Chapter 52

Biopharmaceuticals and Biosimilars: A Consensus Statement

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ABSTRACT

Biopharmaceuticals or biologics are widely used in the management of several diseases such as diabetes, certain types of cancers and immunologic conditions. Insulin is the most commonly used biopharmaceutical or biologic agent worldwide. This is true for India as well, which has one of the largest populations of people living with diabetes with numbers estimated to be more than 60 million and this is expected to reach a mammoth 100 million by the year 2030. Although there are multiple therapeutic agents available, insulin and insulin analogs are the mainstay of treatment for diabetes mellitus, and are expected to remain so for the foreseeable future. In India itself there are several brands of insulin and biosimilar insulin available including insulin analogs.

Biopharmaceuticals are large, diverse, spatial protein molecules with distinct primary, secondary, tertiary or quaternary structures produced from living organisms and manufactured by complex processes, wherein the source materials and manufacturing processes can vary from manufacturer to manufacturer even while producing a similarly named product. Differences between an innovator product and a biosimilar can be identified analytically (e.g. batch-to-batch consistency, product stability alongside clinical safety and efficacy). Considering the narrow therapeutic window of several of these products where their dosing is highly dependent on the formulation and quality of the molecule along with administration device, it is important that adequate safety standards are established for all these products whether an innovator or a biosimilar, especially in the light of some safety concerns expressed with the latter. It is also essential that the physician is highly vigilant and sure about the quality of the product being used and ensure that while using a biosimilar molecule he has access to and knowledge of the complete comparative profile validating its quality, safety and efficacy. The purpose of this article is to provide guidance to the practicing clinician on the evaluation criteria while considering the use of a biosimilar product.

BACKGROUND

There has been a tremendous growth in the availability of biopharmaceuticals over the past couple of decades. The Indian biotechnology industry has also gained considerable momentum, which has triggered the growth of several National Research Laboratories employing thousands of scientists. This has in turn triggered a spurt in the number of college level educational and training institutes offering degrees and diplomas in biotechnology, bioinformatics and the biological sciences, producing nearly 5 lakh students annually. Given this backdrop, biotechnology is certainly the next big frontier for the Indian economy. However, this exploding scenario can put immense pressure on the healthcare regulators to facilitate the growth of biosimilar products without suitably modifying the procedure for approval and marketing of these products, which still rely on the standards set for chemical generic copies. While the government has taken a welcome step toward addressing this anomaly and released a draft robust guideline on biosimilars; this has still not been notified as a law.

In the absence of such guidance, India has standards, which are more lax than most countries in the world as a result of which there has been a spurt of introductions of several versions of a biologic product all claiming to be "biosimilar" to the innovator product. The purpose of this article is to present a consensus statement on this issue and also introduce the practicing clinicians to the various issues and complexities presented by biopharmaceutical products or biologics especially by the biosimilar versions as these have a direct impact on the disease outcome. It also provides guidance on the standards needed and the reasons for the same so that the clinician is suitably educated and consequently empowered to make appropriate decisions on behalf of the patient. It also aims to ensure that Indian patients are protected with similar standards of medicinal quality as patients in the rest of the world and as envisaged by the World Health Organization (WHO).

BIOPHARMACEUTICALS AND BIOSIMILARS

Biologics can be broadly defined as those medicines produced using a living system or genetically modified organism. They are different from traditional chemical medicines[1] in many ways. Size is one of the most obvious distinctions: the molecules of a biologic are much larger, have far more complex spatial structures and are much more diverse ("heterogeneous") than the chemical molecules which make up classical drugs. The conditions in which biologics are produced largely define the final product. Each biotech company uses unique cell lines and as a consequence develops its own unique manufacturing process (**Figure 1**).[2]

The manufacturing process defines the product quality and safety profile; it is vital to precisely control the whole manufacturing process in order to obtain consistent results and to guarantee the safety and efficacy of the end product. Variations at any stage in the manufacturing process can impact on the product's clinical profile and raise the safety concerns. Biosimilars can never be identical copies of the originator molecules, even when they have demonstrated comparable physicochemical and biological properties to a reference product using currently available tests. For nonglycosylated products such as human insulin, pharmacokinetic (PK) and pharmacodynamic (PD) differences are most probably caused by differences in formulation, while for glycosylated products

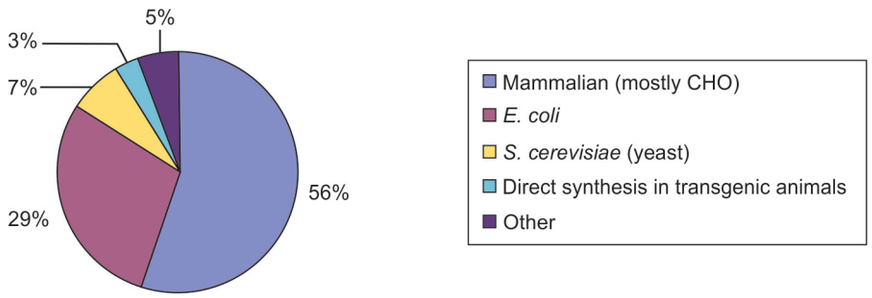

Figure 1: Expression systems used for manufacture of approved drugs

(e.g. epoetin), the glycosylation pattern is probably the major source of PK/PD variations.[3]

Additionally, compared to chemical drugs, proteins are relatively unstable, introducing additional challenges in their storage, formulation and delivery. The criticality of the manufacturing process can be emphasized with the example of the increased incidence of pure red cell aplasia (PRCA) in patients being treated with erythropoietin (EPO). Extensive investigation revealed that most likely change in excipient and manufacturing process may have caused the incidence of PRCA. No matter what the ultimate cause or causes of PRCA may be, the foregoing demonstrated the potential for immunogenicity from even slight changes in any facet of the manufacturing process for a biotechnology-derived protein product.[4,5]

Biosimilar medicines are follow-on versions of original biopharmaceutical medicines (innovator products). Biosimilar medicines are intended to have the same mechanism of action as the original biopharmaceutical medicines, and are designed to treat the same diseases as the innovator's product.

There is a considerable debate surrounding the definition, licensing and marketing of biosimilar medicines. The crux of this debate rests on the differentiation between biosimilar medicines and traditional generic copies of chemical medicines. Generic copies of traditional chemical medicines are identical in the molecular structure and are approved for use in humans based on a strict definition of "sameness", usually based on bioequivalence studies. However, due to the size, complexity of structure and sensitivity to manufacturing processes, a corresponding definition cannot be established for biosimilar medicines. As a result, biosimilar products can merely meet a "similarity" standard for approval. The ability or lack thereof to scientifically develop and manufacture identical generics compared to similar biosimilars necessitates other regulatory safeguards to ensure product safety and efficacy.[6]

COMPLEX ISSUES

Thus, the manufacture and use of biopharmaceuticals and so called biosimilar products raise several new questions in evaluation and comparability of different products. This also raises new challenges for the practicing clinician who is neither trained nor equipped with enough knowledge to perform this task while prescribing these products.

The important issues that need to be addressed include:

- *Manufacture:* Small changes in the manufacture of biopharmaceutical medicinal products can dramatically affect the safety and efficacy of the therapeutic molecule.

  The very nature of a biologic means it is practically impossible for two different manufacturers to manufacture two identical biopharmaceutical active substances if nonidentical host expression systems, processes and equivalent technologies are used.[1] This has to be demonstrated in an extensive comparability program which not only includes a clinical program but also several nonclinical parameters.
- *Quality and immunogenicity:* A product that claims to be a biosimilar should demonstrate similarity for quality, safety and efficacy with the reference innovator product. It should also be noted that biologicals being proteins have the inherent potential to evoke immune reactions. The potential to evoke immune reactions can differ from product to product and rare effects can be detected and assessed only when large numbers of patients have been exposed to the product. The immunogenicity profile of a biosimilar product must also be shown to be similar to the reference product.[7]
- *Substitution and interchangeability:* Unlike chemical drugs, biosimilar medicines can be "similar" but not "identical" to the innovator reference products. Substitution of the innovator product with a biosimilar product 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.[8] Thus, certain regulators like the European Medical Agencies (EMA) and the authorities in France, Germany, Greece, Italy, Slovenia, Spain, Sweden and UK do not permit substitution or interchangeability. Indian Insulin Technique Guidelines 2012 also do not permit interchange.[9] The major reason for this being that, in case of any adverse reaction the cause needs to easily sourced which may not be the case where there has been frequent swapping between the different versions of the biologic product.[10]
- The US Food and Drug Administration permits interchangeability only if the developer of the biosimilar has conclusively demonstrated that it can be expected to produce the same clinical result in any given patient and that the risk associated with alternating or switching between the two products is not greater than that involved in continuing to use the reference product.
- *Efficacy variations:* Besides safety of a biosimilar product, data suggests that the efficacy can also be a concern. Efficacy of a variety of EPO biosimilars from different manufacturers was tested using a mouse bioassay, and the measured *in vivo* activity varied from 71% to 226%, with five samples failing to meet their own specifications.[11]
- *Regulatory standards:* While it is reasonable to permit the generic versions of product to have an abbreviated pathway toward regulatory approval as compared to the innovator product due to the inherent economic advantages they offer, it is important that pathway is more stringent than that permitted for chemical generics. To ensure the efficacy and safety of biosimilar products, these products should only be approved following the submission of appropriate data generated with the biosimilar drug. This data should include extensive preclinical tests, quality testing, immunogenicity profiles, robust and adequately powered

clinical efficacy studies versus the innovator products and finally an extensive postmarketing safety evaluation to ensure that adequate patient numbers have been exposed to these products.[7]

- *India:* Although, the Central Drugs Standard Control Organization (CDSCO) has released draft guidelines governing biosimilars, this has not yet been notified as a law. As a result these drugs are still governed by laws framed for chemical entities.[12]

REGULATORY STANDARDS FOR BIOSIMILAR PRODUCTS

Europe[10]

The level of data required for a product claiming to be a biosimilar is substantially less than that required for an original biological product. Since 2003, the European Union (EU) has created a legal and science-based regulatory pathway to enable the development and marketing of biosimilars. The EU regulatory approval process includes guidelines containing details of clinical, nonclinical and quality requirements for biosimilar protein therapeutics. These guidance documents reflect the distinct development and manufacturing challenges of biosimilars. They have also released individual guidelines pertinent to specific biological products, e.g. insulin, human growth hormone, granulocyte colony-stimulation factor, EPO, interferon and heparin.[13]

The EU's biosimilar approval pathway requires a biosimilar manufacturer to demonstrate similarity for quality, safety and efficacy with a reference product already licensed in the EU. Specifically, the biosimilar must demonstrate, through clinical studies in which the biosimilar is directly compared with the reference product, that it has no significant clinical differences with the reference product.

There have been several cases where applications for a biosimilar product has been given a negative opinion[4] [Alpheon (interferon alpha), Biferonex (interferon beta 1a)]. Among the common concerns expressed while rejecting these applications are:

- Differences between the two medicines in terms of their impurity profile
- Stability data of the active substance and of the medicine to be marketed
- The process used for producing the final medicinal product was not adequately validated
- The test used in the study to investigate the potential for the medicine to trigger an immunological response was not sufficiently validated
- European medical agencies refusal, European public assessment reports available.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000585/human_med_000643.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124&jsenabled=true

Marvel Life Sciences (UK) withdrew its EU marketing authorization application (MAA) for biosimilar human insulin (Insulin Human Rapid Marvel), neutral protamine Hagedorn insulin (Insulin Human Long Marvel) and premix 30/70 (Insulin Human 30/70 Mix Marvel) in December 2007. The reasons for rejection by the Committee for Medicinal Products for human use were as follows:

- It was not possible to conclude that the purity of the Marvel Life Science products was 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.

In November 2012, Marvel Life Sciences (UK) again withdrew their application and in their withdrawal letter they mentioned that they took the decision to withdraw the products so as to give it time to repeat and submit bioequivalence (PK and PD) data on each Clamp study in order to comply with the planned new EMA guideline on biosimilar insulin.

Withdrawal assessment reports available:

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_asessment_report/2010/01/WC500067170.pdf

(Long-acting)

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067169.pdf

(Mix 30/70)

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067086.pdf

(Rapid)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001665.jsp&mid=WC0b01ac058004d5c1

(Solumarv, Isomarv and Combimarv)

World Health Organization[14]

The WHO has come with a comprehensive and practical guideline on evaluation of similar biotherapeutic products (SBPs) in October 2009. The WHO opines 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 a biological products of assured quality, safety and efficacy that have been licensed based on a full licensing dossier.

Among the key principles proposed by the WHO are:

- The development of a biosimilar involves stepwise comparability exercises starting with comparison of the quality characteristics of the biosimilar and the reference product
- 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.
- Biosimilars are not "generic medicines" and many characteristics associated with the authorization process generally do not apply. Biosimilars, like other biological products, require effective regulatory oversight for the management of their potential risks and in order to maximize their benefits
- The 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.[15]

A description of other guidelines from other countries is beyond the scope of this article but suffice to say that countries such as USA, Australia, Malaysia, Turkey, Taiwan, Japan, Israel, Canada, Korea, Singapore and South Africa, essentially follow the above principle while framing their guidelines.

A PROPOSED APPROACH

The standard generic approach (for oral formulations it means the demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically-derived medicinal products. Due to the complexity of biological/biotechnology-derived products, the same generic

TABLE 1 | Biosimilars: Issues and approaches

Sr. No.	Issues with biosimilars	Approaches toward biosimilars
1.	Manufacturing cell lines, quality, impurities, potency	Proving comparative physicochemical similarity
2.	Safety and immunogenicity	Comparative preclinical and clinical studies as per guidelines Comparative immunogenicity studies as per guidelines for 12 months with 6 months of comparative period. Prescription by trade name
3.	Efficacy variations	Comparative PK/PD and pivotal studies
4.	Regulatory standards	Strict adherence to applicable guidelines such as those from the WHO
5.	Substitution and interchangeability	Not recommended unless following advice from the healthcare professional.

Abbreviations: WHO, World Health Organization; PK, Pharmacokinetics; PD, Pharmacodynamics

approach is scientifically not appropriate for these products. The "Similar Biological Medicinal Products" approach as proposed by the WHO, based on the comparability exercise, will then have to be followed **(Table 1)**.

The following approaches could be considered:

- The WHO guideline on biosimilars provides a practical and good guidance for approving and regulating the standards of these products for developing countries such as India
- All biological products should be considered as "new" drugs in order to ensure that they come under the purview of the central drugs standard control organization (CDSCO). This would ensure that uniform standards are followed by all manufacturers and the standards would not be dependent on the location of the manufacturing plant or the quality and knowledge of the local drug inspectors
- As proposed by the WHO, the prescriptions of biologics should not be based on their generic name but on a unique name, for example the trade name. Product labeling should be transparent and clear, summarizing clinical data submitted for approval, enabling prescriber and patient to make informed decision on the use of product. Automatic substitution of biosimilar products for originator products is not appropriate
- In case of products such as insulins, switching between products should be avoided. It should be recognized that response to insulin manufactured by different manufacturers and methods can be unique and they are not identical even if named similarly. Thus, the efficacy of the product as well as incidence of hypoglycemia could vary between products implying that these products are not interchangeable. Regarding substitution the EMA recommends that any decision to treat a patient with a reference product or biosimilar medicine should be taken only following advice from a health professional.[16] Additionally, in case of insulins there is also a tendency to induce antibodies which could have an impact on the efficacy of the product[17,18] and in such a situation if the products have been frequently switched the source of the antibody would not be easily traced[10]
- Insulins are also complicated by the fact that the delivery device raises another level of complexity as they are unique and have been tested with particular brands of insulin.[3]

CONCLUSION

Biopharmaceuticals have revolutionized the management of several diseases such as diabetes, cancer and several immunologic conditions. India is well-poised to exploit this growth due to its inherent strength in pharmaceutical manufacturing. While this needs to be exploited, it is also important to ensure that the patient's safety is not sacrificed at the altar of commerce. It should be recognized that biologics are different from other chemicals and thus need to have different standards than their chemical brethren. These standards have been well laid down by the WHO and India should at a minimum follow these standards. This would ensure that the Indian patient is protected with a similar standard as patients in other parts of the world.

The clinician should recognize these differences and also appreciate the impact that these can have on the patient's safety. While prescribing these medications the physician should take care of prescribing them by their brand names and also educate the patients especially in case of products such as insulins that they are not interchangeable and any decision to do so should only be done by the physician. This would also ensure that the physician retains his traditional role as the principle decision maker in disease management.

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