Journal of Scientific and Innovative Research 2013; 2 (4): 833-842
Available online at: www.jsirjournal.com

Review Article

ISSN 2320-4818
JSIR 2013; 2(4): 833-842

Received: 30-07-2013
Accepted: 10-08-2013

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An Overview of Similar Biologics

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Abstract

Generics are chemical or drugs with expired patency, while biological molecules manufactured similar to the original product after the expiry of the patent is popularly called as 'biosimilar'. Biosimilars can be broadly defined as those medicines produced using a living system or genetically modified organism. They are different from conventional generics in many ways, in size, structure, stability, heterogeneity, and analytical characterization. Strictly speaking Biosimilars are not true generics, but exhibit a high degree of similarity to the reference biologic. Biosimilars have to be biologically and clinically comparable to the innovator product. Biosimilars are considered to be therapeutically important drugs, because in contrast to other therapeutic agents, biosimilars are highly selective drugs, offering effective treatments against various dreaded diseases like cancer with fewer side effects. Some countries have issued regulatory guidelines both for biosimilars in general and product specific requirements. Each country regulations are different and there is no simple mechanism for the approval of biosimilars related bioequivalence when compared to generic drugs. The first regulations for development of biosimilars were issued by European medicines agency followed by United States and World Health Organisation. India has recently issued guidelines on similar biologics. This article will provide an overview of biosimilars discussing the differences between biosimilars and chemical generics, the scientific and regulatory challenges and concerns with the use of biosimilars.

Keywords: Biosimilars, Biologics, Biopharmaceuticals, Regulations, Comparability.

Introduction

Biogenerics are biological products manufactured after expiry of the patent of innovator biopharmaceutical, also called as Biosimilars, Follow-on biologics, similar biologics, Subsequent entry biologics, Follow-on protein products and in different countries.[1] In India they are termed as 'similar biologics'. Similar biologic is defined as "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, which has been granted a marketing authorization in India by Drug Controller General of India (DCGI) on the basis of a complete dossier, and with a history of safe use in India Biologics are derived from living organisms".[1] Recombinant DNA biotechnology has facilitated large scale production. Approximately 90% of all biological products are produced from three sources: *E. coli*, Yeast or Chinese Hamster ovary cells.[2, 3]

The global Biosimilars market is expected to be worth $19.4 billion by 2014, growing at a Compound Annual Growth Rate of 89.1% from 2009 to 2014.[4]

Additionally, biological drugs make up a large proportion of new product approvals by the FDA with the prediction that this could rise to 70% of all new drug approvals by 2025.[5, 6] The global biosimilars market is estimated to touch $10 billion by 2015 and currently India has a share at around 3 per cent and is expected to capture 20-25% market share in biosimilars market over the next five years.[7]

Biological drugs that have been produced and are commercially available include insulin, human growth hormone, erythropoietin, granulocyte colony-stimulating factor (G-CSF), interferon-a (IFNa) and monoclonal antibodies such as rituximab and trastuzumab, amongst others.[2] Owing to affordability and easy accessibility, biosimilars have established a good reputation among healthcare professionals. Regulations for approving biosimilars was first developed by the European Union, India and the United States have recently issued applicable guidelines for evaluation and overall regulation for biosimilars.

Difference between Biosimilars and Generics (Chemical Drugs)

Biosimilars differ from chemical drugs in molecular properties and have complex manufacturing process. The major differences between generic drugs and biosimilars is shown in table 1.[3, 8]

Table 1: Difference between generics and biosimilars

Property	Generics	Biosimilars
Size	Small (10 – 1000 Daltons)	100 to 1000 times larger
Structure	One dimensional	Three dimensional
Stability	Stable	Unstable
Characterization	Easy to characterize	Almost impossible
Manufacturing	Predictable chemical process	Unique line of living cells
Immunogenicity	Less	More potential for immunogenicity

Generic drugs are approved through simple registration procedure as abbreviated new drug application (ANDA). Such drugs need to exhibit the same strength, dosage form, and route of administration as the reference drug. If these criteria are met, it is assumed that the generic product's safety and efficacy are also equivalent to that of the branded product. However, it is not possible to employ the same standards for the evaluation or appraisal of biosimilars. Chemical drugs are easy to reproduce and specify by mass spectroscopy and other techniques, there is a lack of appropriate investigative tools to define the composite structure of large proteins.[3, 8]

Complex Issues of Concern with Use of Biosimilars

The manufacture and use of biosimilars has complex issues related to evaluation and comparability of biosimilars to reference products. Another challenge is for the physician, because in majority of the cases, physician is not trained on prescribing the biosimilars.

Clinical Efficacy

Guidelines issued by different countries for biosimilar manufacturers provide detailed guidance on pharmacokinetics, Pharmacodynamics, and toxicology, preclinical and clinical studies to receive drug approval. The goal of the clinical development for the biosimilar is to demonstrate no clinically meaningful difference relative to the innovator product. Studies have demonstrated the differences between the biosimilars and their innovator products. In a study comparing 11 epoetin alfa products from four different countries (Korea, Argentina, China, and India), in vivo bioactivity ranged from 71 to 226%, with five samples failing to fulfill their own specifications.[9] Also, a significant difference in the level of purity was observed among various brands of biosimilars of G-CSF and erythropoietin.[10]

The most effective way to prevent this difference is to conduct equivalence trials of adequate sample size which should ideally be double-blinded. One of the first items required in designing an equivalence trial is to establish a 'minimally clinically important difference (MCID)' in the primary trial endpoint. The MCID is defined as the

minimum difference in a meaningful clinical endpoint between two treatments beyond which regulatory bodies would consider the two drugs to be non-equivalent.

From a trial design point of view, the smaller the MCID set during the design of an equivalence trial, the larger the final sample size.[11] Indian guidelines[1] recommend one or more adequately powered, randomized, parallel group, blinded confirmatory clinical safety and efficacy trials are desirable based on the comparability established during Preclinical, Pharmacokinetic and Pharmacodynamics studies.

Safety considerations

Immunogenicity is an important safety concern for biosimilars. The risk of immunogenicity increases due to factors such as the presence of impurities, structural modifications as a result of the manufacturing process and/or suboptimal storage conditions.[12] Biosimilars provoke immune reactions, which can differ from product to product and these effects can only be detected and assessed during appropriately powered clinical studies which should ideally be double-blinded and cross over with pre-defined adequate follow up. A good example of immunogenicity is increase in number of cases of pure red cell aplasia associated with a specific formulation of epoetin alfa. Most of the cases occurred in patients treated with Eprex, the biosimilar of epoetin alfa. The most likely cause was changes in the manufacturing process. In the formulation Eprex, the human albumin stabilizer was replaced by polysorbate 80 and glycine. Polysorbate 80 is supposed to have increased the immunogenicity of Eprex by eliciting the formation of epoetin-containing micelles or by interacting with leachates released by the uncoated rubber stoppers of prefilled syringes.[3, 9]

The route of administration can also affect immunogenicity. Generally, intravenous administration is less immunogenic than intramuscular or subcutaneous administration, as was the case with erythropoietin.[9] The tests conducted during its development cannot predict immunogenicity. Hence, the best way to establish the safety of a biosimilar is via clinical trials. Post-marketing surveillance is another tool by which the safety can be continuously monitored as the differences between biosimilars may not become apparent in the pre-approval period, where a limited numbers of patients receive the product over a short period.

Indian guidelines[1] recommend "immunogenicity study should be conducted at least in one non-comparative post-marketing clinical study with focus on safety and immunogenicity (on case by case basis) should be performed. This study must be designed to confirm that the similar biologic does not have any concerns with regards to the therapeutic consequences of unwanted immunogenicity. If immunogenicity is evaluated in clinical studies, it is not mandatory to carry out additional non-comparative immunogenicity studies in post marketing studies".

Manufacturing process

Even a small change in the manufacturing process of can dramatically affect the safety and efficacy of the biosimilar. It is practically impossible for two different manufacturers to manufacture two identical biopharmaceutical active substances if not identical host expression systems, processes and equivalent technologies are used.[13] The pharmaceutical companies are not required to share their process even after expiry of the patent.[14] Even a small change in the manufacturing process can lead to severe and life threatening adverse reactions as in case of epoetin alfa.[3, 9]

Indian guidelines[1] mention that the "data requirements for review of manufacturing process at preclinical submission stage include a complete description of the manufacturing process from development and characterization of cell banks, stability of clone, cell culture/ fermentation, harvest, excipients, formulation, purification, primary packaging interactions (if different from reference biologic), etc. and the consequences on product characteristics. For the establishment and characterization of the cell banks, the guidelines issued by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use should be referred for guidance".

Another important aspect in manufacturing process is substitution or interchangeability. Substitution can have clinical consequences as patients could respond differently to the two products. For example, one of the major concerns while switching between various brands of insulin products is the issue of hypoglycemia and the development of antibodies.[15] Indian Insulin Technique Guidelines 2012 also do not permit interchange.[16]

Substitution for generics and biosimilars is different. The rationale behind substitution of chemical drugs is that the original drugs and their generics are identical and have the same therapeutic effect. For majority of chemical generics, automatic substitution is appropriate and is cost saving.

However, the same substitution rules should not be applied to biosimilars, as it may produce therapeutic failure or serious adverse effect. The prescribers and pharmacists should be aware of it and avoid this inappropriate substitution.[3, 17, 18]

Pharmacovigilance

Immunogenicity is a unique safety issue with biosimilars as described earlier. However, there is lack of validation and standardization of methods for detection of immunogenicity. Data from pre-authorization clinical studies are usually too limited to identify all potential unwanted effects of a SBP. In particular, rare adverse events are unlikely to be encountered in the limited clinical trial populations being tested with biosimilars.

In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified. To facilitate this and for clear prescribing and dispensing, biologic products should be identified by a unique name. Additionally, the WHO guideline Similar Biotherapeutic Products states that the prescriptions of biologics should not be based on INN name but on a unique name, for example the trade name, in order to enable pharmacovigilance and ensure traceability in case of adverse events.[19] Indian guidelines[1] mention "The pharmacovigilance plan should include the submission of periodic safety update reports (PSURs). The PSURs shall be submitted every six months for the first two years after approval of the similar biologic is granted to the applicant. For subsequent two years the PSURs need to be submitted annually to DCGI office as per the Schedule Y". All cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant as per Schedule Y.

Extrapolation of clinical data

Extrapolation refers to the approval of a drug for indications for which it has not been evaluated in clinical trials. It is only applicable in a handful of cases such as new formulations, indication in closely related diseases etc.[20] Indian guidelines[1] mention the following criteria:

• Similarity with respect to quality has been proven to reference biologic

• Similarity with respect to preclinical assessment has been proven to reference biologic

• Clinical safety and efficacy is proven in one indication

• Mechanism of action is same for other clinical indications

• Involved receptor(s) are same for other clinical indications

• New indication not mentioned by innovator will be covered by a separate application.

The rationale is that if a biosimilar shows adequate comparability to the innovator product for one indication, it may be reasonable to extend the approval of the biosimilar to all the indications of the innovator product. Recently, two biosimilar growth hormones have been approved which included extrapolation of clinical data for some indications. The reasons for the same were cited as the long history of safe use of growth hormone, high therapeutic index, the rarity of reports of neutralizing antibodies and assays available to characterize the biological activity of growth hormone.[21]

Naming and labeling

An International Nonproprietary Name (INN), is the official nonproprietary or generic name given to a pharmaceutical substance, as designated by the World Health Organization. "In the case of biological, INN can be either identical or different for similar products made by different manufacturers. For instance, the INN for recombinant growth hormone is the same (somatropin) for all growth hormones made by different originators or biosimilar companies. By contrast, the INN for recombinant human erythropoietin is different for different originator products (epoetin alpha, beta or theta) and can be identical or different for biosimilar products (epoetin alpha or zeta)".[22]

European Medicine Agency (EMA) guidance indicates standard reporting of brand name, manufacturer's name and batch number for all adverse events caused by biological medicines. Therefore, biological medicines should only be prescribed by their brand name, and not by their INN, which identifies medicines by their active pharmaceutical ingredients. Biosimilars require unique INNs, as this would facilitate prescribing and dispensing of biopharmaceuticals and also aid in precise pharmacovigilance.[3, 17] There should be comprehensive labeling of biosimilars including the deviations from innovator product and unique safety and efficacy data, which would assist the physician and pharmacist in making informed decisions.[3, 17]

Regulatory Standards for Biosimilar Products

Regulatory framework in Europe

The European Medicines Agency (EMA) was among the first guidelines issued for the approval of biosimilars. Biosimilar is defined by EMA as "A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies".

The approval pathway requires a Biosimilar manufacturer to demonstrate similarity for quality, safety and efficacy with a reference product already licensed Europe. The Biosimilar must demonstrate in clinical studies, that it has no significant clinical differences with the reference product. EMA's clinical trial and pharmacovigilance data requirement makes the regulatory process rigorous. EMA revises the guidelines at regular intervals and the recent information can be found at EMA website.[23]

In addition to general guidelines for Biosimilar medicines, EMA has also issued product specific Biosimilar guidelines for individual drugs, for e.g., recombinant human insulin, follicle-stimulating hormone, low molecular weight heparins and somatropin. There are some cases where the application was rejected by EMEA, for e.g. aplheon, the biogeneric of interferon, due to the concerns over manufacturing technique and quality control.[24] The application of Biosimilar Marvel Insulin was also disapproved because of inadequate data to prove similarity with innovator product.[25]

Regulatory framework in United States

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of The Patient Protection and Affordable Care Act, and has laid down regulations for approval of Biosimilar products. U.S. Food and Drug Administration (U.S.FDA) define biosimilarity and interchangeability follows. Biosimilarity means "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product".[26, 27]

"Interchangeability means that the biologic product is Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient. 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 will not be greater than the risk of using the reference product without such alternation or switch. Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider".[27]

The US FDA issued draft guidance documents recently in 2012 on Biosimilar product development to assist industry in developing such products. The guidelines mention structural analysis of the Biosimilar followed by its functional analysis to justify animal testing, followed by animal toxicity and immunogenicity studies. Lastly human clinical data, immunogenicity studies and post marketing safety considerations.[28] According to this new guidelines, biological products will be approved on demonstrating that they are Biosimilar to, or interchangeable with, a biological product that is already approved by the US FDA. These regulatory guidelines will help biosimilars manufacturers to enter the US market. So far, the biggest challenge for manufacturers was the absence of clearly defined regulations in different countries to develop biosimilars.

World Health Organization (WHO) Guidelines

The WHO issued guidelines on evaluation of similar biotherapeutic products (SBPs) in 2009. It provides globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier.[1, 19]

The key principles of WHO guidelines are:

• On the basis of proven similarity, the licensing of a SBP will rely, in part, on non-clinical and clinical data generated with an already licensed reference biotherapeutic product (RBP).

• The basis for licensing a product as a Biosimilar depends on its demonstrated similarity to a suitable reference product in quality, nonclinical and clinical parameters. If relevant differences are found in the quality, nonclinical or clinical studies, the product will not likely qualify as a Biosimilar

• This guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are however, excluded from the scope of this document

• WHO also states "although International Nonproprietary Names (INNs) served as a useful tool in worldwide pharmacovigilance, for biologicals they should not be relied upon as the only means of product identification or as an indicator of product interchangeability". It states that prescriptions of biologics should not be based on INN but on a unique name, for example the trade name. This guideline can be adopted as a whole, or partially, by National regulatory authorities (NRAs) worldwide or used as a basis for establishing national regulatory frameworks for licensure of these products.

Regulatory framework in India

In India, Central Drugs Standard Control Organization (CDSCO) and the Department of biotechnology have issued guidelines on similar biologics in 2012. The important features of the guidelines are summarized below:[1]

1) Applicable Regulations and Guidelines

The similar biologics are regulated as per the Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended from time to time) and 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. Various applicable guidelines are as follows:

• Recombinant DNA Safety Guidelines, 1990

• Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other biologicals, 1999

• CDSCO guidance for industry, 2008:

- Submission of Clinical Trial Application for Evaluating Safety and Efficacy
- Requirements for permission of New Drugs Approval
- Post approval changes in biological products: Quality, Safety and Efficacy Documents
- Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011

2) Competent Authorities

Three competent authorities are involved in the approval process:

Review Committee on Genetic Manipulation (RCGM)

RCGM functions in the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India. RCGM is responsible for authorizing import/export for research and development and review of data up to preclinical evaluation.

Genetic Engineering Appraisal Committee (GEAC)

GEAC functions under the Ministry of Environment and Forests as statutory body for review and approval of activities involving large scale use of genetically engineered organisms (also referred as living modified organisms) and products thereof in research and development, industrial production, environmental release and field applications.

Central Drugs Standard Control Organization (CDSCO)

CDSCO is responsible for grant of import/ export license, clinical trial approval and permission for marketing and manufacturing. State Food and Drug Administration works with CDSCO in each state and is responsible for issuance of license to manufacture similar biologics in India.

3) Selection of Reference Biologic

The following factors should be considered for selection of the reference biologic:

• The reference biologic should be licensed in India and should be innovator product. The reference biologic should be licensed based on a full safety, efficacy and quality data. Therefore another similar biologic cannot be considered as a choice for reference biologic.

• In case the reference biologic is not marketed in India, the reference biologic should have been licensed and widely marketed for 4 years post approval in innovator jurisdiction in a country with well established regulatory framework. In case no medicine or only palliative therapy is available or in national healthcare emergency, this period of 4 years may be reduced or waived off.

• The same reference biologic should be used throughout the studies supporting the safety, efficacy and quality of the product (i.e. in the development programmed for the similar biologic)

• The dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic.

• The active substance (active ingredient) of the reference biologic and that of the similar biologic must be shown to be similar

Pharmacodynamics Studies

In vitro studies: Comparability of test and reference biologic should be established by in vitro cell based bioassay (e.g. cell proliferation assays or receptor binding assays).

In vivo studies: In vivo evaluation of biological/ pharmacodynamic activity may be dispensable if in vitro assays are available, which are known to reliably reflect the clinically relevant pharmacodynamic activity of the reference biologic. In cases where the in-vitro assays do not reflect the pharmacodynamics, in vivo studies should be performed.

Toxicological Studies

"In case of in vivo toxicity studies, at least one repeat dose toxicity study in a relevant species is required to be conducted. The duration of the study would be generally not less than 28 days with 14 days recovery period. However the duration may vary depending on the dosage and other parameters on case by case basis. Regarding the animal models to be used, the applicant should provide the scientific justification for the choice of animal model(s) based on the data available in scientific literature. However if the relevant animal species is not available and has been appropriately justified, the toxicity studies need to be undertaken in two species i.e. one rodent and other non rodent species, as per the requirements of Schedule Y".

Study groups of animals in repeat dose toxicity testing will consist of:

i) Historical Control (Optional)

ii) Vehicle Control

iii) Vehicle Control for recovery group

iv) Formulation without protein (for vaccines) if multiple adjuvants-each to be checked independently

v) 1X similar biologic for study duration (lowest dose)

vi) 1X Reference biologic for study duration

vii) 2X Medium dose similar biologic

viii) 5X High dose similar biologic

ix) Similar biologic with a recovery group going beyond the end of study period for 7 to 14 days.

Other toxicity studies, including safety pharmacology, reproductive toxicity, mutagenicity and carcinogenicity studies are not generally required for evaluation of a similar biologic unless warranted by the results from the repeat dose toxicological studies

Immune Responses in Animals

"Antibody response to the similar biologic should be compared to that generated by the reference biologic in suitable animal model. The test serum samples should be tested for reaction to host cell proteins. For evaluating immune toxicity of the similar biologic under study, the results of local tolerance (part of repeat dose or stand alone test) should be analyzed with the observations regarding immunogenicity in sub-chronic study. Therefore, the immunogenicity testing should be included as part of the sub-chronic repeat dose study while developing the protocols. The other parameters for evaluating immune toxicity include immune complexes in targeted tissues may be considered while evaluating histopathology observations, etc".

Pharmacokinetic Studies

Comparative pharmacokinetic (PK) studies should be performed in healthy volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics between similar biologic and reference biologic on case to case basis.

The design of comparative pharmacokinetic studies should take the following factors into consideration.

• Half life

• Linearity of PK parameters

• Endogenous levels and diurnal variations of similar biologic under study (where applicable)

• Conditions and diseases to be treated

• Route(s) of administration, and

• Indications

Appropriate design considerations can be combined into single dose or multiple dose studies with adequate justification. These design considerations include:

• Single dose, comparative, PK studies

• Parallel arm or

• Cross over

• Multiple doses, comparative parallel arm steady state PK studies

Pharmacodynamic Studies

"As for the PK studies in the similar biologic clinical development program, the Pharmacodynamic (PD) studies should also be comparative in nature. Comparative, parallel arm or cross-over, PD study in most relevant population (patients or healthy volunteers) is required for detecting differences between reference biologic and similar biologic. If PD marker is available in healthy volunteers, PD in healthy volunteers can be done. Comparative PD studies are recommended when the PD properties of the reference biologic are well characterized with at least one PD marker being linked to the efficacy of the molecule. PD study can also be a part of Phase III clinical trials wherever applicable".

The detailed guidelines on other issues such as safety and immunogenicity data, extrapolation of efficacy data, pharmacovigilance, archiving of data, etc are described in the relevant sections in the article. Additional detailed information can be obtained from the CDSCO website. Some of the biosimilars approved in India are listed in table 2.[10, 29, 30]

Table 2: Similar biologics approved in India

Product name	Active molecule	Indication
Epofer	Epoetin alfa	Anemia due to chronic renal failure
Fegrast	Filgrastim	Neutropenia
FostiRel	Follitropin beta	Female infertility
Insugen	Human insulin	Diabetes mellitus
Mirel	Reteplase	Myocardial infarction
Reditux	Rituximab	Leukaemias. Lymphomas Rheumatoid arthritis
Relibeta	interferon beta-1a	Multiple sclerosis
Reliferon	interferon alpha 2b	Chronic hepatitis B, Chronic hepatitis C, Follicular lymphoma, Multiple myeloma
Etacept	Etarnecept	Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis

Conclusion

Biosimilars have revolutionized the management of several diseases of global impact such as diabetes, cancer and various immunologic conditions. Biosimilar will play a major role in the manage¬ment of these diseases in future. India has the potential to become one of the key players in the development and manufacture of biosimilars, due to its inherent strength in pharmaceutical manufacturing and also has potential for export to developed markets. The development of biosimilars will help in providing economical and proper care to the patients especially in developing countries like India.

At present some issues needs to be addressed, like uncertainty related to safety and efficacy, particularly when the reference biological has multiple indications and disease like cancer, where patient and disease characteristics can affect drug activity. Over the next decade, more agents will emerge which may lead to with increased complexity. While prescribing biosimilars, physician should prescribe them by their brand names and

also educate the patients about interchangeability, especially in case of products such as insulins as they are not interchangeable. Finally, as India has sub optimal pharmacovigilance system, success of biosimilars depends upon the implementation of adequate pharmacovigilance systems and regulatory guidelines.

Conflict of interest: None

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