



Indigence for Robust Pharmacovigilance in Biosimilars: A review

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ABSTRACT

Treatments with biologics drugs have become the order of the day for many diseases and ailments including cancer. Unlike the availability of small molecule generics at lower costs, generic versions of biologics are not available at costs that are affordable to the patients in the developing countries. This is mainly due to factors such as immunogenicity, interchangeability, and difficulties in the manufacturing and characterisation of these biosimilars. These factors also raise a question on the conductance of pharmacovigilance programme, since each version of biologic is different. In this review, we analyse the major issues and the regulatory mandates concerning biosimilars and discuss some recommendations for the pharmacovigilance programme.

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Introduction

Pharmacovigilance is the science of safety monitoring of all the drugs and biologics in spotting, assessing, minimising, precluding of adverse effects. This should take place in all the phases both the pre-approval and post approval for ensuring the safety of the drugs throughout their continuous use, safeguarding patient's health.

The science of biologics has introduced many new treatments for various life threatening and rare maladies since 1980s, from the first FDA approval in 1982 for human insulin fabricated using recombinant technologies¹. The first generation biologics, in their course of conduct are off patent, a majority of them, unfolding the path for the next generation biologics, called as "Biosimilars" in EU, "Follow on Biologics" in US².

The march of introducing biosimilars to an innovator biologic is composite when compared to small drug molecules because of their production by living cells, high molecular complexity, variation in physicochemical characterisation of biosimilars with different manufacturing processes unlike the small molecules. Major changes pharmacological activity can occur even with minor changes in process^{3,4}. Thence automatic substitution is not allowed for biosimilars, which necessitates preclinical and clinical studies for evaluating the clinical safety and efficacy, projecting various gainsays which include the verification of the similarity, the interchangeability, need for unique naming to distinguish the biosimilar product, regulatory framework, intellectual property rights and public safety⁵.

Need For Robust Pharmacovigilance

Biosimilars regardless of their resemblance to innovator drug's efficacy, demonstrate different challenges, thus testifying the inadequacy of the clinical data of the innovator biologic as a basis for the approval of the biosimilar⁴. Safety profile of the biosimilars could be different from that of reference biologic because of use of different cell lines for manufacturing⁵. A classic example is "Valtropine" (cell line-yeast) which is a biosimilar of human growth hormone having different precautions and warnings to that of its innovator "Humatrope" (cell line-*E. coli*)^{1,6}.

Biosimilar development process

Biosimilars typically differ from conventional drug molecules in their origin from living cells using various biotechnology techniques like recombinant DNA technology, controlled gene expression, antibody techniques, etc. Quality of a biosimilar implicitly affects safety and efficacy. Biosimilars are influenced both by the host cell organism and the manufacturing process steps with regard to their quality differences⁴. Replication of the same process exactly even confronts variations in product quality implying sensitivity of manufacturing process of biosimilars. The question unresolved is the quantification of these variations and its effect on therapeutic equivalence of biosimilar with the reference biologic. Change in the quality of the starting source material can change the final product quality characteristics. Biosimilars are mostly proteins comprising recombinant hormones, growth factors, blood products, mono clonal antibodies etc., which get easily degraded (proteins) or denatured during various processing steps of cloning, purification, isolation etc. The impurities generated during the process may lessen the potency or increase the immunogenicity which contributes risks to the patient's safety. Biochemical characterisation of the protein molecule to detect the possible changes in each attribute of protein that affect the quality of the product requires sophisticated technologies.

Immunogenicity

Critical challenge for all the biosimilars is their ability to evoke "Immunogenicity". Almost all therapeutic proteins possess the innate quality of inducing the antibodies production whether they are partly or completely derived from human genes. These immunogenic responses may lessen the therapeutic efficacy or evoke side effects and/or adverse reactions. Regardless of the handiness of numerous novel technologies, complete characterisation of biosimilars with biologics remains a query unrequited. Different manufacturing processes and poly step production process unlike the trivial drugs are liable to variations that can inherently change the attributes of the biosimilar molecules which significantly affect the clinical

safety and efficacy. In short biologics are highly process dependent products⁸. Modest structural dissimilarities ignored can pose critical clinical safety and efficacy concerns as these molecules act through receptors directly. Immunogenicity is a major cause for concern for biologics^{8,10}. According to a research report, the global biosimilar market will be on its way to hit US \$19.4 billion market value by 2018¹¹. With the advent of increasing use of biotechnological products steadily, the cause for concern would be the patient's safety which is governed by both patient/disease related factors and product related factors (Table 1). Immunological responses elicited are generally complex involving antibody formation, T- cell activation or innate immune response activation. The prognostic value of preclinical testing of biotechnological products in animals is of less value as majority of them elicit immunological responses inevitably being proteins. Approximation of clinical responses from the clinical data of reference product does not establish the safety of the biosimilar product, thence complete data that will have impact on the safety and efficacy of the biosimilar should be collected to apply interpret the clinical consequences of the immune response as they many vary from transient appearance of antibodies without any clinical significance to severe life threatening conditions¹².

Table 1: Tabulation of patient/disease related factors and product related factors

Patient/disease related factors	Product related factors
<ul style="list-style-type: none"> ➤ Genetic factors modulating the immune response ➤ Genetic factors related to gene defect ➤ Age ➤ Disease related factors (malnutrition, advanced metastatic stage, advanced HIV etc.) ➤ Concomitant treatment ➤ Previous exposure to similar proteins ➤ Duration, route of administration and treatment modalities 	<ul style="list-style-type: none"> ➤ Protein structure: Origin and nature of the active substance (structural homology, post translational modifications), modification of the native protein (e.g. pegylation) ➤ Product and process related impurities (e.g. breakdown products, aggregates and host cell proteins, lipids or DNA), and formulation.

Panoptic pharmacovigilance is the most reliable tool for assessing immunogenicity of biosimilars. The best example is of Hospira's biosimilar epoetin zeta (Retacrit®), which was approved by EMEA to the reference biologic Eprex® (Amgen/Johnson & Johnson), a synthetic erythropoietin (epoetin alpha) used to replace the erythropoietin that is deficient in renal failure patients who cannot make enough, also to treat cancer patients developing anaemia because of chemotherapy treatment. Whilst preapproval nonclinical *in vivo* physicochemical studies proved epoetin zeta is biosimilar to Eprex®, clinical trials showed low potency, depicting differences in the proteins that are discerned by the available technologies. Unforeseen burst of pure red cell aplasia (PRCA) happened in patients with anemia of renal failure treated with eprex in 1998^{8,13,14}. In order to comply with EMA request, to minimize the risk of serious infections with proteins of human origin, the company replaced human serum albumin (HSA) with polysorbate 80. The unexampled formulation resulted in the development of antibodies that neutralised both the recombinant protein and the native hormone leading to PRCA. After fastidious investigation on the immunogenic reaction, the

company made further modifications of the final product and roots to the problem. Incidence of PRCA with eprex made the world to look at biologics with caution.¹⁵

Interchangeability

Another important cause for concern is the issues relating interchangeability and substitution^{7,16,17}. Direct substitution of the biosimilar to the reference biologic is called as interchangeability and the task of interchanging by a physician to a patient is called switching which ensures similar safety and efficacy of the biosimilar to the reference biologic. Interchangeability eases incursion of the biosimilars into the market.

But the unanticipated issues that arise when a patient is switched from an innovator biologic to biosimilar taking into consideration the patient, disease and product related factors heighten the need for post marketing monitoring as an essential component in tracking rare but serious adverse events. Table 2 summarises some of the differences in interchangeability issues of small molecule generics and biosimilars.

Table 2: Differences in interchangeability issues of small molecule generics and biosimilars

Small molecule generics	Biosimilars
Physician can directly replace the branded drug with many other available generics in the market.	If and only if the biosimilar is proved interchangeable with the reference then only the physician can replace.
Pharmacy chains generally prefer to substitute the branded with generics for a prescription as generics have typically higher margins-doesn't impose safety concerns	Automatic substitution by the pharmacist is never encouraged as it directly affects the patient's safety, as biosimilar and reference product can be derived from different cell lines.
Within one year of the entry of the generics into the market, there will be significant loss in the market share for branded drugs.	Only if the interchangeability is proved, the biosimilar can be substituted with the reference biologic-less market ease for incursion of biosimilars

Automatic substitution can have two headstone issues for pharmacovigilance^{18,19}. One issue is that, it will be difficult to establish the limited relation between an adverse reaction and the product responsible for it (most pertinent to chronic therapy). Another issue is that, it will be difficult to identify the specific product used by the patient (traceability). Adverse events associated with biological products can sometimes take time to show clinical manifestations. With the varying stock levels in the pharmacy, a single patient can receive different products over a time period, and thus making it impossible for the pharmacist to trace which brand, batch and lot number is dispensed to that particular patient associated with the event.

In rare cases the event could be imputed to a wrong brand if the prescriber is incognizant about the possible substitution made.

Status of legislations for the substitution of biosimilars varies around the world²⁰. In US and Canada the decision is state level. In Europe, independent individual member states take decision. Belgium does not allow the substitution of the biosimilar. South Africa and Japan do not allow the interchangeability and automatic substitution of the biosimilars. Japan additionally quotes the avoidance of the substitution of biosimilar with the originator product all through the patient's treatment period.

Naming and labelling of biosimilars

Only World health organization (WHO) and Japan established clear guidelines for naming of biosimilars. The guidelines of WHO states that every biosimilar should have a unique brand name, INN name (International Non-proprietary Name) if defined, lot number for its easy traceability^{16,20}. Japan states that the INN names should be followed by 'Follow-on 1' (2, 3 etc) and brand names should be followed by the letters 'bs' along with dosage form, dosage and company/manufacturer. European Union does not have any clear guideline on the naming of biosimilar; however it emphasises the importance of traceability and clear identification of the biological to affirm the pharmacovigilance monitoring. USP has indicated in submissions to FDA and elsewhere that the issuance of a monograph should dictate the nomenclature for a biological medicine, since biosimilars WILL share some, but not necessarily all, elements of their biochemical identity and quality attributes with an originator product it makes sense that biosimilars be linked through common public standards, even if they are not named identically¹¹. In an opening move to come out with a unique labelling system, generics company Hospira is implementing the technology of barcodes to all its injectable drugs and IV solutions, incorporating barcode reading technology into infusion devices to ensure patients safety in appropriate delivery of the dose and medicine rightly at right time. In 2010, the company was licensed to produce Retacrit (epoetin zeta) as the first biosimilar for both SC and IV delivery for the treatment of renal anaemia^{8,21}.

Regulatory mandates

In the US, after the approval of first follow-on-biologic "Omnitrope" in 2006, FDA stated that it will not approve further follow on biologics till the complete framework of legislation for the approval process is established. It paved way for Biosimilars act of 2009 and patient protection and affordable care act of 2010 for approval of follow on generics¹⁴. Labelling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that "This product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s)".²³ FDA recommends that sponsors use a stepwise procedure to establish the totality of the evidence that supports a demonstration of biosimilarity. FDA also advises sponsors intending to develop biosimilar products to meet with FDA to present their product development plans and establish a schedule of milestones that will serve as landmarks for future discussions with the Agency.²³

In the European Union, EMEA mandates the submission of risk management plan (EU-RMP) and pharmacovigilance programme with the marketing authorisation application enclosing the details of potential differences in manufacturing process of the biosimilar with the reference biologic that may spring up the safety matters¹⁰. It also emphasises on immunogenicity issues inclusion in the risk management plan⁵. As per the legislation, clinical safety of the biosimilar must be closely monitored post approval including risk benefit assessment. Updating of the risk management plan should be done when a change in the manufacturing process occurs as it directly affects the changes in the immunogenicity. It mandates the member states to record of the name and the batch number of dispensed medicinal product to avoid confusion, easy traceability of the adverse event reported in that particular territory. Specific obligations for pharmacists, health care

professionals and physicians include that, they are required to maintain the specific, accurate records of prescribing and dispensing, to trace the product even if the pharmacist by chance substitutes without the concern of the physician. Legislation also necessitates that; pharmaceutical companies should include warnings in their product information leaflet as it's applicability to restrict the usage for specifically named biological product. Changing to any other biological medicinal product should be authorised by the prescribing physician who should document the name of the product prescribed for pharmacovigilance reasons".

In India, as per the new biosimilar guidelines²⁴, Central Drug Standard Control Organization (CDSCO) mandate the submission of the pharmacovigilance plan, periodic safety update reports (PSURs) and post marketing studies (PMS) reports. PSURs shall be submitted half yearly for the first 2 years of the approval, and then annually according to schedule Y. Unexpected adverse reactions should be reported within 15 days of initial receipt of information according to schedule Y.

The UK health authority, Medicines and Healthcare products Regulatory Agency (MHRA) mandates black triangle symbol for all biosimilars indicating they are not identical to the innovator products²⁵. The black triangle symbol will be supplanted by EU additional monitoring system in 2013 which will be mandatory for all biological medicines manufactured 1st January 2011 afterwards.

Recommendations and challenges

- Pharmacovigilance systems should differentiate between innovator product and biosimilar products, so that effects of biosimilars are not lost in the back ground of reports on innovator products²³.
- Concomitant medications and other patient-related factors like the underlying disease have to be taken into account, since these can also influence the clinical presentation of immunogenicity. Concomitant medication in addition can represent bias in the adverse event reporting.
- Since systematic sampling might not be feasible in a post-marketing setting, it is important to conclude on potential unwanted immune responses based on suspicious safety and (loss of) efficacy signals. This requires that the evaluation of such events is defined prospectively in the RMP.
- Summary of product characteristics should clearly reference the source of relevant clinical studies or whether it has been taken from the originator biologic.²⁵
- Biosimilars should never be indicated automatically based on extrapolation.²⁵
- The INN of the reference biologic and the biosimilar should have a common shared root. Shared root demonstrating the relationship of the biosimilar with the innovator and distinct prefix helping in tracing the manufacturer easily.^{8,26}
- For the accurate detection of the adverse events, the *interchangeable products* should be distinguished with distinct names with respect to the reference biologic. Pharmacovigilance systems should be capable of distinguishing the reference and biosimilar, so that in the light of innovator the adverse effects of biosimilars are not neglected.
- Establishment of "at-risk window", the period imputed for the specific adverse event of a biologic/biosimilar in a patient is unmanageable due to the extended pharmacodynamics of biologics/biosimilar.
- Biologics pose serious safety risks. It was through the spontaneous suspected adverse drug report the risk of

tuberculosis with the administration of infliximab was discovered, projecting the need for robust pharmacovigilance for biosimilar.

Conclusion

There is no such thing called “Me-too” biologic. Development of biosimilars from their starting stage to post marketing pharmacovigilance is like a riddled puzzle. Switching or substitution of innovator biologic and biosimilar should be regarded as a change in clinical management. Pharmacovigilance plans developed and implemented by the companies are frequently part of post approval commitments to regulatory agencies to provide follow up safety assessments. It was years of pharmacovigilance that helped in detecting the real cause for the problem associated with Eprex that occurred possibly due to the replacement of human serum albumin with polysorbate 80. Thus to guarantee the patients safety there is a need for robust pharmacovigilance in biosimilars when compared to small drug molecules due to their structural complexities.

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