

# Reading List | Biosimilar Medicines

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## 1 - General information about biosimilar medicines

### What I need to know about biosimilar medicines: Information for patients

A consensus information document published by the European Commission, 2017  
Full text available [here](#) (open access – Available in DE, EN, ES, FR, IT, PO, PT).

#### Abstract

This leaflet has been written for patients who want information on biosimilar medicines. It aims to provide answers to some questions patients may have on biosimilar medicines. If you would like to read more about biosimilar medicines, there are references for further information at the end of this leaflet.

### What you need to know about biosimilar medicinal products

A consensus information document published by the European Commission, 2013.  
Full text available [here](#) (open access – Available in DE, EN, ES, FR, IT, PO, PT).

#### 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.

## Other relevant publications

- **Biosimilars: the challenges to bring a 'new' concept to market. A short review of the first decade of biosimilars**  
Cornes P. & Muenzberg M. Published in Pharma Horizon 2017;1(2):30-34.  
*Full text available [here](#)*
- **Biosimilars at the interface of science, medicine and economic**  
Gudat U. Published in Pharma Horizon 2017;1(2):35-38.  
*Full text available [here](#)*
- **Roundtable on biosimilars with European regulators and medical societies, Brussels, Belgium, 12 January 2016**  
Giezen T. et al. Published in Generics and Biosimilars Initiative (GaBI) Journal 2016;5(2):74-83.  
*Full text available [here](#) (open access)*
- **Biosimilar Medicines Handbook (new edition)**  
Medicines for Europe Biosimilar (2016)  
*Full text available [here](#) (open access)*
- **Biosimilars: what it is not**  
de Mora, F. Published in British Journal of Clinical Pharmacology 2015: 80(5): 949-956.  
*Full text available [here](#) (open access)*

## 2 -Biological variability

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

Vezer B. et al. Published in Current Medical Research and Opinion 2016;32(5):829-834.  
*Full text available [here](#)*

#### 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.

## Acceptable changes in quality attributes of glycosylated biopharmaceuticals

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

Full text available [here](#)

### Abstract

No abstract available

## Other relevant publications

- **Biosimilars in rheumatology: the wind of change**

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

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

## 3 -Regulatory & scientific framework

### Biosimilar regulation in the EU

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

Full text available [here](#)

### 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.

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

Schneider CK. & Weise M. Published in Zeitschrift für Rheumatologie 2015;74(8):695-700.  
*Full text available [here](#)*

### 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.

## Other relevant publications

- **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.  
*Full text available [here](#) (open access)*
- **Safety assessment of biosimilars in Europe: a regulatory perspective.**  
Giezen T & Schneider CK. Published in Generics and Biosimilars Initiative (GaBI) Journal 2014;3(4):180-183.  
*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.  
*Full text available [here](#)*

## 4 - Information for prescribers

### Physicians, Hippocrates and biosimilars: applying ancient principles in a modern society

Kurki P. Published in Generics and Biosimilars Initiative (GaBI) Journal 2016;5(4):149-150.  
*Full text available [here](#) (open access)*

### Abstract

Physicians are pondering the clinical use of biosimilars. A reliance on clinical trials is deeply rooted in the modern healthcare system, whereas comparability and totality of evidence remain unknown concepts. This editorial explores these ideas, with reference to a case study of Italian gastroenterologists.

## Biosimilars: what clinicians should know

Weise M et al. Published in Blood 2012;120(26):5111-5117.  
Full text available [here](#) (open access)

### 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.

## Other relevant publications

- **Biosimilars for prescribers**

Kurki P. Published in Generics and Biosimilars Initiative (GaBI) Journal 2015;4(1):33-35.  
Full text available [here](#) (open access)

## 5 -Terminology

### Terminology for biosimilars - a confusing minefield

Thorpe R. & Wadhwa M. Published in Generics and Biosimilars Initiative (GaBI) Journal 2012;1(3-4):132-134.  
Full text available [here](#) (open access)

### 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.

## Biosimilars: why terminology matters

Weise M. et al. Published in Nature Biotechnology 2011;29(8):690-693.

Full text available [here](#)

### Abstract

No abstract available

## 6 - Extrapolation of indications

### Opportunities and challenges of extrapolation for biosimilars (in German)

Weise M & Wolff-Holz E. Published in Zeitschrifts für Gastroenterologie 2016;4:1211-1216.

Full text available [here](#)

### Abstract

Although biosimilars approved in the European Union have proved to be safe and efficacious, their licensing requirements continue to be disputed by medical professionals. In particular, extrapolation to indications of the originator without one's own clinical data of the biosimilar is controversial. Conceptually, the development of biosimilars is derived from that of generics. However, due to their complexity and inherent variability, considerably more data are necessary for biosimilars to demonstrate comparability with the originator (the reference product) than for the usually low-molecular generics. Biosimilars increase competition and help contain healthcare, and they improve access for patients to valuable treatments with biologicals. However, biosimilar development is a laborious and lengthy process and requires major biotechnological know-how. The basis is comprehensive, structural, and functional characterization of the biosimilar and reference product as well as their comparison with suitable and sensitive methods. The clinical development programme is reduced and tailored to address remaining uncertainties and to confirm comparable clinical performance. Extrapolation of data to other indications of the reference product is the greatest cost advantage of biosimilar development, but must always be scientifically justified and, if necessary, substantiated by further data. The scientific principles underlying the comparability exercise for a biosimilar are the same as those applied to a change in the manufacturing process of an already licensed biological. In both cases, different versions of a biological substance are compared and the clinical relevance of observed differences is assessed. Competent authorities do have decades of experience in evaluating changes in the manufacturing process, which they can now apply to biosimilars. For approval of a biosimilar and extrapolation of data, the totality of the evidence from the complete comparability exercise is considered, as has been the case for the first biosimilar infliximab.

## Biosimilars: the science of extrapolation of indication

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

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

### 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.

## Other relevant publications

- **Biosimilars: Extrapolation for oncology**  
Curigliano et al. Published in Critical Reviews in Oncology/Hematology 2016;104:131-137.  
*Full text available [here](#) (open access)*
- **Biosimilars: In support of extrapolation of indications**  
Ebbers, HC. Published Journal of Crohn's and Colitis 2014;8(5):431-435.  
*Full text available [here](#) (open access)*

## 7 - Immunogenicity

Multidisciplinary approach to evaluating immunogenicity of biosimilars: lessons learned and open questions based on 10 years' experience of the European Union regulatory pathway.

Chamberlain PD. Published in Biosimilars 2014;4:23-43.  
*Full text available [here](#) (open access)*

### Abstract

Clinical evaluation of comparative immunogenicity represents an important component of the European Union regulatory review process for candidate biosimilar products. The clinical evaluation is part of a multidisciplinary review that cross-refers to product quality attributes as well as preclinical and ongoing risk management considerations. Results from the monitoring of anti-drug antibody formation in relevant populations treated for an adequate period of time are interpreted in relation to clinically relevant endpoints, including pharmacokinetics, pharmacodynamics, efficacy, and safety parameters. The European Union regulatory standard for designation of biosimilarity requires a suitable weight of evidence, determined on a product-specific basis, to demonstrate that the immunogenicity associated with the biosimilar product does not lead to a higher negative impact on clinically relevant outcomes compared with the reference product. The experience gained during the 10-year period following the implementation of the European Union biosimilars pathway indicates that a suitably cautious approach was applied, insofar as no immunogenicity-related issues have emerged for the approved applications of the different biosimilar products. In some cases, product quality-related issues were identified in the preauthorization setting as being potentially relevant for heightened risk of immunogenicity and were duly taken



into account for the biosimilarity decision. Some unresolved issues remain, most notably concerning the limitation of non-interventional post-marketing surveillance measures to monitor the potential for changes in immunogenicity over the longer term, e.g. following introduction of changes in manufacture, formulation, or primary product container. Lack of standardization of bioanalytical methods precludes comparison of anti-drug antibody formation for different products that are evaluated in non-comparative clinical studies, and correlation with relevant clinical parameters is also lacking.

## Other relevant publications

- **Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima**  
Ben-Horin S et al. Published in Gut 2016;65(7):1132-1138.  
Full text available [here](#)

## 8 - Traceability of biopharmaceuticals

### Traceability of biopharmaceuticals in spontaneous reporting systems: a cross-sectional study in the FDA adverse reporting system (FAERS) and Eudravigilance databases.

Vermeer N et al. Published in Drug Safety 2013;36(8):617-625.  
Full text available [here](#)

#### Abstract

**Background:** Adverse drug reactions (ADRs) of biopharmaceuticals can be batch or product specific, resulting from small differences in the manufacturing process. Detailed exposure information should be readily available in systems for post-marketing safety surveillance of biopharmaceuticals, including spontaneous reporting systems (SRSs), in which reports of ADRs are collected.

**Objective:** The aim of this study was to explore the current status of traceability of biopharmaceuticals in the US and the EU up to patient level in SRSs.

**Design and setting:** A cross-sectional study was conducted over the period 2004-2010, including ADR reports from two major SRSs: the FDA Adverse Event Reporting System (FAERS) in the US and EudraVigilance (EV) in the EU.

**Main outcome measures:** The availability of batch numbers was determined for biopharmaceuticals, and compared with small molecule drugs. For biopharmaceuticals for which a biosimilar has been approved for marketing in the EU, the identifiability of the product (i.e. the possibility of distinguishing the biosimilar from the reference biopharmaceutical) was determined.

**Results:** A total of 2,028,600 unique ADR reports were identified in the FAERS, reporting a total of 591,380 biopharmaceuticals (of which 487,065 were suspected). In EV there were 2,108,742 unique ADR reports, reporting a total of 439,971 biopharmaceuticals (356,293 suspected). Overall, for 24.0 % of the suspected biopharmaceuticals in the FAERS and 7.4 % of the suspected small molecule drugs ( $p < 0.001$ ) batch numbers were available. A similar pattern was seen in EV: for 21.1 % of the suspected biopharmaceuticals batch numbers were available, compared with only 3.6 % of the small molecule drugs ( $p < 0.001$ ). In both SRSs, consumers were most likely to report a batch number for suspected biologicals (36.3 % in the FAERS and 40.7 % in EV). A total of 13,790 biopharmaceuticals (9,759 suspected) for which a biosimilar has been approved in the EU were identified in EV. For



90.4 % of these biopharmaceuticals and 96.2 % of the suspected biopharmaceuticals the product was clearly identifiable.

**Conclusion:** This study underlines the need for improving traceability of biopharmaceuticals, in particular with respect to individual batches, allowing better identification and monitoring of postmarketing safety issues related to biopharmaceuticals.

## 9 - Physician-led switching

### Interchangeability of biosimilars: A European perspective

Kurki P. et al. Published in Biodrugs 2017 [Epub ahead of print].

Full text available [here](#)

#### Abstract

Many of the best-selling 'blockbuster' biological medicinal products are, or will soon be, facing competition from similar biological medicinal products (biosimilars) in the EU. Biosimilarity is based on the comparability concept, which has been used successfully for several decades to ensure close similarity of a biological product before and after a manufacturing change. Over the last 10 years, experience with biosimilars has shown that even complex biotechnology-derived proteins can be copied successfully. Most best-selling biologicals are used for chronic treatment. This has triggered intensive discussion on the interchangeability of a biosimilar with its reference product, with the main concern being immunogenicity. We explore the theoretical basis of the presumed risks of switching between a biosimilar and its reference product and the available data on switches. Our conclusion is that a switch between comparable versions of the same active substance approved in accordance with EU legislation is not expected to trigger or enhance immunogenicity. On the basis of current knowledge, it is unlikely and very difficult to substantiate that two products, comparable on a population level, would have different safety or efficacy in individual patients upon a switch. Our conclusion is that biosimilars licensed in the EU are interchangeable.

### 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.

Full text available [here](#)

#### 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.

## 10 - The economic case

### Biosimilars: How can payers get long-term savings

Mestre-Ferrandiz J, Towse A & Berdud M. Published in *PharmacoEconomics* 2016;34:609-616.  
*Full text available [here](#) (open access)*

#### Abstract

The term 'biosimilar' refers to an alternative similar version of an off-patent innovative originator biotechnology product (the 'reference product'). Several biosimilars have been approved in Europe, and a number of top-selling biological medicines have lost, or will lose, patent protection over the next 5 years. We look at the experience in Europe so far. The USA has finally implemented a regulatory route for biosimilar approval. We recommend that European and US governments and payers take a strategic approach to get value for money from the use of biosimilars by (1) supporting and incentivising generation of high-quality comprehensive outcomes data on the effectiveness and safety of biosimilars and originator products; and (2) ensuring that incentives are in place for budget holders to benefit from price competition. This may create greater willingness on the part of budget holders and clinicians to use biosimilar and originator products with comparable outcomes interchangeably, and may drive down prices. Other options, such as direct price cuts for originator products or substitution rules without outcomes data, are likely to discourage biosimilar entry. With such approaches, governments may achieve a one-off cut in originator prices but may put at risk the creation of a more competitive market that would, in time, produce much greater savings. It was the creation of competitive markets for chemical generic drugs—notably, in the USA, the UK and Germany—rather than price control, that enabled payers to achieve the high discounts now taken for granted.

### Biosimilar infliximab in inflammatory bowel disease: Outcomes of a managed switching programme

Razanskaite V et al. Published in *Journal of Crohn's and Colitis* 2017:1-7.  
*Full text available [here](#) )*

#### Abstract

**Background and aims:** biosimilar infliximab CT-P13 offers the potential for large drug acquisition cost savings. However, there are limited published data regarding its efficacy, safety, and immunogenicity in inflammatory

bowel disease [IBD], particularly in switching IBD patients from originator to biosimilar infliximab. We present the outcomes of a service evaluation of switching IBD patients established on originator infliximab to biosimilar, using a managed switching programme funded via a gain share agreement in a UK teaching hospital.

**Methods:** Evaluation outcomes included drug persistence, changes in drug acquisition costs, patient-reported side effects, adverse events, patient outcomes assessed using the IBD-control Patient-Reported Outcome Measures [PROM] questionnaire, serum drug and antibody levels, and routinely collected biochemical markers.

**Results:** A total of 143 patients with IBD [118 Crohn's disease, 23 ulcerative colitis, 2 IBD unclassified] were switched from originator infliximab to CT-P13. Patients reported a similar incidence of side effects before and after switch. No clinically significant differences were observed in mean C-reactive protein [CRP], albumin, haemoglobin levels, or platelet and white cell counts after the switch to CT-P13, whereas mean IBD-control-8 score improved from 10.4 to 11.2 [ $p = 0.041$ ]. There was no significant difference in drug persistence between biosimilar and originator infliximab [ $p = 0.94$ ] and no increase in immunogenicity was found. Drug acquisition costs decreased by £40,000-60,000 per month.

**Conclusions:** A managed switching programme from originator infliximab to biosimilar CT-P13 in IBD, using a gain-share agreement, delivers significant cost savings and investment in clinical services while maintaining similar patient-reported outcomes, biochemical response, drug persistence, and adverse event profile.

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