

Biosimilar Insulins: Are they really 'similar' ?

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Abstract

Biosimilars are generic version of biopharmaceutical medicines which try to mimic products which are derived from recombinant technology. These are near identical products which use a separate process for its bioformulation and need to pass strict mandates of regulatory bodies like US FDA and EMEA in Europe. As these compounds need to the process of manufacture requiring fermentation and not traditional reverse chemistry it is difficult to mimic bioidentical compounds. There are clear cut differences in the manufacture process and protein folding. However there is unclear data currently to know if these biosimilar have any clinically relevant impact. Due to the sophisticated nature of these biomolecules and their 3-D structure its an new area of research for pharmaceutical scientists and drug regulators. In India apart from Biogenerics a host of molecules especially have Biosimilar compounds especially in endocrinology namely insulin ,growth hormone,PTH like peptides are made in India. These need evidence based validation if they have clinically relevants effects or side effects

Biosimilars, the 'generic' versions of biopharmaceuticals, continue to enter Indian pharmaceutical market¹ adding to physician's armamentarium to treat a variety of diseases. Biosimilars available in India include monoclonal antibodies for treating various malignant and immunological disorders, growth factors like erythropoietin and granulocyte colony stimulating factor (G-CSF), human insulins for treating diabetes mellitus etc. Even though cost-savings with biosimilars is appealing for patients, physicians, insurance providers and governments, still there are concerns about the safety, efficacy and quality of these products¹ due to the absence of stringent guidelines for evaluating these products in our regulatory system.

Incidence of pure red cell aplasia (PCRA) following a minor change in the packaging process of 'epoetin' (Erythropoietin, EPO) made the world to look at biopharmaceutical products with caution.² It also prompted drug regulatory authorities to establish strict guidelines for evaluating biopharmaceuticals and biosimilar products. Bowing to such stringent criteria recently Marvel LifeSciences Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), that it wishes to withdraw its applications for marketing authorisations for their biosimilar human insulins, as they were unable to meet the standards set by CHMP.³ This 'Marvel insulins' episode is very critical from Indian perspective as biosimilar insulins continue to flood Indian market. It would be worthwhile to dissect 'Marvel insulins' episode to understand what we should look for before prescribing biosimilar insulin to our patients. In this paper we also give an overview of the uniqueness of biopharmaceuticals, concerns with biosimilars and regulatory guidelines available to evaluate the safety, efficacy and quality of these biosimilar products.

Biopharmaceuticals

Biopharmaceuticals are drug products containing biotechnology-derived proteins as active pharmaceutical ingredients.⁴ For example, insulin can be produced by a living organism (such as a bacterium or yeast), which has been given the gene that enables it to produce insulin. Biopharmaceuticals have revolutionized the treatment of many diseases like diabetes, malignant disorders etc. Biopharmaceuticals are fundamentally different from the conventional small molecule chemical drugs.⁴ Important differences include⁴

- The size and complexity of the active substance – in comparison to small molecule chemical drugs biopharmaceuticals are very large molecules with highly complex structure which is difficult to identify with currently available analytical methods
- Nature of the manufacturing process - in biopharmaceutical manufacturing process defines the final product ('process is product') and even a minor change in manufacturing process may lead to disastrous outcomes
- The safety and efficacy profile of these biopharmaceutical products is highly dependent on the robustness and the monitoring of quality aspects.

Biosimilars

Several bio-pharmaceutical products have lost the patent protection in the last few years and few more molecules will lose the same in the next few years.⁵ The expiry of patent protection for many original biotechnological medicines has led to the development of 'generic' versions of these molecules, what are called 'biosimilars' or 'follow-on biologics'. While the term 'biosimilars' is preferred in European Union, the term 'follow-on biologics' is favored in US.⁶

According to European Medicines Agency (EMA), a 'biosimilar' medicine is a medicine which is similar to a biopharmaceutical product that has already been authorized (the 'biological reference medicine').⁷ The active substance of a 'biosimilar' medicine is similar to one of the biological reference

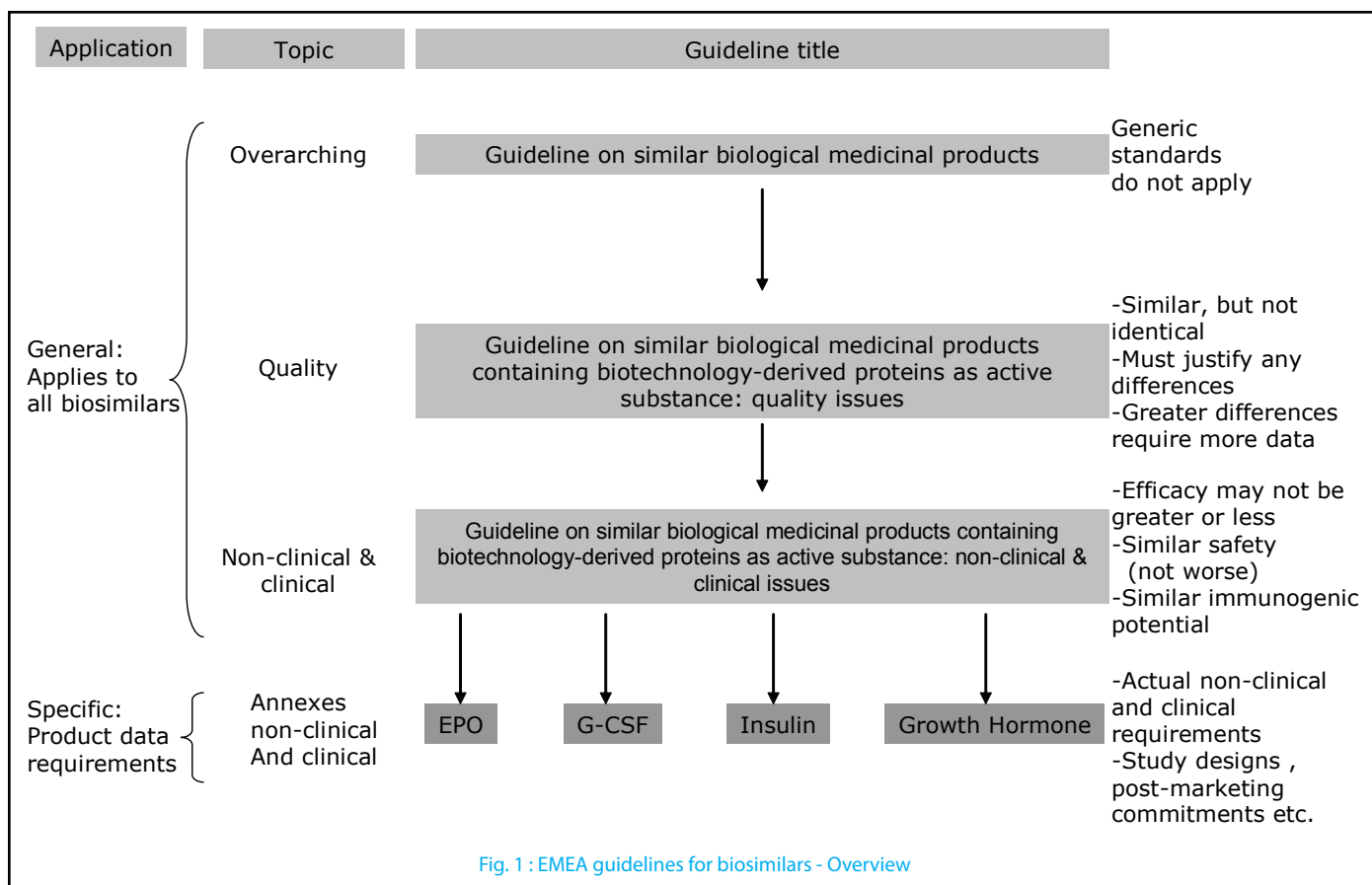


Table 1 : Approval status of biosimilars by EMEA

Biosimilars approved / receiving positive opinion	
Somatropins	Omnitrope Valtropin
Epoietins	Abseamed / Binacrit / Hexal Silapo / Retacrit
G-CSF	Ratiograstim / Biograstim / Tevagrastim
Biosimilars rejected / withdrawn	
Interferon	Alpheon
Human insulin	Marvel insulins

medicine. ‘Biosimilar’ and ‘biological reference’ medicines are used in general at the same dose to treat the same disease.

Biosimilar manufacturers will not have access to the manufacturing processes of innovator products because this is proprietary knowledge. Thus, it will be impossible for biosimilar manufacturers to precisely replicate any protein product.⁸ Since the biosimilar manufacturers use different manufacturing processes, for example different manufacturers use different vectors for synthesizing human insulin, biosimilars are similar but not identical to the innovator product. To establish the similarity in terms of safety, efficacy and quality of biosimilar product EMEA has published product specific guidelines (See Fig. 1).⁷ USFDA and several other regulatory agencies are still working on such a framework.⁹

Like any pharmaceutical product, marketing authorization for biosimilars, is granted after a regulatory authority such as the EMEA, has conducted a scientific evaluation of the safety, efficacy and quality of the medicine at least in developed world.

Owing to the complex structure and sophisticated manufacturing process involved with biopharmaceuticals, ‘biosimilars’ can not be brought to market using the standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) that is normally applied to chemically derived medicinal products.¹⁰ Therefore, studies comparing the original biopharmaceutical and biosimilar products have to be carried out. These studies should involve a step-by-step process starting with a comparison of the quality and the consistency of the medicinal product and of the manufacturing process. Studies should also be conducted to compare the safety and efficacy of the biosimilars. These studies should demonstrate that there are no meaningful differences between the biosimilar and the reference biopharmaceutical product in terms of safety or efficacy. Based on these guidelines several biosimilar products have been approved by EMEA (see Table 1).¹¹ It is interesting to note that till now even single biosimilar insulin is not approved by EMEA / USFDA^{11, 12} despite generic companies claiming easy reproducibility of insulins.

When it comes to evaluation & approval of biosimilar products there is still lot of ambiguity. Unfortunately this ambiguity creates a space for many manufactures to conveniently by-pass full fledged clinical trials, to show comparability between ‘biological reference’ product and their ‘biosimilar’ version. However even with this said ambiguity, there have been incidences where in the past EMEA has rejected marketing applications for biosimilars like ‘Aplheon’ citing concerns over characterization, manufacturing and quality control.¹³ The recent one being the ‘Marvel insulins’ episode.³

'Marvel insulins' episode

Marvel Life Sciences Ltd. presented data from their studies designed to show that the Marvel human insulins were comparable with the reference human insulins (already approved by EMEA) in experimental models and in humans. The company presented the results of studies carried out in 24 healthy volunteers looking at the effect of the Marvel insulins on blood sugar levels, compared with the reference human insulin.¹⁴ It also presented the results of one main study in 526 patients with diabetes mellitus, who received either the Marvel insulins or the reference human insulins for up to 12 months.¹⁴ The main measure of effectiveness was the effect of the insulins on the glycosylated haemoglobin (HbA1c) level, which gives an indication of how well the blood glucose is controlled.

After the review EMEA - CHMP was of the opinion that the Marvel insulins and the reference human insulins were not comparable.¹⁴ Following were the major objections raised by the review committee.¹⁵

Quality aspects

Biosimilarity

- There was paucity of data on general development, manufacture and control of both Drug Substance and Drug Product which prevented proper assessment of this application.
- It was unclear if the comparators used for biosimilarity were valid and only studies performed with a valid reference product can be considered.
- Biosimilarity was not established for Marvel Rapid Drug Substance or Drug Product from a Quality perspective. A full comparability study was required for the Drug Substance in accordance with the CHMP Guidelines. Biosimilarity of the finished product with the reference human insulin was not addressed, as required, in terms of the formulation, specifications, stability.

Drug Substance

- The provided description of the fermentation and harvesting process was not in detail and contained incomplete information about the process.
- The description of the purification and modification process as provided in the dossier was not in detail and contained incomplete information about the process.
- The Applicant failed to provide a complete dossier for Drug Substance process validation. This section of the dossier requires complete revision to address the range of batch sizes and include full data and study reports.
- The information (study design and report) on product related impurities / substances provided by the manufacturer was not sufficient to draw conclusions whether all impurities are detected and whether correct assignments are made for the identity of the impurities.
- The comparative investigation of related impurities / compounds in insulin Drug Substance and reference insulin was not sufficient to draw the conclusion that the purity of biosimilar insulin is comparable to reference insulin.
- With the exception of unclear references to Ph Eur (European Pharmacopeia), USP (United States Pharmacopeia) or both, no information for Drug Substance release test methods was provided. Full descriptions and validation reports of the key drug substance release tests were not provided.

Drug Product

- The dossier did not adequately address the two different presentations of Drug Product (Vials and cartridges).
- The validation data provided for the Drug Product was severely deficient in terms of the manufacturing process steps and the range of batch sizes proposed for each presentation.
- No assurance was provided regarding physical separation measures or cleaning validation procedures used to assure segregation between different products.
- Essential details of source, batch number, site and process of manufacture of Drug Substance used to manufacture Marvel's Insulin Rapid presented in the dossier were absent as were details of where these batches have been used in the clinical and pre-clinical studies.
- Stability data was inadequate and the material appropriateness of the material used unclear. The in-use stability studies for the Drug Product were also inadequate.
- No information was provided in the dossier and the SPC / PL (Summary of Product Characteristics / Product label) on the device intended for the cartridge including suitability testing.

Non Clinical aspects

- The claim of comparability of Marvel insulin to reference Human insulin cannot be considered as sufficiently justified based on the presented data.

Clinical aspects

- An adequate pharmacokinetic comparison to the reference product was not carried out.
- The pharmacodynamic study failed to demonstrate equivalent blood glucose-lowering effect to that of the reference product.
- The efficacy and safety data, which cannot be used to compensate for the failure of pharmacodynamic similarity, showed consistent trends in favour of the reference products.
- The immunogenicity of the Marvel insulin products was not properly evaluated.

The learning's from 'Marvel insulin' episode emphasize that, even if the biosimilars are cost saving, they might push the patients towards therapeutic failure with unidentified risk of long term and short term safety concerns. It is also evident that biosimilar manufacturers have insufficient data to prove the similarity with innovator products. Hence drug approval authorities should take a vigilant look at the quality, safety and efficacy data provided by the manufacturers of biosimilars. In clinical practice this is our responsibility to weigh the risk and benefits for our patients while using a specific drug. Most of the times the decision should be based on published and accepted facts and we should have detailed assurance regarding safety, efficacy, quality, immunogenicity and stability from manufacturers of the biosimilar insulins before we make a choice.

This episode is also important with respect to substitution of medicinal products. Automatic substitution allows for the dispensing of generic drugs in place of prescribed innovator products by pharmacists without the knowledge or consent of the treating physician. For the majority of small-molecule generics, automatic substitution is appropriate and can produce

cost savings. For a variety of reasons, automatic substitution is not appropriate for biopharmaceutical products. As noted, substitution of innovator biopharmaceutical might lead to loss therapeutic efficacy, long term safety and immunogenicity.¹⁶ It will be a moral obligation for manufacturers and physicians share information with all stakeholders (including patients, pharmacists, and other caregivers) providing a clear assessment of the risks involved in switching from an established product to its biosimilar equivalent.

Drug regulatory authorities like EMEA regularly takes a vigilant look before approving biosimilar products. However the Marvel insulins episode should be looked at a case study for regulatory agencies in countries where authorities are willing to accept a greater variation between original biopharmaceutical products and their 'biosimilar' versions. These agencies are not advocating stringent demands on demonstrating similarity because of the potential cost-savings with the so called 'biosimilars'.

If we have a look at the Indian scenario, there are established guidelines for approving generic version of small molecule chemical drugs, however there are no specific guidelines for biosimilars, even though requirements for granting approval for biosimilars are more intricate. In most of the cases manufacturers of these biosimilars, conduct clinical trials with small number of subjects to take advantage of lacunae in the existing system. The OPPI (Organization of Pharmaceutical Producers of India) has compiled a white paper on this subject of "Biosimilars".¹⁷ We need to study as clinicians whether these biosimilar will have a clinical impact on our practice trends. This calls for aggressive pharmacovigilance¹⁸

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