
REVIEW ARTICLE

What Physicians Need to Know About Biosimilars

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ABSTRACT

Biologics are complex proteins derived from living organisms that have been used successfully in treating many different diseases. As some biologics approach patent expiration, the development of drugs that are similar to the approved biological agents, known as biosimilars, has gained significant interest, primarily as a more affordable option for patients. Because of the structural complexity of large proteins and the inherent heterogeneity associated with culturing and manufacturing conditions, biosimilars are highly similar, but not identical to the approved 'reference' agents. Any subtle changes in the manufacturing processes may result in altered function and immunogenicity of the biosimilars, potentially affecting their efficacy and safety profile. Thus, stringent regulatory framework and requirements are necessary to ensure biosimilars are comparable in quality, efficacy, and safety with the reference agents and suitable for clinical use. As this field continues to evolve and more biosimilars are expected to become available in the near future, physicians will need to make informed decisions in the clinical use of biosimilars to ensure that high-quality, safe, and affordable drugs are accessible to patients. This article summarises current considerations, regulatory processes, and challenges in this rapidly evolving field.

Key Words: Biosimilar; Biologic; Generic; Monoclonal antibodies; Rituximab

中文摘要

關於生物製劑的醫生需知

張文勇

生物製劑是來源自活生物的蛋白複合物，已被成功用於治療多種不同疾病。由於部分生物製劑的專利即將期滿，一些與獲批生物製劑相似、稱為生物仿製藥的藥物發展備受關注，成為對病人而言更能負擔的選擇。因為大蛋白質的結構複雜，加上與培植及生產環境相關的變數，所以雖然生物仿製藥與獲認可的「參考」藥物高度相似，但並非完全相同。在製造過程中任何細微的變化，都可能改變生物仿製藥的功能及免疫原性，而可能影響其療效和安全性。因此，必須要有嚴格的監管框架及要求，以確保生物仿製藥與參考藥物在品質、療效及安全性相若，並適合臨床使用。隨着這領域的不斷發展，在不久將來會有更多生物仿製藥面世，醫生將需要在使用生物仿製藥上作出明智的決策，以確保患者可獲得高品質、安全而且負擔得起的藥物。本文總結了在這個正在迅速演變的領域中現今的顧慮、監管程序和挑戰。

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INTRODUCTION

Biologics, also known as ‘biological medicinal products’ or ‘biological medicines’, are drugs that are derived from living organisms by means of recombinant DNA and / or controlled gene-expression methods. Unlike small-molecule drugs, they cannot be easily synthesised from chemical processes. Biologics have been in use in medicine for a long time and the common biologics include vaccines, insulins, hormones, blood products and factors, and antibodies.

Monoclonal antibodies are an important breakthrough in biologic therapies that have become the cornerstone of treatment for cancer and a range of immunological illnesses. Rituximab, a chimeric IgG1, anti-CD20 monoclonal antibody, is a good example of a monoclonal antibody that has revolutionised the treatment of a number of diseases, including non-Hodgkin lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and polyangiitis. Although associated with improved patient outcomes, the high costs of monoclonal antibodies and other biologics raise concerns about the financial burden to patients and health care payers. The cost of rituximab for rheumatoid arthritis can amount to more than HK\$110,000 per patient per year (Table 1). The high costs may be a prohibitive barrier to some patients and may lead to restricted access in many health care systems around the world due to budget constraints.

Since many biologics, including monoclonal antibodies, are approaching their patent-expiration dates, pharmaceutical companies are now developing similar versions of these agents. The advantages of biosimilars over the original biologics include the potential for cost saving and, thus, improving patient access to treatment. However, the replication of complex, intricate proteins with tertiary and quaternary structures is inherently difficult, and any subtle changes in the manufacturing processes may result in altered function, efficacy, and safety profile. In order to gain marketing approval, biosimilars must meet strict regulatory criteria and demonstrate comparability in quality, efficacy, and

safety with the original biologics. As more biosimilars are expected to become available in the near future, physicians will need to make informed decisions in clinical practice when using biosimilars in place of the original biologics. This article summarises current considerations, regulatory processes, and challenges in this rapidly evolving field.

BIOSIMILARS

A biosimilar, also known as a follow-on biologic or subsequent-entry biologic, is defined by the European Medicines Agency (EMA) as a “version of an already authorized biological medicinal product with demonstrated similarity in quality characteristics, biological activity, efficacy and safety, based on a comprehensive comparability exercise”.¹ Similarly, the US Food and Drug Administration (FDA) requires a biosimilar to be “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and for which there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency”.² These strict definitions must be fulfilled by a medicine to be considered as a biosimilar by the two regulatory authorities.

BIOSIMILARS VERSUS REFERENCE PRODUCTS: HOW SIMILAR ARE THEY?

There are substantial challenges associated with the synthesis of a ‘highly similar’ copy of the original biologic. Unlike small-molecule drugs, which are small in size, stable, and have well-defined chemical structures, biologics such as monoclonal antibodies are large and highly complex, with molecular weights up to 150 kDa. Their complexity is not only influenced by the amino acid sequence, but also by the secondary, tertiary and quaternary structures, or, in other words, the way proteins are folded and cross-linked to form three-dimensional structures. Biologics are unstable and the protein structures are often altered by post-translational modifications such as glycosylation, phosphorylation, methylation and deamidation, which may result in intrinsic molecular heterogeneity and affect the biological activity. The heterogeneity is further increased by conditions of cellular synthesis, such as the cell type used to produce the protein, culture conditions, purification methods, stabilisation, storage, and packaging conditions. All biologic agents are also potentially immunogenic; subtle structural differences or alternations in the manufacturing process or conditions

Table 1. Costs of monoclonal antibodies used to treat rheumatoid arthritis in Hong Kong in January 2011.

| | Unit cost (HK\$) | Annual cost per patient (HK\$) |
|------------|------------------|--------------------------------|
| Rituximab | 14,496 | 57,984-115,968 |
| Golimumab | 7,000 | 84,000 |
| Adalimumab | 4,830 | 125,580 |
| Infliximab | 4,800 | 76,800 |

may significantly affect immunogenicity, potentially changing their efficacy and safety profile, and making exact replication a virtual impossibility.

While the structural and therapeutic quality of small-molecule drugs can be replicated in a consistent manner by manufacturers of generic small-molecule drugs, biosimilars cannot be considered identical generic versions of the reference products as their intrinsic complexities, unique cell lines and manufacturing processes mean that there will always be small variations from the original reference agent. The regulatory approval requirements for biosimilars also differ from that for generic small molecules. Recognising the importance of regulating the comparability of biosimilars with the approved reference agents, the EMA was the first to establish a regulatory framework for the approval of biosimilars in the European Union (EU). The first general guidelines on biosimilars were published in 2005¹ followed by approval of its first biosimilar in 2006. In the USA, the FDA established a regulatory framework for biosimilars in 2010 and issued draft guidance on the framework in 2012.²⁻⁵

To date, the approved agents include somatotropin, erythropoietin, and filgrastim biosimilars (Table 2). In June 2013, the EMA recommended granting marketing authorisations for the first two monoclonal antibody biosimilars, Remsima (Celltrion) and Inflectra (Hospira), which contain the same known active substance, infliximab.⁶ This marks the first time that the biosimilar concept has been successfully applied to molecules as complex as monoclonal antibodies. These drugs are

now awaiting final marketing authorisation decision from the European Commission.

Both the EMA and US FDA require biosimilars to have proven comparable levels of quality, efficacy, and safety with the reference product.^{1,2} Fundamental features that must be retained in biosimilars include the same primary amino acid sequence, potency, and route of administration. Higher-order structures, post-translational modifications, and other potential variants must be as similar as possible with the reference product, with adequate analyses performed to demonstrate that any differences do not impact upon clinical efficacy, safety, or immunogenicity. The specific biosimilar given to a patient should also be identifiable for pharmacovigilance monitoring. Similarly, the World Health Organization (WHO) guidelines specified that licensing of biosimilars requires data from clinical trials, evaluation of immunogenicity and pharmacovigilance.⁷

There are many potential differences between biosimilars and the reference products such as the formulation, post-translational modifications, impurity, and potency that could lead to a major difference in the product functions. Thus, it is important for regulatory authorities to provide a rigorous and balanced approach to the approval process. For example, the EMA rejected the marketing authorisation of a biosimilar, interferon alfa-2a (Alpheon; BioPartners GmbH) in 2006.⁸ The reasons for the rejection included quality and clinical differences between the biosimilar and the reference product, inadequate data on the stability of the active substance, inadequate validation of the process for the finished process, and insufficient validation of immunogenicity testing.⁸ Outside the EU and US, the regulatory framework for biosimilars varies widely, and it is ultimately up to local regulatory authorities to decide on the standard and procedures for approval. Some so-called 'biosimilars' are available in countries such as India and over the Internet, which apparently meet local regulatory requirements.⁹ However, as these agents do not have proven comparability with the original products under the stringent regulatory processes issued by the EMA or US FDA, they should not be considered biosimilars, but rather, as 'intended copies' or 'non-innovator biologics'.¹⁰

DEMONSTRATING BIOSIMILARITY: THE APPROVAL PROCESS AND OTHER CONSIDERATIONS

The regulatory processes and clinical and non-clinical

Table 2. Biosimilars approved in Europe.

| Reference product | Year of approval | Brand name (manufacturer) of biosimilar |
|-------------------|------------------|---|
| Somatotropin | 2006 | Omnitrope® (Sandoz) |
| | 2006 | Valtropin® (BioPartners) |
| Epoetin alfa | 2007 | Binocrit® (Sandoz) |
| | 2007 | Epoetin alfa HEXAL® (Hexal) |
| | 2007 | Abseamed® (Medice Arzneimittel Pütter) |
| | 2007 | Retacrit® (Hospira) |
| | 2007 | Silapo® (Stada) |
| Filgrastim | 2008 | Ratiograstim® (Ratiopharm) |
| | 2008 | Filgrastim Ratiopharm® (Ratiopharm) |
| | 2008 | TevaGrastim® (Teva) |
| | 2008 | Biograstim® (CT Arzneimittel) |
| | 2008 | Zarzio® (Sandoz) |
| | 2009 | Filgrastim HEXAL® (Hexal) |
| | 2010 | Nivestim® (Hospira) |

studies required to demonstrate biosimilarity differ significantly from requirements for generic drug approval, where only bioavailability and bioequivalence must be shown. Extensive, non-clinical physicochemical and biological characterisation is required to address structural, functional, and immunogenicity concerns prior to efficacy and safety trials. Both the EMA and FDA require clinical data from randomised controlled trials to establish equivalent efficacy and safety to the reference agent. Furthermore, a suitable primary endpoint should be selected to detect differences.^{2,11,12} For assessment of rare adverse events and long-term efficacy and safety, post-marketing pharmacovigilance and risk management plans are required by regulatory authorities. Adverse event reports should contain as much information as possible, particularly for documenting events occurring as a result of switching between reference and biosimilar agents.

Extrapolation of clinical similarity shown in one indication to other indications of the reference product is allowed by the EMA and FDA, particularly when the mechanism of action is the same, and provided extrapolation is founded on scientific justification and the overall evidence of comparability.^{4,12} However, extrapolation is complex, especially when the drug, such as a monoclonal antibody, has different mechanisms of action, some of which are not fully understood. For example, rituximab can exert its effect through multiple mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis and inhibition of proliferation; moreover, the net contribution of each mechanism in vivo is unknown.¹³ In these circumstances, the EMA and FDA will consider extrapolation on a case-by-case basis, based on totality of evidence.^{4,12} Potential safety issues in different subpopulations should also be addressed.

The ability to differentiate between reference and biosimilar agents is also important, hence the use of a unique product name for each biosimilar is preferred over the generic name to facilitate accurate prescribing and tracking. Interchangeability of the biosimilar and reference product is controversial because of unavoidable differences in immunogenicity that could affect hypersensitivity reactions, pharmacokinetics, and efficacy. There should be no automatic substitution of biosimilar and the reference agent by pharmacists without prior consent of the treating physician. For safe prescription of biosimilars in clinical practice, it is important that biosimilars are prescribed by product

names, not interchangeable with reference agents, and monitored by a robust pharmacovigilance and risk management system.

Because of the manufacturing complexity, stringent quality control, longer approval process, and the necessity for outcome trials, the magnitude of cost saving in producing biosimilars may not be as robust as with producing generics. Previous experience suggested cost savings of 15 to 30% compared with the reference biologic, which is substantially less than the 80 to 90% cost savings for generic drugs.^{14,15} In the future, expansion of the availability of biosimilars to include biosimilar monoclonal antibodies and other agents will likely provide new opportunities for cost saving, allowing greater patient access to more affordable biologic therapy while maintaining high-quality standards.

CONCLUSION

The manufacturing of large, complex biologics and biosimilars has to be highly controlled, as even minor modifications may alter biological function and / or immunogenicity, potentially changing the efficacy and safety profile. Thus, stringent regulatory processes are paramount to ensure that biosimilars have high standards of comparability with the reference agents at all levels. The currently approved biosimilars have provided high-quality and safe therapeutic choices to patients, and the hope for the future is to improve patient access to a wider range of biologic therapies at affordable prices. Once available, physicians should be vigilant in the use of biosimilars by prescribing with product names, avoiding automatic substitution, and closely monitoring patients to ensure long-term safety and efficacy of biosimilars.

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