



ORGANISATION OF PHARMACEUTICAL PRODUCERS OF INDIA

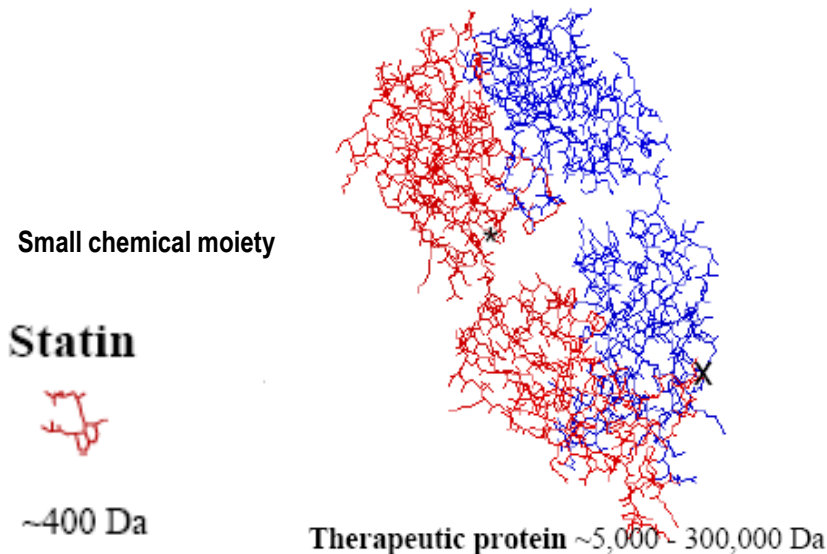
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OPPI POSITION PAPER ON BIOSIMILARS

1. Introduction

Biotherapeutic products have a successful record in treating many life threatening and chronic diseases. The expiration of patents and/or data protection for the first major group of originators' biotherapeutics has led to development of products that are designed to be 'similar' to a licensed originator product.

Unlike small molecule pharmaceuticals, it is not possible for two unrelated manufacturers to produce biologics that are the same. This is due to the complexities of their production and massive size of the protein molecules. Hence, efforts to duplicate these molecules may result in products that are similar, but not the same, as there will always be small differences in the molecular structure compared to the original molecule and even minor differences in the manufacturing process of a biological product can lead to a different impurity profile and differences in the product's properties and clinical characteristics, including immunogenicity.



Adapted from: Behram, Rachel E. (2008, November 21) Follow-on Biologics: A Brief Overview.

2. Rationale for Update

The Dept. of Biotechnology, Ministry of Science & Technology, Government of India issued “[National Biotechnology Development Strategy](#)” in 2007 which laid out key policy interventions to enable the accelerated growth of this sector.¹ The Indian biosimilars market (domestic plus exports) is expected to reach around \$580 million by 2012 from around \$200 million in 2008². While this highlights the magnitude of opportunities for Indian industry, it is also likely to result in immense pressure on the government to facilitate the growth of biosimilar products without stringently regulating the procedure for their approval and marketing.

According to ‘Global Biosimilars Market (2009-2014)³, a report published by Markets and Markets (www.marketsandmarkets.com) in August 2010, the global biosimilars market is expected to be worth US\$ 19.4 billion by 2014, growing at an expected CAGR of approximately 89% in the period 2009-14. ‘The Biosimilars market today and tomorrow’: an article published in Pharmtech (September 2010 issue)⁴ mentions that “Whatever the forecast, there remains a \$50 billion potential for biosimilars; however, the delivery of this will be dependent on legislation, substitutability and originator strategies.”

Significant progress has been made in the past few years with European Medical Agency⁵ (EMA) leading the way, when it developed and issued comprehensive guidelines for licensing of biosimilars in 2005. EMA followed an extensive and broad-based process that involved seeking opinion from multiple stakeholders (including scientists, regulators, physicians, patient groups, general public, others). These guidelines have enabled 14 biosimilars to be approved in the EU so far. Subsequently, similar guidelines have come into force in various countries across the globe. Of particular interest are countries in Asia such as South Korea, Malaysia⁶, Taiwan, Turkey, Sri Lanka and Japan which have enforced national guidelines that draw heavily from European guidelines. In 2009, World Health Organization (WHO)⁷ issued guidelines to provide globally acceptable principles for licensing biotherapeutic products that claim to be similar to approved reference biotherapeutic product (RBP). These guidelines can be adopted by National Regulatory Agencies (NRA) worldwide for establishing national regulatory frameworks for licensure of biotherapeutic products.

In light of these significant changes in the global scenario, there is a strong case for establishing guidelines for the approval of biosimilars in India which like WHO and EMEA guidelines are scientifically driven and yet can be customized to the local scenario without compromising patient safety or product quality as was done by countries such as South Korea, Malaysia, and Taiwan. Such science-driven, customized regulatory framework and guidelines will go a long way in ensuring that biosimilar products developed, manufactured and marketed in India are indeed similar in terms of safety, quality and efficacy to the RBP and also meet standards for export to other developed nations - a very significant business opportunity for the domestic industry.

This update to the [position paper](#)⁸ on biosimilars previously issued by OPPI in 2008 intends to:

- 1) Provide overview of guidelines adopted by regulatory bodies across the globe.
- 2) Highlight key issues for consideration with regard to licensing / regulatory approvals of biosimilars.

- 3) Underscore the urgent need for appropriate regulatory framework and guidelines for biotherapeutic products approved in India to ensure demonstrable similarity with regards to quality, efficacy and safety profile of the RP.

3. Scope

This document applies to the regulatory considerations for well-characterized biological medicines containing recombinant DNA-derived therapeutic proteins, including monoclonal antibodies. It does not address vaccines, plasma-derived products, and their recombinant analogues.

4. Scientific Background

4.1 Definitions

Biotherapeutic products can be broadly defined as those medicines produced using a living system or genetically modified organism.

A biosimilar is a biological medicine that is similar, but not identical, to an already registered reference biotherapeutic product in terms of quality, safety, and efficacy. These products rely, in part, for licensing on prior information obtained from the innovator product and a demonstration of similarity based upon detailed and comprehensive product characterization. A variety of terms, such as ‘biosimilar products’, ‘follow-on protein products’ and ‘subsequent-entry biologics’ have been coined by different jurisdictions to describe these products.

4.2 Key Considerations

Biotherapeutic products are different from traditional chemical medicines in many ways. The molecules of a biotherapeutic product are much larger, have more complex spatial structures and are much more diverse (“heterogeneous”) than the chemical molecules. Unlike chemically synthesized drugs, each biotherapeutic product is comprised of a number of active components (i.e. the desired protein product plus co-purified product-related substances), the composition of which is controlled by specific details of the manufacturing and purification processes.

The key considerations that differentiate the relative stringency of pre-approval assessments are:

i. “Process defines product”

- The manufacturing process for a biotherapeutic product defines the product’s quality, efficacy and safety profile.
- Small process differences in the manufacture of innovator biotherapeutic products and biosimilar medicinal products, despite having identical primary amino acid sequence, can result in significant differences in the safety and efficacy of the therapeutic molecule.
- Post –translational modifications such as glycosylation and their unpredictability further add to the complexity and heterogeneity in product characterization and clinical impact thereof.

- Hence, it is practically impossible for two different manufacturers to manufacture identical biopharmaceutical substances. Therefore, a ‘generic’ biopharmaceutical active substance cannot exist. At best, the product can be termed ‘similar’ to the RP.
- ii. *The clinical action of biotherapeutic products is significantly determined by the dosage and route of administration*
- The comparability assessment must ensure that the biosimilar demonstrates similarity through appropriately powered clinical studies, for quality, safety and efficacy profile with an approved reference product; wherein, the following must be the same as the RP:
 - Route of administration
 - Dosage
 - The dose strength of the biosimilar
 - The aforementioned trials should assess endpoints that are validated and are acceptable in global peer reviewed scientific forum.
- iii. *Immunogenicity*
- Biotherapeutic products are injectables that typically provoke immune reactions, which can differ from product to product and these effects can only be detected and assessed during appropriately powered clinical studies with pre-defined adequate follow up. The timing and extent of analyses will also depend on the risk identified for a particular drug and the clinical consequences. Therefore, immunogenicity assessment should be part of the clinical trials, with the analysis of its correlation to clinical efficacy and safety results.
- iv. *Substitution issues*
- Biosimilar medicines can be ‘similar’ but not ‘identical’ to the innovator reference product. This implies that substitution of the innovator product with a biosimilar product could have clinical consequences. Therefore, there is a need for system that enables identification of individual biosimilars with a unique name.
- v. *Approval pathway*
- The accepted standard method for licensing generic medicines through bioequivalence studies alone is not scientifically appropriate for biosimilars.
 - While the pre-approval testing required for a biosimilar can be less than the innovator, it must be substantially more extensive than it is for generic chemistry-based drugs. To ensure the safety and efficacy of biosimilar products, these products should only be approved following the submission of appropriate data generated with the biosimilar drug which should include pre-clinical tests and controlled clinical trials with a significantly relevant number of patients addressing all the issues highlighted above in their respective study designs.

5. Regulatory Background

5.1 European Union: EMEA Guidelines

The European Union (EU) defined a legal and science-based regulatory pathway to enable the development and marketing of biosimilars that includes guidelines pertaining to quality, non-clinical and clinical requirements for biosimilar protein therapeutics. The [EMEA guidelines](#) were themselves an expansion of the general guideline released in September 2005 and of two earlier documents, a note for guidance containing non-clinical and clinical issues (December 2003) and a quality guideline (also December 2003). Each of these regulatory guidance documents reflects the distinct development and manufacturing challenges of biosimilars.

The EU biosimilar approval pathway requires a biosimilar manufacturer to demonstrate similarity with regard to quality, safety and efficacy with a reference biotherapeutic product already licensed in the EU. Biosimilar manufacturers provide all pre-clinical and clinical data required to demonstrate similarity between their product and the reference product, if appropriate. Specifically, the biosimilar must demonstrate, through clinical studies that it has no significant clinical differences with the reference product.

The EU provides 10 years data exclusivity, with an additional year for products with multiple indications.

In light of the variability in complexities of different biotherapeutic products, the EMA has over the past few years, been publishing guidelines on clinical and non-clinical issues pertinent to specific biological products to address product specific requirements for insulin, Human Growth Hormone (HGH), Granulocyte Colony-Stimulation Factor (CCSF), Erythropoietin (EPO), Interferon and Heparin.

The EMA assesses the level of data required for a biosimilar marketing authorization application on a case-by-case basis, but the level of data required is still less than is required for an original biological product.

As of date, the European Commission has granted 14 approvals for biosimilar drugs. In the same time period, there have been some applications which have been given a negative opinion- Alpheon ([interferon alpha](#)); Biferonex ([interferon beta 1a](#)). The aforementioned decisions came because of one or more of the following concerns,

- Differences such as impurities.
- Data on the stability of the active substance and of the medicine to be marketed.
- The process used for producing the final medicinal product had not been adequately validated.
- The test used in the study to investigate the potential for the medicine to trigger an immunological response had not been sufficiently validated.
- In the case of Biferonex, efficacy could not be demonstrated despite clinical trial data submission. EMA cited concerns with regards to study design and robustness of results and raised objections to the fact that the pharmacodynamic characterization revealed poor dose response relationship.

Marvel Life Sciences (UK) withdrew its EU Marketing Authorization Application (MAA) for [biosimilar human insulin](#) (Insulin Human Rapid Marvel), NPH insulin (Insulin Human Long Marvel), and pre-mix 30/70 (Insulin Human 30/70 Mix Marvel) in December 2007 following the concerns expressed by the Committee for Medicinal Products for Human Use (CHMP):

- Concerns regarding the purity of the Marvel Life Sciences products being comparable to the reference product.
- Other information on key sections was considered incomplete, unclear and inadequately presented.
- The efficacy (Clamp) study did not demonstrate equivalent blood glucose-lowering effect to that of the reference product (Humulin®). In addition, efficacy (HbA_{1c}) and safety data showed consistent trends in favor of the reference product.
- The MAA lacked information about production procedures, and processes had not been validated.

5.2 World Health Organization (WHO) Guidelines for Evaluation of Similar Biotherapeutic Products (SBP)

WHO guidelines adopted in October 2009 opined that the clinical experience and established safety profile of the originator products should contribute to the development of SBPs. The WHO guidelines provide globally acceptable principles for licensing biological products that are claimed to be similar to originator biological products of assured quality, safety and efficacy that have been previously licensed based on a full licensing dossier.

The following key principles for the licensing of biosimilars were provided:

- SBPs are not 'generic medicines' and many characteristics associated with the authorization process generally do not apply.
- The development of an SBP involves stepwise comparability exercise starting with comparison of the quality characteristics of the SBP and the reference biotherapeutic product (RBP).
- SBP, like other biotherapeutic products, require effective regulatory oversight for the management of potential risks. As development of biotherapeutic products is a rapidly evolving area, regular review by the NRA of the adequacy of the processes and policies that constitute the regulatory framework for providing oversight, is essential.
- The basis for licensing a product as an SBP depends on its demonstrated similarity to a suitable reference product in quality, non-clinical, and clinical parameters.
- If relevant differences are found in the quality, non-clinical, or clinical studies, the product will not likely qualify as a SBP.
- If comparability exercise with the reference product is not performed throughout the development process as outlined in the guidelines, the final product should not be referred to as a SBP.

The choice of a RBP is of critical importance for the evaluation of SBP. The rationale for the choice of the RBP should be provided by the manufacturer of the SBP in the submission to the NRA. Traditionally, the agencies have required the use of a nationally licensed reference product for licensing of generic medicines. The NRA may need to consider establishing additional criteria to guide the acceptability of using a RBP licensed or resourced in other countries such as:

- The RBP should have been marketed for a suitable duration and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy of the product.
- The RBP should be licensed based on a full quality, safety, and efficacy data.
- The drug substance of the RBP and the SBP must be shown to be similar. The dosage form and route of administration of the SBP should be the same as that of the RBP.

- A SBP should not be considered as a choice for RBP.
- The same RBP should be used throughout the development of the SBP (i.e. for the comparative quality, non-clinical, and clinical studies).

5.3 United States (US): The Biologics Price Competition and Innovation Act of 2009

In March 2010, the United States (US) Congress passed the [Biologics Price Competition and Innovation Act of 2009](#)⁹, which established the legal pathway for the regulatory approval of biosimilar in the US. The act recognized that a biosimilars pathway balancing innovation and consumer interests should be established.

The legislation requires that the licensure of biological products as biosimilar will be granted based on provision of data derived from analytical studies, toxicity and clinical studies including the assessment of immunogenicity, pharmacokinetic and pharmacodynamic properties. These should be sufficient to demonstrate safety, purity, and potency in one or more indications for which the reference product is licensed and for which licensure is sought for the biological product. It allows the US Food and Drug Administration (FDA) to determine the number and scope of trials deemed appropriate to demonstrate product safety and efficacy.

A biological product is “interchangeable” with a reference biological product if (i) it meets the criteria for being biosimilar to the reference product, and (ii) it can be expected to produce the same clinical result as the reference product in any given patient, and (iii) the risk in terms of safety or diminished efficacy in alternating or switching between use of the biological and reference product is not greater than the risk of using the reference product without such alteration or switch.

The legislation provides 12 years of regulatory data protection for reference products. Additionally, the US law defines the duration of data exclusivity for the reference product and subsequent interchangeable product.

5.4 Additional Regulatory Jurisdictions

Taking cue from EMEA regulations, number of countries, as listed below, across different geographies have adopted and adapted guidelines for biosimilars. Countries such as Argentina, [Australia](#)¹⁰, Brazil, [Canada](#)¹¹, Columbia, Japan, [Malaysia](#), Mexico, Saudi Arabia, [Singapore](#)¹², South Africa, South Korea, Sri Lanka, Taiwan, Turkey, Venezuela etc, have put in place guidelines to introduce basic principles of biosimilar products and provide applicants with relevant guidance.

6. Additional Regulatory Considerations

6.1 Naming / Nomenclature

The advent of biosimilars has caused a debate as to whether the current International Non-proprietary Name (INN) system for medicines should be revised to assign each biological product a distinct INN. The INN system was established by the World Health Organization in 1953 to provide health professionals with a unique and universally accepted available designated name to identity each pharmaceutical substance.

The EU view is that the INN is a classification system based on molecular structure and mechanism of action. The assignment of INN to biological drug substances should be based on scientific criteria. It is recognized that 'biosimilar' is a regulatory and legal term and is distinct from the INN assignment process for biological drug substances. The EU recognizes the complexity of biotherapeutic products and that variability may exist between innovator biological products with the same INN or even within the same manufacturer. Effects of post-translational modifications in the field of biotherapeutic products contribute to that complexity and variability.

The US FDA is of the opinion that INN for biologicals should not be used to imply product interchangeability in the absence of credible scientific evidence. Likewise, however, INN should not be used to differentiate biological products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist. In the context of global pharmacovigilance, the INN is a useful tool but should not be the sole means of product identification for drug products including biologicals.

WHO guideline "Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)" states that prescriptions of biologics should not be based on INN only, but additionally on a unique name, for example the trade name. It is important that all biologics, both innovator and biosimilar, have a unique name to identify them and to enable pharmacovigilance and ensure traceability of adverse events.

6.2 *Interchangeability*

US legislation has mentioned two primary criteria for defining standard of approval for interchangeability of biosimilars:

- 1) information in application is sufficient to show that the biological product :
 - a. is biosimilar to reference product and
 - b. meets legislations standards for interchangeability and is interchangeable with reference product
- 2) applicant consents to inspection of facility

US legislation clearly defines interchangeability under section 351(k), whereby the regulatory agency can determine that a biological product is interchangeable with the reference product if it demonstrates that the information submitted in the application (or supplement) is sufficient to show that:

- (1) The biological product is biosimilar to the reference product;
- (2) The biological product can be expected to produce the same clinical result as the reference product in any given patient; and
- (3) If the product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the two products is not greater than the risk of using the reference product without such alternating or switching.

Issue of Interchangeability and substitution though not elaborated upon, has been listed as an important issue in WHO guidelines along with other aspects such as intellectual property issues, labeling and prescribing information.

6.3. Data Protection

As per US legislation, for a period of four years after the date on which the reference product was first licensed, no application can be entertained. Approval of an application under biosimilar cannot be made effective until 12 years after the date on which the reference product was first licensed.

Interchangeable Biological Product Exclusivity: Under section 351(k), the first biological product determined to be interchangeable with a particular reference product for any condition of use (“first interchangeable biosimilar biological product”) receives a period of exclusivity, during which no other product may be deemed interchangeable to that reference product for any condition of use.

The EU as well, provides 10 years data exclusivity, with an additional year for products with multiple indications.

7. Position Statement

Availability of biosimilars is an attractive option, particularly in developing countries as they may provide reductions in cost of therapy and may result in increased access to these therapies. The need to define the regulatory pathway for approval of biosimilars is being recognized and addressed in various countries across the globe.

In view of India’s potential to emerge as a key player in the biosimilar segment, the current lack of clear guidelines which address the issues at hand, poses a serious concern in terms of ensuring the safety of patients in India.

There is an urgent need to establish robust guidelines which provide for the approval of biosimilars in India in an expedited manner whilst also ensuring that biosimilars which are developed, manufactured and marketed in India demonstrate safety, quality and efficacy in patients. Meeting global standards for safety and efficacy, will also allow for export of these products to other developed nations.

8. Recommendations: Basic Scientific Consideration for Licensing of a Biosimilar drug

The recommendations below enlist some basic scientific requirements that are primarily drawn from WHO guidelines. These also represent the varied customization to the local environment as has happened in countries such as Australia, Brazil, Canada, Columbia, Japan, Malaysia, Saudi Arabia, Singapore, South Africa, South Korea, Taiwan, Turkey. Any prospective guideline that addresses these considerations, can enable an abbreviated regulatory pathway for approval of biosimilars which ensure product quality, efficacy and patient safety.

They include the following:

- The innovator product is deemed suitable as a reference biotherapeutic product if:
 - a. It was originally authorized for sale in India based on a complete data package.
 - b. It has significant safety and efficacy data accumulated such that the demonstration of similarity to it will bring into relevance a substantial body of reliable data.

- The same reference product must be used for comparative assessment throughout the development program
- The approval of the biosimilar product requires submission of:
 - a full quality package (i.e. the same level of data expected for an originator product)
 - comparative quality, clinical and non-clinical data generated with the biosimilar
- The biosimilar product, through characterization analysis as well as non-clinical and clinical studies (for safety, efficacy and immunogenicity) can be judged similar to the reference biotherapeutic product.
- Given the current state of science, biosimilars should not be considered interchangeable (as in automatic substitution without physician direction). The decision to prescribe or change to a biosimilar should always be taken by the treating physician based on clinical experience, medical and scientific literature available for the product and the individual needs of the patients.
- It is important that both innovator and biosimilar have different unique names (e.g., brand name or unique non-proprietary name) to distinguish and identify them.

[Note: Jurisdictions in the following sections refer to requirements as laid out in the guidelines of the countries mentioned thereafter]

8.1 Reference Biotherapeutic Product (RBP)

The RBP should be licensed based on a full quality, safety and efficacy data set. Therefore, a biosimilar should not be considered as a choice for the RBP*. The same RBP should be used throughout the entire comparability exercise and it must be approved in India ** and widely marketed in another jurisdiction with a well-established regulatory framework for and experience in evaluation and post-market surveillance of biologics.

The biosimilar product should be expressed and produced in the same host cell type as the RP. Biosimilars employing clearly different approaches to manufacturing than the RP may not be suitable for consideration as a biosimilar.

***Jurisdictions:** WHO, Australia, Bangladesh, Brazil, Canada, EU, Japan, Malaysia, Mexico, Saudi Arabia, Singapore, South Africa, South Korea, Taiwan, Turkey

****Jurisdictions that require local market approval:** Brazil, Canada, EU, Japan, Malaysia, Mexico, Saudi Arabia, Singapore, South Africa, Taiwan, Turkey.

8.2 Quality Comparisons

General considerations—The application must contain a full quality dossier for both the drug substance and the drug product detailing the raw materials, manufacture, stability, and control of the process.

The applicant should also carry out a comprehensive physiochemical and biological characterization of the biosimilar in head-to-head comparisons with the RP. All aspects of product quality and heterogeneity should be assessed. Differences should be assessed for their impact on safety and efficacy and justified, including potentially, through additional non-clinical or clinical studies.

Isolation of Drug Substance—If the active substance in the RP needs to be purified from a formulated RP in order to be suitable for characterization, studies must be carried out to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process.

The approach employed to isolate and compare the biosimilar active substance to the reference active substance should be justified (with data) as appropriate for the intended purpose. Where possible, the product should be tested with and without manipulation.

Physicochemical Analysis—the comparative physicochemical characterization should include the determination of primary and higher order structure and other biophysical properties using appropriate analytical methods (e.g. mass spectrometry, NMR).

The RP and the biosimilar are likely to contain a mixture of post-translationally modified forms, and appropriate efforts should be made to investigate, identify, and quantify these forms.

Biological and Immunological Analysis—Biological assays like receptor-binding assays or cell-based assays should be used to establish comparability. Molecular characterization should include analysis and comparison of antigenic epitopes that could lead to adverse reactions.

Impurities—Product-related and process-related impurities should be evaluated in conjunction with the efficacy of the purification process.

Analytical Specifications—The manufacturer should confirm that the specifications for the biosimilar are appropriate to ensure product quality.

Jurisdictions: Australia,, Brazil, Canada, Columbia, EU, Japan, Malaysia , Saudi Arabia, Singapore, South Africa, South Korea, Taiwan, Turkey.

8.3 Non-Clinical Evaluations

General considerations—Prior to performing clinical studies, the biosimilar applicant must conduct non-clinical studies to verify that the product can be safely administered to humans. The studies should be designed to detect differences in response between the biosimilar and the RP. These non-clinical studies may be conducted with reference to ICH S6. Prior to any non-clinical studies, each biosimilar must be subjected to full quality characterization.

Pharmacology (In Vivo & In Vitro) – Appropriately validated in vitro receptor binding studies or cell-based assays should be conducted when appropriate. In vivo studies should include animal pharmacodynamic studies relevant to the clinical application(s), at least one repeat-dose toxicity study conducted in a relevant species, and other relevant safety observations.

Toxicology—for recombinant proteins: At least one repeat-dose toxicity study in relevant animal species of sufficient duration to allow detection of relevant differences between the biosimilar and RP in toxicity and/or immunogenicity between biosimilar and RP is required.

Safety pharmacology, reproduction toxicity, mutagenicity, and carcinogenicity studies may not be required unless indicated from results of repeat dose studies.

Jurisdictions: Australia, Brazil, Canada, EU, Japan, Malaysia, Saudi Arabia, Singapore, South Africa, South Korea, Taiwan, Turkey

8.4 Clinical Evaluations

General—for recombinant proteins, usually comparative clinical trials are necessary to demonstrate clinical comparability. The clinical requirements depend on the existing knowledge about the RP and the claimed therapeutic indication(s). Available product / disease specific guidelines should be followed where appropriate.

The clinical comparability exercise is a stepwise procedure beginning with PK and PD studies followed by clinical efficacy and safety trial(s), or, in certain cases, PK/PD studies for demonstrating clinical comparability.

PK/PD Studies—Comparative PK studies should be conducted. The design of the study (e.g., cross-over vs. parallel) should take into account, among other things, half-life, route(s) of administration, dosage, frequency of administration and indications. The comparison parameters should include both absorption and elimination.

Parameters evaluated in comparative PD studies should be clinically relevant and surrogate markers should be validated.

Safety—Safety data should be obtained in a sufficient number of patients to provide a comparison of type, frequency and severity of adverse events. Safety data from the efficacy trials may be sufficient for this purpose (or may need to be extended), but in any case additional monitoring is usually necessary after approval.

Immunogenicity—The frequency of sampling and the timing and extent of analyses will also depend on the risk identified for a particular drug and the clinical consequences, and has to be justified. Immunogenicity assessment should be part of the clinical trials, since the correlation to clinical efficacy and safety is important. The assays should be validated and able to characterize content (concentration or titer) and type of antibodies. When neutralizing antibodies are detected, the impact on PK/PD parameters and overall efficacy and safety should be analyzed.

Jurisdictions: Australia, Brazil, Canada, EU, Japan, Malaysia, Saudi Arabia, Singapore, South Africa, South Korea, Taiwan, Turkey

8.5 Pharmacovigilance

The dossier should include a risk specification and PV plan including possible safety issues and risks identified during development. Monitoring imposed to the RP or product class should be taken into consideration and applied if relevant.

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.

Jurisdictions: WHO, Argentina, Australia, Bangladesh, Brazil, Canada, Columbia, EU, Japan, Malaysia, Mexico, Nepal, Saudi Arabia, Singapore, South Africa, South Korea, Sri Lanka, Taiwan, Turkey.

9. Conclusion

India has the potential to become one of the key players in the development and manufacture of biosimilars, not only to serve the needs of the local population but also for export to large developed markets. However, for this to materialize, India needs science driven guidelines. These guidelines should provide an abbreviated regulatory framework that ensures that such products approved in India are of good quality and demonstrated to be biosimilar in efficacy, safety and immunogenicity to the original reference products. The need for such a regulatory framework and guidelines is even greater in light of currently suboptimal pharmacovigilance system in India.

Considerable developments have occurred across the globe, in the scientific and regulatory understanding of biosimilars. Nearly all developed nations and several of the developing countries have now defined appropriate regulatory framework, drawing heavily from EMEA guidelines and adapting in parts for local scenario. More recently approved WHO guidelines further provide a good basis for developing countries to draw upon and adapt. Currently due to the lack of such definition in India, there are so-called “biosimilar” drugs which are being approved with sub-optimal testing and dossiers, thereby putting into question product quality, comparability and patient safety. In view of the foregoing, there is an urgent case for the Indian government to formulate guidelines for the regulatory approval of biosimilars. These guidelines must address the key scientific considerations highlighted above given the complexity and inherent heterogeneity of biologic drugs. It should be prepared as a legislated document with inputs from key stakeholders such as government, physicians, scientists, international biologics regulatory experts, patient advocacy groups, patients and industry (Indian and multinational companies). This will represent a critical step forward to ensure safety, quality and efficacy of more affordable biosimilar drugs available to patients in India and across the globe.

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