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Regulatory overview of biosimilars in Europe

Shailaja Pashikanti, Jyothi Sri Durga V*, Sowmya A. N. V. L

Department of Regulatory Affairs, Andhra University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

A biosimilar is a biological medicine similar, but not identical, to an already registered reference bio therapeutic product in terms of quality, safety, and efficacy. These drugs are also called as biosimilar products', follow-on protein products' and subsequent-entry biologics'. The EU has pioneered the regulation of biosimilar medicines by establishing a solid framework for their approval and by shaping biosimilar development globally. Since the EU approved the first biosimilar in 2006, healthcare professionals have gained increasing experience with their use. Today, biosimilars are an integral part of the effective biological therapies available in the EU, supported by adequate safeguards protecting patient safety. In Europe, in 2001, legislation concerning biosimilar was codified as Directive 2001/83/EC to create a new marketing authorization procedure for similar biological medicinal products and also Committee for Medicinal Products for Human Use (CHMP) of the EMA is concern with these biosimilar products. The aim of biosimilars development is to demonstrate bio similarity - high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile. Safety of biosimilars is monitored through pharmacovigilance activities, in the same way as for any other medicine. Biosimilars can offer advantages to EU healthcare systems, as it is expected to improve patients' access to safe and effective biological medicines with proven quality.

Keywords: Biosimilars, Marketing Authorization, EMA (European medical agency), CHMP (Committee for Medicinal Products for Human Use).

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Corresponding author Tel.: +91-9491218651;

E-mail address: jyothivanacharla@gmail.com (Jyothi Sri Durga V).

1. Introduction

A biological medicine is a medicine whose active ingredient is prepared by or derivative of a living organism. E.g. Insulin produced from a living organism bacterium or yeast, which has been given the gene that enables it to produce insulin.

A biosimilar medicine ('biosimilar') is a medicine highly similar to another biological medicine already marketed in the EU ('reference medicine'). The active ingredient of a biosimilar medicine is analogous to the biological reference medicine (1, 2).

Table 1 Differences between biologics and Biosimilars (3, 4)

Parameter	Biologic	Biosimilar
Definition	Biologicals are proteins that are derived using recombinant DNA technology for their use in the treatment, diagnosis or prevention of various diseases.	A biosimilar is a **biological medicine** highly similar to another already approved **biological medicine** (the 'reference medicine').
Properties	Derived from living sources such as cells. Complex mixtures whose active ingredients (usually proteins) are hundreds of times larger than the compounds found in most pills.	The active ingredient of Biosimilars closely resembles the reference biologic. However they are identical, generic equivalents due to differences in manufacturing processes, protein source and extraction/purification processes.

Studies conducted	• Pharmaceutical quality studies • Non-clinical studies • Clinical studies – ✓ Safety and efficacy ✓ PK/PD ✓ Immunogenicity • Risk management plan	• Pharmaceutical quality studies • Comparative quality studies • Comparative non-clinical studies • Comparative Clinical studies - ✓ Safety and efficacy ✓ PK/PD ✓ Immunogenicity • Risk management plan
Safety	Post marketing safety monitoring includes the detection, assessment, understanding and prevention of adverse effects after the launch of the biologic onto the market**.**	Post marketing surveillance to address immunogenicity and potential rare adverse events. Strict monitoring due to limitations of clinical data compared to the reference product.

Biosimilar products do not meet the conditions for being defined as generic medicinal products, mostly because of differences between the similar biological medicinal product and the reference biological medicinal product in terms of raw materials or manufacturing processes. Therefore, for a biosimilar product to be approved, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided (5).

2. Manufacturing of Biosimilar

It involves a series of steps like selecting cell lines, modifying its properties, replicating genetically modified cell lines, culturing over specific media, harvesting cells from vector molecule, purification and viral inactivation. The final steps of filling, compressing, packaging, storage and quality assurance are common to both shown in figure 1. So large molecules have more complex manufacturing processes and it is virtually impossible to reproduce them without minor alterations. Hence they are known as Biosimilars (6).

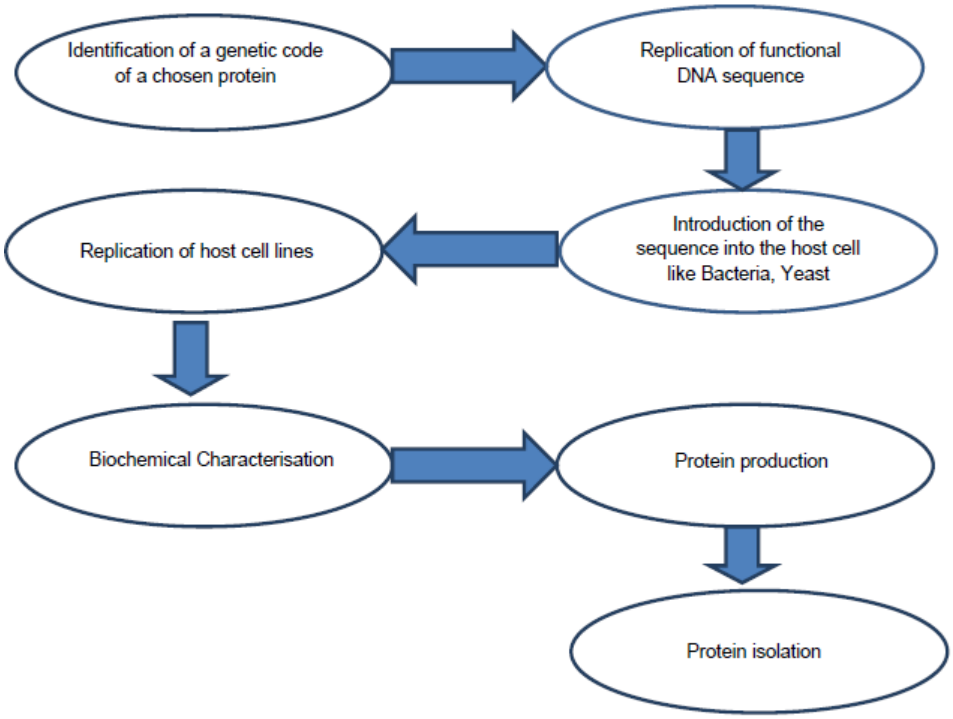

Figure 1. Steps in manufacturing of biosimilar (6)

In January 2001, the European Medicines Agency (EMA) began formal consideration of scientific issues presented by biosimilar products (7). In 2003, the European Commission amended the provisions of the EU secondary legislation governing requirements for marketing authorization applications for medicinal products and established a new category of applications for "similar biological medicinal products in 2005, the EMA issued a general guideline on similar biological medicinal products. In 2011, a concept paper on the revision of the guideline on similar biological medicinal products was published by EMA (8). In order to grant a biosimilar product, the EMA requires that the active substance, the pharmaceutical form, strength, route of administration of the biosimilar should be the same as reference product and comprehensive and justified comparability studies between the biosimilar and the reference products in the quality, nonclinical, and clinical level, which are explained in detail in the EMA guidelines (9).

The EMEA has laid down the following requirements for the Marketing Authorization Applications of a biosimilar product:

- Comparability studies are required between the biosimilar and the chosen reference medicinal product.
- Nonclinical studies, although usually less extensive than those for innovatory applications, will be required for the biosimilar.
- Clinical studies will be needed to support the safety and effectiveness of a biosimilar. In particular, the studies must address immunogenicity concerns.
- Post-market pharmacovigilance plans will be expected as part of approval commitments (10).

Table 2 Requirements for the Marketing Authorization Applications of a biosimilar product (11)

Quality	Nonclinical	Clinical
Drug substance • Manufacture • Characterization • Control of drug substance • Reference standards or materials • Container and closures • Stability • Comparability data (analytical comparison with reference product) **Drug product** • Description and composition • Pharmaceutical development ✓ Manufacture ✓ Control of excipients • Control of drug product • Reference standards and materials • Container closure system • Stability • Comparability data (analytical comparison with reference product)	**Pharmacology** • Primary • Comparability data (primary pharmacodynamics) • Repeat-dose toxicity studies • Comparability data (repeat-dose)	**Pharmacology** **Pharmacokinetics** • Single dose • Comparability data (single-dose PK) **Pharmacodynamics** • Appropriate markers • Comparability data (PD) **Efficacy and safety** Pivotal ✓ Indication x ✓ Comparability data (indication x) **Post-marketing** • Safety • Other indications • Immunogenicity

3. Approval Process for Biosimilars

In Europe, pharmaceutical products derived from biotechnology will solely be registered using the Centralized Procedure, (showed in table3) leading to an European Union (EU) license which is valid in all Member States. Once a company applies for marketing authorization at EMA, data are evaluated by EMA's scientific committees on human medicines and on safety (the CHMP and PRAC), also by EU experts on biological medicines (Biologics working Party) and specialists in biosimilar (Biosimilar working Party).The review by EMA leads to a scientific opinion, which is sent to the European Commission, that ultimately grants an EU-wide marketing authorization (12, 13).

Upon receipt of the application, the Agency will start the validation on the upcoming submission stated on its website. Validation need to be completed by the corresponding starting date of the procedure. Applicants must be ready to answer within few days to any issues raised at this stage. At the end of the validation process, provided the Rapporteur and (Co) Rapporteur have received the dossier, the EMA starts the procedure at the monthly beginning date published on the EMA website. For Biosimilars of centrally authorized medicinal products, provided successful validation, the procedure starts the same month. If the application concerns a Biosimilar of a medicinal product authorized through a National/MRP/DCP procedure, the EMA can request from the Member State where the reference medicinal product received a marketing authorization to transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorized together with the information on the full composition of the reference medicinal product and if necessary other relevant information. Hence the evaluation process will only start once all relevant information has been received. If, within a month from the beginning of the procedure, any other member of the CHMP has not received the requested parts of the dossier from the Applicant, the EMA will stop the clock till the problem is resolved. A timetable is prepared by the Agency and given to the CHMP for information.

Applicants are suggested to submit the MAA according to the published EMA calendar.

The Agency shall ensure that the perspective of the CHMP is given within 210 days (not counting clock-stops within the procedure) and in accordance with the standard time table shown in table 3.

Table 3 Centralized Procedure for Biosimilars Approval (14)

Day	Action
1*	Start of the procedure

80	Receipt of the Assessment Reports from CHMP Rapporteur and (Co) Rapporteur by CHMP members and EMA. EMA sends CHMP Rapporteur and (Co) Rapporteur Assessment Reports to the Applicant making it clear that it only sets out their preliminary conclusions. The so-called Day 80 Assessment Reports in no ways bind the CHMP and are sent to the Applicant for information only.
87	PRAC Rapporteur circulates the RMP assessment report and proposed RMP LoQ
90	Adoption of GxP Inspection Request
100	Rapporteur, (Co) Rapporteur, other CHMP members and EMA receive comments
101-104	PRAC adopts PRAC RMP Assessment Overview and Advice for D120 LOQ
115	Receipt of draft List of Questions (LoQ) from CHMP Rapporteur and (Co) Rapporteur, including the CHMP recommendation and scientific discussions together with the PRAC RMP Assessment Overview and Advice, by CHMP members and EMA (If applicable). Quality part of the dossier reviewed by BWP.
120	CHMP adopts the LoQ as well as the overall conclusions and review of the scientific data to be sent to the Applicant by the EMA. Clock stop. At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (inspection procedure starts).
121*	Submission of the responses, including revised SmPC, labeling and package leaflet texts in English.
	Restart of the clock. After receipt of responses, the CHMP will adopt a timetable for the evaluation of the responses. In general, the following timetable will apply:
150	PRAC Rapporteur circulates the RMP assessment report and proposed LoOI
157	Circulation of the CHMP Rapporteur (Joint) Response Assessment Report (so-called Day 150 Assessment Report). EMA sends this (joint) Assessment Report to the Applicant making clear that it is sent for information only and does not yet represent the position of the CHMP
167	PRAC adopts PRAC RMP Assessment Overview and Advice for D180 LoOI
170	Comments from CHMP members to Rapporteur and (Co) Rapporteur, the EMA and other CHMP members. Responses to quality questions reviewed by BWP.
180	CHMP discussion and decision on the need for adoption of a list of "Outstanding Issues" and/or an Oral Explanation by the Applicant. If an Oral Explanation is needed, the clock is stopped to allow the Applicant to prepare the Oral Explanation. Submission of final inspection report to the EMA, Rapporteur and Co-Rapporteur by the inspection team (at the latest by day 180).
181	Restart of the clock. Oral explanation (if needed) and circulation of the final GxP Inspection Report
183	PRAC Rapporteur circulates the RMP assessment report
197	PRAC adopts the final PRAC RMP Assessment Overview and Advice
By day 210	Adoption of CHMP Opinion + CHMP Assessment Report Adoption of a timetable for the provision of translations

Committee for Medicinal Products for Human Use, Pharmacovigilance Risk Assessment Committee, List of questions, European medicines agency, Summary of Product Characteristics.

4. Pharmacovigilance

Pharmacovigilance helps in detecting and prevention of adverse events. It implies quick detection, early reporting and attributing a reaction to correct product, manufacturer and batch number. This is done by formulating a risk management plan. Pharmacovigilance is significant for Biosimilars. Information from preregistration clinical investigations is generally inadequate to recognize rare adverse effect. Generally the clinical development program of biosimilars is shorter compared to originators and in this manner less appropriate to sufficiently distinguish tolerability risks. Along these lines it is suggested that the clinical tolerability of biosimilars can be closely monitored during post marketing phase. Accordingly inside the approval procedure, the candidate should show an explanation of the pharmacovigilance program and a risk management plan as per current EU legislation and pharmacovigilance guidelines. Any specific tolerability monitoring imposed on the originator or medicinal class should be adequately addressed in the pharmacovigilance design of the biosimilar, and immunogenicity should be considered in this specific circumstance. There is requirement for post marketing observational studies to evaluate the impact of observed differences in the frequency of ADAs and magnitude on long term treatment benefit. Such investigations are performed in both children and adults because toxic and long term sequelae may differ. Data collection by organizations outside the pharmaceutical industry has also proven to be reliable across different national registries. For example: In 2006, the EMEA rejected the approval of a biosimilar interfere on product due to concern about its product characterization, manufacturing and quality control. In 2007, a range of biosimilar insulin was withdrawn from the market during post marketing authorization (6, 15, 16).

5. Conclusion

Europe has been way ahead of the other countries including US in terms of developing Biosimilars. Biosimilars face several challenges, which include consequence of the molecular complexity, uncertainty of an evolving regulatory environment, developing a reproducible manufacturing process, demonstrating equivalence, safety and efficacy and challenges in achieving a competitive price. The development of a biosimilar is in fact more technically challenging than

generating an originator product because of the narrow constraints in terms of product quality. These steps would ensure more affordable and safe biosimilar drugs being manufactured and made available to patients both in domestic and export markets. Considering the current expansion of Biosimilar market world-wide sophisticated clinical development strategies, effective communication between the regulatory agencies plays a crucial role while foreign clinical data ensures that medicines are evaluated in diverse but representative patient population before approval.

For efficient development of Biosimilars and to avoid duplicative clinical studies, manufacturers should seek harmonization of global approval requirements and propose global development programs, using a reliable global reference product, which should be sourced from different regions so that a patient in a given region might receive it without any adverse effects.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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