

Reading List | Biosimilar Medicines

What you need to know about biosimilar medicinal products.

A consensus information document published by the European Commission 2013.

Abstract

This multi-stakeholder consensus document has been developed to provide comprehensive information on the concept of biosimilar medicinal products, including science, regulatory and economic aspects. All elements in this document are relevant to decision makers such as scientific societies, healthcare professionals and competent authorities, as well as to patients and their representative organisations. The document includes a Q&A for patients, physicians and payers.

Full text available [here](#) (open access – Available in English, French, German, Italian, Polish, Portuguese and Spanish).

Biosimilars: what clinicians should know.

Weise M et al. Published in Blood 2012;120(26):5111-5117.

Abstract

Biosimilar medicinal products (biosimilars) have become a reality in the European Union and will soon be available in the United States. Despite an established legal pathway for biosimilars in the European Union since 2005 and increasing and detailed regulatory guidance on data requirements for their development and licensing, many clinicians, particularly oncologists, are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product. In this article, the members and experts of the Working Party on Similar Biologic

Medicinal Products of the European Medicines Agency (EMA) address these issues. A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients. This will become even more important with the advent of biosimilar monoclonal antibodies. The issues also highlight the need for improved communication between physicians, learned societies, and regulators.

Full text available [here](#) (open access)

Biosimilars: the science of extrapolation of indication.

Weise M et al. Published in Blood 2014;124(22):3191-3196.

Abstract

Despite the establishment of a specific approval pathway, the issuance of detailed scientific guidelines for the development of similar biological medicinal products (so-called "biosimilars") and the approval of several biosimilars in the European Union, acceptance of biosimilars in the medical community continues to be low. This is especially true in therapeutic indications for which no specific clinical trials with the biosimilar have been performed and that have been licensed based on extrapolation of efficacy and safety data from other indications. This article addresses the concerns frequently raised in the medical community about the use of biosimilars in such extrapolated indications and explains the underlying scientific and regulatory decision making including some real-life examples from recently licensed biosimilars.

Full text available [here](#) (open access)

Regulatory aspects of biosimilars. Myths and facts (in German).

Schneider CK and Weise M. Published in *Zeitschrift für Rheumatologie* 2015;74(8):695-700.

Abstract

Background: Biosimilars are currently a hot topic and there are many unsolved questions, misunderstandings and sometimes considerable uncertainty, especially among clinicians and patients. Regulatory agencies, such as the European Medicines Agency (EMA) issue guidelines for the development and approval of biosimilars, which are based on scientific principles.

Objective: This article addresses some of the frequently noted misunderstandings and misperceptions. For example, why biosimilars are (or can only be) “similar” but not “identical” compared to the original pharmaceutical product, and aspects, such as the pharmaceutical quality of biosimilars, immunogenicity and the approval process for biosimilars are highlighted.

Full text available [here](#)

Biosimilar regulation in the EU.

Kurki P and Ekman N. Published in *Expert Review of Clinical Pharmacology* 2015;8(5):649-659.

Abstract

In the EU, the EMA has been working with biosimilars since 1998. This experience is crystallized in the extensive set of guidelines, which range from basic principles to details of clinical trials. While the guidance may appear complicated, it has enabled the development of biosimilars, of which 21 have managed to get marketing authorization. Currently marketed biosimilars in the EU have a good track record in safety and traceability. No biosimilars have been withdrawn from the market because of safety concerns. The most controversial issues with biosimilars are immunogenicity and extrapolation of therapeutic indications. The available data for these topics do not

raise concerns among EU regulators. Interchangeability and substitution are regulated by individual EU member states.

Full text available [here](#)

Biosimilars for prescribers.

Kurki P. Published in *Generics and Biosimilars Initiative (GaBI) Journal* 2015;4(1): 33-35.

Abstract

Biosimilars are copies of original biological medicines. Biosimilarity is a new concept in drug development. Physicians prescribing biologicals need more neutral information on the quality, safety and efficacy of biosimilars.

Full text available [here](#) (open access)

ECCO position challenged by European drug regulators.

Kurki P et al. Published in *Journal of Crohn's and Colitis* 2014;8(3):258,

No abstract available - Full text available [here](#)

The EU regulatory approach to generics and biosimilars is essentially similar.

van der Plas M et al. Published in *Generics and Biosimilars Initiative (GaBI) Journal* 2015;4(1):9-10.

Abstract

Notwithstanding the scientific and regulatory differences between generic and biosimilar medicines, the European Medicines Agency/Committee for Medicinal Products for Human Use has consistently applied a ‘same active substance’ approach to both.

Full text available [here](#) (open access)

Biosimilars in rheumatology: the wind of change.

Schneider CK. Published in *Annals of the Rheumatic Diseases* 2013;72(3):315-318.

No abstract available. Full text available [here](#) (open access)

In support of the European Union biosimilar framework.

Schneider CK et al. Published in *Nature Biotechnology* 2012;30(8):748-749.

No abstract available. Full text available [here](#)

Setting the stage for biosimilar monoclonal antibodies.

Schneider CK et al. Published in *Nature Biotechnology* 2012;30(12):1179-1185.

No abstract available. Full text available [here](#)

Terminology for biosimilars - a confusing minefield.

Thorpe R and Wadhwa M. Published in *Generics and Biosimilars Initiative (GaBI) Journal* 2012;1(3-4):132-134.

Abstract

Biosimilars are firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval. Unfortunately, inconsistency in nomenclature for biosimilars has caused confusion. This problem of terminology has been the subject of a

recent publication. The confusion is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions in published reports. Several examples of this have occurred, some of which are discussed below. The definitions provided should be adopted for clarity in the future.

Full text available [here](#) (open access)

Safety assessment of biosimilars in Europe: a regulatory perspective.

Giezen TJ, Schneider CK. Published in *Generics and Biosimilars Initiative (GaBI) Journal* 2014;3(4):180-183

Abstract

Clinical safety is important during the development of a biosimilar. This paper provides an overview of the main aspects related to the safety assessment of biosimilars. The European Medicines Agency's 'Guideline for similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues', which is currently under revision, forms the basis for the topics discussed in this paper. Topics discussed include adverse events related to an exaggerated pharmacology, immunogenicity including assay development, extrapolation of indications in relation to safety assessment and pharmacovigilance.

Full text available [here](#) (open access)

The safety of switching between therapeutic proteins.

Ebbers HC, Muenzberg M and Schellekens H. Published in *Expert Opinion on Biological Therapy* 2012;12(11):1473-1485

Abstract

Introduction: The approval of several biosimilars in the past years has prompted discussion on potential safety

risks associated with switching to and from these products. It has been suggested that switching may lead to safety concerns. However, data is limited on the clinical effects of switching.

Areas covered: In this review we provide an overview of data related to switching between human recombinant growth hormones, erythropoietins and granulocyte colony stimulating agents. We reviewed data from clinical trials, pharmacovigilance databases and an overview of the literature on the frequency of switching between these products. The review covers both switching between innovator products within the same product class and switching to and from biosimilars.

Expert opinion: Data on the frequency of switching in clinical practice is scarce, but it seems most frequent for erythropoietins. We have found no evidence from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns.

Full text available [here](#)

Biosimilars: In support of extrapolation of indications.

Ebbers, HC. Published Journal of Crohn's and Colitis 2014;8(5):431-435.

Abstract

Biosimilars have the potential to lead to enormous cost savings in healthcare without reducing the level of care for patients. In Europe, biosimilars have to demonstrate comparability in an extensive biosimilarity exercise including analytical, preclinical and comparative clinical studies. By successfully completing the biosimilarity exercise, the biosimilar shows that all aspects that are considered relevant for the clinical activity of the product fall within the same range as observed for the innovator. It should be carefully considered whether the benefit of additional information from more comparative clinical studies weighs up to the additional barriers such studies create for biosimilars to enter clinical practice.

Full text available [here](#)

Biosimilars: what it is not.

de Mora, F. Published in British Journal of Clinical Pharmacology 2015: 80(5): 949-956.

Abstract

A biosimilar is a high quality biological medicine shown to be in essence the same as an original product. The European Medicines Agency (EMA) paved the way in the regulatory arena by creating a safeguarding framework for the development of biosimilars. Biosimilar is thus a regulatory term that alludes to the evidence-based studies required to demonstrate such very high similarity. They are therefore not innovative products but the pathway laid down by the EMA for their approval represented a new paradigm. This has brought some confusion and has cast doubts among healthcare professionals about the scientific evidence behind their authorization. Many papers have been published to clarify the concept, and to reassure those professionals, but misconceptions frequently still arise. Unfortunately, this prevents biosimilars from deploying their full therapeutic added value. This paper is intended to approach those misconceptions from a new angle, by explaining what a biosimilar is not...and why. A biosimilar is neither a generic, nor an original product. It is not a bio-better or a 'stand-alone'. Therefore, it should not be managed as such therapeutically, commercially or from a healthcare policy viewpoint. The EMA's criteria were acknowledged by other agencies, but a significant regulatory gap with a vast majority of regulatory bodies still remains. This leaves room for the so-called non-original biologics (NOB), i.e. non-biosimilar biologics, to be launched in many regions. Raising awareness of what a biosimilar is and what it is not, will generate trust in biosimilars among healthcare professionals and will ultimately benefit patients.

Full text available [here](#)

Acceptable changes in quality attributes of glycosylated biopharmaceuticals.

Schiestl M et al. Published in Nature Biotechnology 2011;29:310-312.

No abstract available. Full text available [here](#)

Authorised manufacturing changes of therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents.

Vežer et al. Current Medical Research and Opinion 2016:829-834.

Abstract

Background: The quality of biologicals, including biosimilars, is subject to change as a result of manufacturing process modifications following initial authorization. It is important that such product changes have no adverse impact on product efficacy or safety, including immunogenicity.

Objectives: The aim of this study was to investigate the number and types of manufacturing changes of originator mAbs (the reference for the comparability exercise to confirm biosimilarity) according to European Public Assessment Report (EPAR) documentation and to ascertain the level of risk these changes might impart. The extensive body of evidence contained in the EPAR documents can help support the EMA during the EC marketing authorisation approval process for biosimilars, since it provides a broad base of scientific experience.

Research designs and methods: For EPAR-listed mAbs, details of all changes listed chronologically in the EPAR were evaluated and described. Based on these

descriptions the manufacturing changes can be categorised by risk-status (low, moderate or high).

Results: Entries for 29 mAbs with publicly available EPAR reports were reviewed. These contained details of 404 manufacturing changes authorized by the European Medicines Agency (EMA): 22 were categorised as high-risk, 286 as moderate risk and 96 as low-risk manufacturing changes. A limitation of this analysis is that only summarises publicly available data from EPAR documents.

Conclusions: Manufacturing change data indicate that the EMA has significant experience of process changes for originator mAbs, and the impact they may have on the efficacy and safety of biologicals. This experience will be useful in biosimilar product development to ensure adherence to sound scientific principles. Compared with the established manufacturing process for a reference product, the production of biosimilars will usually be different. Consequently, in addition to a comprehensive comparative functional and physicochemical characterization analysis, clinical data is required to confirm mAb biosimilarity.

Full text available [here](#)

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