapolation of indication

Another important consideration for similar biologics is whether the available evidence for a specific indication can be extrapolated to exhibit similarity in other indications approved for the reference biologic. Guidelines from US FDA, EMA and WHO[8-10] suggest providing appropriate justification based on the totality of evidence for the extrapolation of all indications. The evidence must support comparable efficacy and safety of biosimilar, individually in each of the therapeutic indications approved for reference product[45-47]. EMA approved the first biosimilar infliximab in 2013 along with the extrapolation of all indications, including inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis, psoriasis and ankylosing spondylitis, licensed for the reference biologic[48]. Generally, the extrapolated indications are handled on a case-to-case basis, and the final decision depends on the regulatory agencies[49] (Table). In India, the extrapolation of indication is currently possible if the similarity in terms of quality or outcomes from preclinical evaluation has been established between the similar biologic and the reference product. In addition, demonstration of efficacy and safety in one indication allows extrapolation for other indications if the mechanism of action or receptors involved is the same[7]. The guidelines also mention that new indications that are not specified by innovator will need a separate application.

Key considerations in the current regulatory pathway for similar biologics

Interchangeability

Interchangeability status for a biosimilar is achieved if similar clinical outcomes with regard to quality, efficacy and safety in any given patient are demonstrated during switching (by the physician) or

substitution (by the pharmacist) with its respective original biological product (or reference product) when compared with the reference product alone. According to the US FDA, "an interchangeable biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability"[50]. The interchangeability status allows substitution of reference product with the interchangeable biologic by a pharmacist without the interference of the clinician who prescribed the reference biologic[50]. The US FDA has distinguished the biosimilars approval from the approval process for 'interchangeable biosimilar'. The approval pathway for interchangeability is stringent, and insists to establish the safety data with no additional risk to patients when switching between two biological agents compared to the use of original biologic alone[51,52]. Unlike the US FDA, EMA does not evaluate the interchangeability of biosimilar, and the approval of the interchangeability between biosimilars and innovator products is delegated to the Member States in the European Union (EU) (Table). Each country in the EU has the authority to provide substitution bill in their respective legislative assemblies[53]. The approval of biosimilars does not indicate that it can be interchangeable. Moreover, it is not as simple as chemical generics, where replacement with another drug can be made without apprehension for safety issues. This has the potential for creating confusion in the interpretation of safety data collected over time as most of these therapies are for chronic conditions. The regulatory bodies in India have not provided any guidance on interchangeability. Interchangeability designation should be applied by the applicant in the dossier submitted additionally for the label, along with the clinical data to support the same. In addition to the demonstration of similarity exercise, approval for interchangeability should be rigorous and the safety data should ensure that there are no additional safety risks to the patient when switched between innovator product and biosimilar or *vice versa* compared to the use of the innovator product alone. Such data should always be included in the dossier submitted for the label, along with the clinical data.

Nomenclature for biosimilars

The international nomenclature [International Nonproprietary Name (INN)] by the WHO is usually followed for generic products[54]. As biosimilars are different from the innovator product, a distinguishable nomenclature is required to clearly identify, prescribe and dispense the correct medication. Several countries have adopted their unique naming convention[55]. The EU follows the same INN as the original product for biosimilars; Japan follows INN followed by letter 'BS' which stands for biosimilars and a number indicating the order that the biosimilar was approved[56]. In 2014, the WHO released draft guidelines for nomenclature of biosimilars called Biological Qualifier scheme, where it provided a unique four-letter identification code different from INN[57]. On a similar line, the US FDA has proposed to use INN, followed by a four-letter suffix that is unique and devoid of meaning[58]. Though the WHO has offered clarity, there is still a debate in the use and acceptance of this global nomenclature for biosimilars[48,58]. It has also raised a question of whether following this nomenclature would bring value in traceability of biosimilars, particularly in pharmacovigilance.

Labelling

When similar biologics are licensed, healthcare professionals and patients should be made aware of the relevant data and information about similar biologic and the risk/benefit associated with it for safe and effective use. The package insert should clearly indicate whether the data were generated on similar biologic or innovator product, including differences in characterization and extent of similarity with the reference biologic on safety, immunogenicity and efficacy. Data from clinical studies must be described with statistical considerations and sample size in labelling. This is important from transparency perspective to keep the healthcare professionals, patient and other stakeholders informed about the extent of data generated on the similar biologic and its similarity to the reference product.

Conclusions

Access to quality and affordable treatment is the right of every individual. All possible efforts should be made to allow access to effective and safe medical interventions. India, like other countries having an established regulatory system, ensures patient safety with the early introduction of similar biologics, which are not proven enough for their similarity. From 2016, only a few similar biologics gained approval, reflecting the stringency in the approval process and criteria. All precautions must be taken without compromising the safety requirements and international conventions on guidelines for such products. Given the complexity of

biologics, a 'one-size-fits-all' strategy for biosimilars may not be appropriate. Biosimilars of monoclonal antibodies should go through a more stringent process of approval when applied on a case-to-case basis.

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