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## REVIEW ARTICLE

# Update on Biosimilars — Complexity of Biologics and Clinical Concerns: Importance of Proper Evaluation

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## ABSTRACT

*Biopharmaceuticals or biologics were first introduced at the beginning of the 1980s and are now well established in the treatment of a wide variety of diseases. Biosimilars are biopharmaceuticals that are similar, but not identical, to a marketed innovator product, typically one with an expired patent. Although the market share of biosimilars remains in its infancy in many places, this is expected to change markedly over the coming decades. In the clinical setting, it is vital that prescribers understand that biosimilars cannot be considered interchangeable generic versions of the original biologic. The exceptionally complex manufacturing processes required for biologics makes it highly unlikely that another manufacturer will generate a product identical to the original biopharmaceutical. Any slight variation in the conditions of manufacture can result in a deviation from the reference compound structure with consequent changes in clinical performance. The potential dangers of such a situation have already been clearly illustrated by the emergence of antibody-mediated pure red cell aplasia in patients treated with recombinant human erythropoietin. Expert and regulatory authorities in Europe and the USA have recognised that the established process for evaluation and market approval of generic drugs cannot be applied to biosimilars; the current recommended procedures for regulatory approval and ongoing safety monitoring of biosimilars will be reviewed.*

***Key Words:*** *Biosimilar pharmaceuticals; Drug approval; Pharmacovigilance*

# 中文摘要

## 生物仿製藥的最新資料：生物製劑的複雜性和臨床關注，其正確評價的重要性

**李詠恩**

生物製藥或生物製劑在八十年代初開始，時至今日已廣泛用作醫治多種類型的疾病。生物仿製藥是與市場上已過專利期的生物製劑有類似（但非一模一樣）的藥物。雖然從多方面的角度看，生物仿製藥的發展仍屬初步階段，但在未來的日子，情況預計會有巨大的轉變。臨床上，處方者必須明白生物仿製藥不能被視為等同原本的生物製劑的。這點相當重要，因為生物製劑極其複雜的製造過程，令其他製造商不可能產生一種相同的生物藥品。製造條件中任何輕微的變化都可以引致與參考化合物結構有所偏差，而導致臨床表現有不同。類似的情況可以從重組人類紅血球生成素治療引發抗體造成的純紅血球再生不良的病例中顯示生物仿製藥的潛在危險。歐洲及美國的專家和監管機構已經意識到，用來評估和審批生物製劑的既定過程不能應用在生物仿製藥上。本文回顧監管部門對於生物仿製藥目前使用的審查程序和安全監測。

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## INTRODUCTION

Biopharmaceuticals or biologics were first introduced at the beginning of the 1980s and include therapeutic recombinant DNA proteins, growth-like factors, interleukins, hormones and enzymes, and therapeutic monoclonal antibodies. Biologics are now well established in the treatment of a wide variety of diseases, including rheumatoid arthritis, anaemia, growth deficiency, haemophilia, transplant rejection and leukaemia, and other cancers.

A biosimilar (the term used in Europe) or 'follow-on' biologic (the term used in the USA) is a biopharmaceutical that is similar, but not identical, to a marketed innovator product whose patent has typically expired. The European Medicines Agency (EMEA) defines biosimilars as having identical sequences to an innovator product, but may exhibit dissimilar therapeutic effects.

There are a number of forces driving the development of biosimilars to innovator products. These include the large revenue potential of this market sector, the impending expiry of patent protection on many innovator products, the need to reduce healthcare expenditure by obtaining a less expensive version of the novel biologic, and the rights of patients to access effective treatments at a reasonable cost. Within the next 10 years, many of the top earning biologic agents (e.g. Herceptin® [Genentech USA, South San Francisco, CA, USA], Avastin® [Genentech USA], Epogen® [Amgen Inc, Thousand Oaks, CA, USA], Humira® [Abbott Laboratories, Abbott Park, IL, USA) will lose patent protection. This represents a multi-billion dollar potential market for biosimilars that may be attractive to industry players, particularly in India and China, both of which have rapidly growing healthcare markets.

## BIOSIMILARS ARE NOT GENERIC BIOLOGICS

It is vital to be aware that, unlike generic versions of chemically derived pharmaceutical agents, biosimilars cannot be considered interchangeable generic versions of the original biologic. Given the extremely complex nature of the manufacturing process for biologics, particularly the larger molecular weight biologics, it is highly unlikely that a product identical to the original biopharmaceutical will be generated. The manufacturing process for biologics can involve more than 5000 critical steps, and any slight variation in the conditions of manufacture can result in a deviation from the reference compound structure with consequent changes in its clinical performance and long-term safety profile.

The dramatic spike in the number of cases of antibody-mediated pure red cell aplasia (PRCA) in patients treated with recombinant human erythropoietin[1] illustrates the potentially serious consequences of even slight modifications to the manufacturing process of a biologic agent. First identified by French investigators,[2] the spike in cases of PRCA was noted from 1998 to 2004 and was confined largely to Europe and Canada, with 215 confirmed cases documented by 2005.[1] Thorough investigations identified a change in the formulation of the product — replacing human serum albumin with polysorbate 80 and glycine to alleviate concerns about potential transmission of Creutzfeldt-Jakob disease — as one of the probable causes of the product's increased immunogenicity.

## MARKET APPROVAL AND EVALUATION OF BIOSIMILARS

In the case of generic drugs, demonstrating the structural sameness and bioequivalence of the generic medicine to the original product is usually considered appropriate to infer therapeutic equivalence between the two.[3] However, expert and regulatory authorities in Europe and the USA have recognised that the established process for evaluation and market approval of generic drugs cannot be applied to biosimilars,[3-5] since biologics consist of relatively large and complex proteins that are difficult to characterise.[3] The World Health Organization,[3] the EMEA[4] and, most recently, the US Food and Drug Administration[5] have all prepared guidelines on the appropriate evaluation of biosimilars. Based on these authorities, some of the essential evidence that must be provided in support of licensing of biosimilars includes characterisation and evaluation studies on the quality attributes of the product, pre-clinical and clinical studies, and demonstration of safety, purity, and potency. In addition, a comprehensive pharmacovigilance plan is mandatory throughout the life of the product. The Figure shows a comparison of the regulatory process for evaluation and licensing of a novel biologic and a biosimilar, underlining that the procedure for biosimilars must be almost as rigorous as that for the original biologic or new biologic compound.

## BIOSIMILARS IN CLINICAL PRACTICE

The market share for biosimilars is predicted to increase

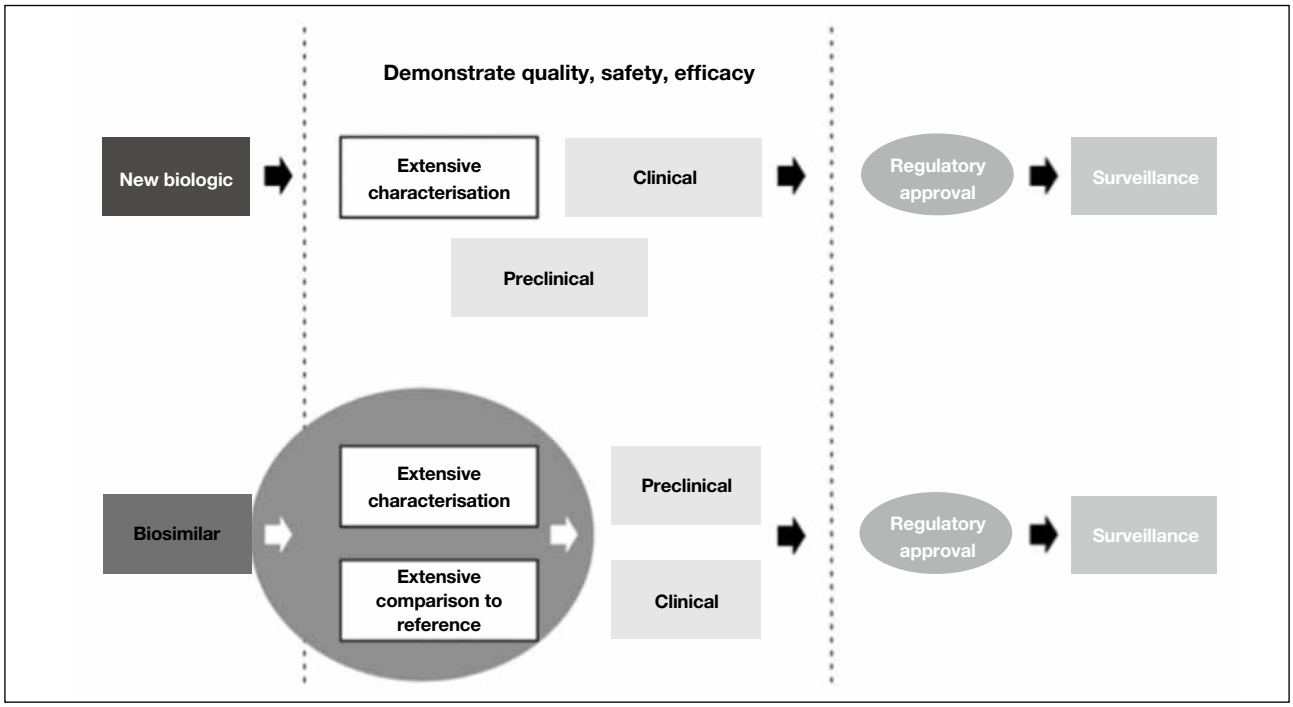


**Figure.** No short cuts: pathways to regulatory approval of a new biologic versus a biosimilar.

markedly in the coming decades, and it is essential that clinicians understand the nature of biosimilars and how to use them appropriately and safely in clinical practice. As the name implies, a biosimilar is not identical to the innovator biologic, and this must be borne in mind when prescribing. When prescribing biologics, the brand name, not the generic name, must be stated, strict pharmacovigilance must be followed, and auto-substitution is not recommended.

## CONCLUSION

The number of biosimilars available in clinical practice is likely to increase greatly in the coming years. In the world of biosimilars, there is heavy reliance on phase III and IV clinical data, and the manufacturing processes for the product must be detailed and strictly adhered to in order to avoid deviations from the intended therapeutic effects. Finally, continuous evaluation, with pharmacovigilance to confirm safety and clinician education on the proper prescribing practice for biosimilars, is also very important.

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