biosimilar medicines
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Reading List| Biosimilar Medicines

April 2022

Contents by topic

biosimilar medicines
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1 - General information about biosimilar medicines

What I need to know about biosimilar medicines: Information for patients – Q&A

A consensus information document published by the European Commission, 2016 (reviewed end of 2017)
Full text available here (open access – Available in all EU languages).

An information video created by the EMA is available here. Translations of the same video in European languages other than English can also be found in the dedicated playlist in the EMA's YouTube channel, here.

Biosimilars in the EU: Information guide for Healthcare Professionals

A consensus information document published jointly by the EMA and European Commission, 2019
Full text available here (open access – Available in all EU languages).

Abstract
Since the EU approved the first biosimilar medicine ('biosimilar') in 2006, the EU has pioneered the regulation of biosimilars. Over the past 10 years, the EU has approved the highest number of biosimilars worldwide, amassing considerable experience of their use and safety. The evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines.

Other relevant publications

- **Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price!**
  Dutta B et al. Published in BioDrugs 2019
  Full text available here
- **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

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2 - Biological variability

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

Vezér 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

3 - Regulatory & scientific framework

Evolution of the EU Biosimilar Framework: Past and Future

Wolff-Holz H et al. Published in BioDrugs 2019
Full text available here

Abstract

The approval of biosimilars in the EU follows a comprehensive scientific assessment based on stringent regulatory standards. While the initial approach to biosimilars was understandably cautious and conservative in that uncharted territory to protect patients' safety, the analytical and scientific progress and accumulated experience with biosimilars continues to reshape regulatory requirements, generally leading to a reduced burden of clinical trials. This trend is expected to continue, for example, by increasingly employing pharmacodynamic endpoints and biomarkers, but much work remains to make this happen, especially for complex molecules with several or unknown mechanisms of action. We reviewed the available guidance and European Public Assessment Reports (EPARs) of biosimilars approved in the EU via the centralised procedure. This review focuses on the nature and extent of clinical confirmation of biosimilarity considered necessary in addition to analytical and functional data. Taken together, analytical and functional comparison is the foundation of any biosimilar development. In addition, pharmacokinetic similarity is an indispensable prerequisite for any biosimilar approval, so careful planning on behalf of the applicant is mandated to avoid potential failure of such studies, for example, because of large interindividual variability, underpowered trial designs or other methodological causes. We conclude that the EU biosimilar regulatory framework is robust and able to adapt to advancing knowledge and experience and to strike a balance between regulatory standards, patient safety and feasibility of biosimilar development.

The Path Towards a Tailored Clinical Biosimilar Development

Schiestl M et al. Published in BioDrugs 2020
Full text available here

Abstract

Since the first approval of a biosimilar medicinal product in 2006, scientific understanding of the features and development of biosimilar medicines has accumulated. This review scrutinizes public information on development programs and the contribution of the clinical studies for biosimilar approval in the European Union (EU) and/or the United States (US) until November 2019. The retrospective evaluation of the programs that eventually obtained marketing authorization and/or licensure revealed that in 95% (36 out of 38) of all programs, the comparative clinical efficacy studies confirmed similarity. In the remaining 5% (2 out of 38), despite meeting efficacy outcomes, the biosimilar candidates exhibited clinical differences in immunogenicity that required changes to the manufacturing process and additional clinical studies to enable biosimilar approval. Both instances of clinical differences in immunogenicity occurred prior to 2010, and the recurrence of these cases is unlikely today due to state-of-the-art assays and improved control of process-related impurities. Biosimilar candidates that were neither approved in the

EU nor in the US were not approved due to reasons other than clinical confirmation of efficacy. This review of the development history of biosimilars allows the proposal of a more efficient and expedited biosimilar development without the routine need for comparative clinical efficacy and/or pharmacodynamic studies and without any compromise in quality, safety, or efficacy. This proposal is scientifically valid, consistent with regulation of all biologics, and maintains robust regulatory standards in the assessment of biosimilar candidates. Note: The findings and conclusion of this paper are limited to biosimilar products developed against the regulatory standards in the EU and the US.

Streamlined approval of biosimilars: moving on from the confirmatory efficacy trial

Bielsky MC et al. Published in Drug Discovery Today 2020
Full text available here

Abstract
Licensing of biosimilars is essential to promote patient access to 21st-century biological medicines. Regulatory approval of biosimilars is based on the totality of evidence from a head-to-head comparison with reference products (RPs). A clinical efficacy trial is usually required, but this is increasingly questioned. Based on a thorough review of biosimilar applications in the European Union (EU), we conclude that in-depth knowledge of the reference product, allied with high-performing analytical tools, largely predicts clinical comparability, subject to confirmation by a comparative pharmacokinetic (PK) trial. We provide a blueprint for a biosimilar pathway that reduces the need for clinical efficacy trials in exceptional cases, together with qualifying criteria and requirements for streamlined assessment to expedite wider access to affordable biological medicines.

Other relevant publications

- **Comparability of Biologics: Global Principles, Evidentiary Consistency and Unrealized Reliance.**
  Webster CJ et al. Published in BioDrugs 2021.
  Full text available here (open access)
- **An Efficient Development Paradigm for Biosimilars.**
  Webster CJ et al. Published in BioDrugs 2019.
  Full text available here (open access)
- **Biosimilar regulation in the EU.**
  Kurki P and Ekman N. Published in Expert Review of Clinical Pharmacology 2015.
  Full text available here (open access)

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4 – Further information for patients

Digestive cancers Europe resources on biosimilar medicines

A Dedicated website containing information on biosimilar medicines for digestive cancer patients has been setup by Digestive Cancers Europe (DiCE) and can be accessed here. It includes a call to action, which is available here.

Summary

The DiCE Call to Action highlights the important inequalities across Member States in relation to patient access to biological treatments. It is noted that the European Union (EU) has the power to provide strategic guidance for Member States and support the exchange of best practices for policy interventions related to the use of biosimilar medicines, biosimilar-related savings allocation, and to enhance overall education about biosimilar medicines.

DiCE calls on the European Commission to:

- Support transparent and tangible benefit-sharing practices around biosimilars across Europe that aim to improve the services and care offered to patients.
- Build a dedicated Europe-wide online resource centre to support the exchange of best practices on biosimilar savings reinvestment.
- Set up a dedicated Europe-wide online resource centre on biosimilars for HCPs and patients.

The Call includes several asks to Member States, among them the need to adjust national policies to ensure that biosimilar-related savings are reinvested locally in a tangible and transparent way, while encouraging all stakeholders to support patient organisations in raising overall awareness about biosimilars.

European Cancer Patient Coalition (ECPC) educational modules on biosimilars

The European Cancer Patient Coalition (ECPC) has developed dedicated educational modules on biosimilars, which are available here.

Summary

Biosimilar cancer medicines present a necessary and timely opportunity for patients in Europe. A highly similar copy of an off-patent biological medicine which is already available on the market under a different trademark, biosimilars may increase access to medicines by improving the financial sustainability of our healthcare systems. Increased availability of effective biosimilars translates directly into driving down the costs of biological medicines as the market becomes more competitive and potentially allowing more cancer patients to access the medicines they need. The safety of biosimilars in the EU is assured by the European Medicines Agency, and their availability in countries depends on the company and national authorities' decision. Currently, there is an inconsistent approach to biosimilars across Europe, and while pricing policies and instruments to enhance the uptake of generics are advanced, countries appear to be struggling to find the most appropriate approach for biosimilar medicines. As many more biosimilars for cancer treatment are expected in the coming years, ECPC is becoming increasingly engaged in the topic, education and policy perspectives.

Informing Patients about Biosimilar Medicines: The Role of European Patient Associations

Vandenplas Y. et al. Published in Pharmaceuticals 2021 ;*14*(2), 117.
Full text available here (open access)

Abstract
This review identified five main strategies to inform patients about biosimilars: (1) provide understandable information, (2) in a positive and transparent way, (3) tailored to the individual's needs, (4) with one voice, and (5) supported by audiovisual material. Moreover, the importance of a multistakeholder approach was underlined by describing the role of each stakeholder. Patients are a large and diffuse target group to be reached by educational programs. Therefore, patient associations have become increasingly important in correctly informing patients about biosimilar medicines. This has led to widespread biosimilar information for patients among European patient associations. […] We found that the level of detail, correctness, and the tone of the provided information varied. In conclusion, it is paramount to set up a close collaboration between all stakeholders to communicate, develop, and disseminate factual information about biosimilars for patients.

5 – Further information for healthcare professionals

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. Generics and Biosimilars Initiative (GaBI) Journal 2015;4(1):33-35.
  Full text available here (open access)

6 - 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

7 - 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

- **Extrapolation: Experience gained from original biologics**
  Rojas-Chavarro, de Mora; Drug Discovery Today Volume 26, Issue 8, August 2021, Pages 2003-2013
  Full text available here
- **Biosimilars: Extrapolation for oncology**
  Curigliano et al. Critical Reviews in Oncology/Hematology 2016;104:131-137.
  Full text available here (open access)
- **Biosimilars: In support of extrapolation of indications**
  Ebbers, HC. Journal of Crohn's and Colitis 2014;8(5):431-435.
  Full text available here (open access)

8 - 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

9 - Traceability of biopharmaceuticals

Identifiability of Biologicals: An Analysis Using EudraVigilance, the European Union's Database of Reports of Suspected Adverse Drug Reactions.

Correia Pinheiro et al. Published in Clinical Pharmacology and Therapeutics 2021
Full text available here

Abstract

The relevance of biological therapies for an increasing number of conditions is on the rise. Following the expiry of the initial period of market exclusivity, many of these successful therapies have seen the arrival of biosimilars on the market. The clear identification of the precise medicine responsible for an adverse drug reaction (ADR) report is an important element for pharmacovigilance, allowing timely detection of potential product-specific safety signals. We looked at the identifiability of biologicals up to the level of commercial product name in ADR reports received from European clinical practice between 2011 and December 2019. A good level of identification (91.5%) was observed overall, but at the same time a downward trend was observed in the last 5 years. This reduction in the level of identifiability of biological products (originators and biosimilars) at the commercial name level in general was driven by five widely used substances, whereas the identification of all other biologics stayed consistent over time (at over 90%). We observed that those five substances were used mostly within oncology. The introduction of the first biosimilar in the market did not appear to affect their identifiability. These results show that although the general level of identification at the commercial product name level in ADRs in Europe is robust and generally stable over time, decreasing trends can be down to a few commonly used substances, which need to be monitored to reverse the trend.

Identifiability of Biologicals in Adverse Drug Reaction Reports Received From European Clinical Practice.

Vermeer NS et al. Published in Clinical Pharmacology and Therapeutics 2018
Full text available here

Abstract

Biologicals are established treatment options that require pharmacovigilance adapted to their specific nature, including the need for products to be identifiable up to the specific manufacturer in reports of adverse drug reactions (ADRs). This study explored the identifiability of 10 classes of similar and related biologicals up to the level of the manufacturer in ADR reports received from European clinical practice between 2011 and June 2016. Adequate identifiers were reported for 96.7% of the suspected biologicals, ranging from 89.5% for filgrastim to 99.8% for interferon beta-1a. The product identifiability remained consistently high over time for classes of biologicals for which biosimilars were introduced during follow-up. The overall batch traceability was, however, only ensured for 20.5% of the suspected biologicals and needs further improvement. This study shows that the European system for identification of ADRs to the level of the manufacturer is robust, allowing for the timely detection of potential product-specific safety signals for biologicals.

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 (paywall)

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.

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10 - Physician-led switching

Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective

Kurki et al. Published in Drugs 2021
Full text available here

Abstract

Background: Biosimilars have been used for 15 years in the European Union (EU), and have been shown to reduce costs and increase access to important biological medicines. In spite of their considerable exposure and excellent safety record, many prescribers still have doubts on the safety and interchangeability of biosimilars, especially monoclonal antibodies (mAbs) and fusion proteins.

Objectives: The aim of this study was to analyse the short- and long-term safety and interchangeability data of biosimilar mAbs and fusion proteins to provide unbiased information to prescribers and policy makers.

Methods: Data on the safety, immunogenicity and interchangeability of EU-licensed mAbs and fusion proteins were examined using European Public Assessment Reports (EPARs) and postmarketing safety surveillance reports from the European Medicines Agency (EMA). As recent biosimilar approvals allow self-administration by patients by the subcutaneous route, the administration devices were also analyzed.

Results: Prelicensing data of EPARs (six different biosimilar adalimumabs, three infliximabs, three etanercepts, three rituximabs, two bevacizumabs, and six trastuzumabs) revealed that the frequency of fatal treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation of treatment, serious adverse events (SAEs), and main immune-mediated adverse events (AEs) were comparable between the biosimilars and their reference products. The availability of new biosimilar presentations and administration devices may add to patient choice and be an emerging factor in the decision to switch patients. Analysis of postmarketing surveillance data covering up to 7 years of follow-up did not reveal any biosimilar-specific adverse effects. No product was withdrawn for safety reasons. This is in spite of considerable exposure to biosimilars in treatment-naïve patients and in patients switched from the reference medicinal product to the biosimilar. Analysis of data from switching studies provided in regulatory submissions showed that single or multiple switches between the originator and its biosimilar versions had no negative impact on efficacy, safety or immunogenicity.

Conclusions: In line with previous reports of prelicensing studies of biosimilar mAbs and etanercepts, this study demonstrated comparable efficacy, safety, and immunogenicity compared with the reference products. This is the first study to comprehensively analyze postmarketing surveillance data of the biosimilar mAbs and etanercept. An analysis of more than 1 million patient-treatment years of safety data raised no safety concerns. Based on these data, we argue that biosimilars approved in the EU are highly similar to and interchangeable with their reference products. Thus, additional systematic switch studies are not required to support the switching of patients.

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Cohen HP. et al. Published in Drugs 2018; 78(4):463-478.
Full text available here

Abstract

Introduction: To evaluate the possibility that switching from reference biologic medicines to biosimilars could lead to altered clinical outcomes, including enhanced immunogenicity, compromised safety, or diminished efficacy for patients, a systematic literature review was conducted of all switching studies between related biologics (including biosimilars).

Methods: A systematic search was conducted using the Medline® and Embase® databases up to 30 June 2017 employing specific medical subject heading terms. Additionally, the snowball method and a hand search were also applied. Publications were considered if they contained efficacy or safety information related to a switch from a reference medicine to a biosimilar. Non-English, non-human studies, editorials, notes, and short surveys were excluded.

Results: Primary data were available from 90 studies that enrolled 14,225 unique individuals. They included protein medicines used in supportive care as well as those used as therapeutic agents. The medicines contained seven different molecular entities that were used to treat 14 diseases. The great majority of the publications did not report differences in immunogenicity, safety, or efficacy. The nature and intensity of safety signals reported after switching from reference medicines to biosimilars were the same as those already known from continued use of the reference medicines alone. Three large multiple switch studies with different biosimilars did not show differences in efficacy or safety after multiple switches between reference medicine and biosimilar. Two publications reported a loss of efficacy or increased dropout rates.

Conclusions: While use of each biologic must be assessed individually, these results provide reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine.

Interchangeability of biosimilars: A European perspective

Kurki P. et al. Published in Biodrugs 2017; 31(2):83-91.
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.

Other relevant publications

- **Interchangeability of biosimilars: Overcoming the final hurdles**
  Barbier et al. Drugs 2021
  Full text available here
- **Biosimilar-to-Biosimilar Switching: What is the Rationale and Current Experience?**
  Mysler et al. Drugs 2021
  Full text available here
- **Is there a reason for concern or is it just hype? A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars**
  András I. et al. Expert Opinion on Biological Therapy 2017
  Full text available here
- **Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial**
  Jørgensen K. et al. The Lancet 2017;389:2304-2316
  Full text available here
- **A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry**
  Glintborg B. et al. Annals of the Rheumatic Diseases 2017;
  Full text available here

11 – Policy & Access

Effective Strategies to Advance Access to Biologic Therapies for Non-Communicable Diseases – a biosimilar medicines access policy blueprint

Whitepaper published by the IGBA Biosimilars Committee (October 2021).

Full text available here

Summary

Key areas of the biosimilar medicines access policy blueprint:

- Enhancing regulatory efficiency for greater access
- Adapting reimbursement and co-payment policies for affordable access
- Improving market predictability and resilience for timely and stable access
- Advancing understanding and trust in biosimilar medicines for sustained access

Country scorecards for biosimilar sustainability

IQVIA institute report (June 2020).

Scorecards downloadable here

Summary

Biosimilars make an important contribution to the sustainability of health systems by providing alternatives to originator biologic products once those products no longer have patent or other forms of market exclusivity.

Across Europe, the level of competition among biosimilars differs widely by country and by molecule, as does their impact on pricing, and the extent of their use by patients. Much of this variability can be linked to differences in policy elements across health systems that contribute to sustainable market conditions for biosimilars.

This set of scorecards maps these elements per country and measures the overall contribution of biosimilars to the health system. They are a useful tool to help countries assess their current performance and identify areas for improvement.

European healthcare systems share commonalities but have specific differences which mean that policy scores should not be compared directly to each other. Therefore, 'The Sustainable Market' scorecard has been developed which acts as a gold-standard market by which comparisons can be made. This avoids misinterpretation or inaccurate comparison of countries.

The European Country Biosimilar Scorecards and Appendix, which provides detailed methodologies and explanations of the metrics and assessments incorporated into the scorecards, were developed by the IQVIA Institute for Human Data Science with funding from the Biosimilar Medicines Group, a sector group of Medicines for Europe.

Policies for biosimilar uptake in Europe: An overview

Moorkens E. et al. Published in PLoS One. 2017;12(12):e0190147.

Full text available here (open access)

Abstract

Background: Across European countries, differences exist in biosimilar policies, leading to variations in uptake of biosimilars and divergences in savings all over Europe.

Objectives: The aim of this article is to provide an overview of different initiatives and policies that may influence the uptake of biosimilars in different European countries. Recommendations will be formulated on how to create sustainable uptake.

Methods: An overview of policies on biosimilars was obtained via a questionnaire, supplemented with relevant articles. Topics were organized in five themes: availability, pricing, reimbursement, demand-side policies, and recommendations to enhance uptake.

Results: In all countries studied, biological medicines are available. Restrictions are mainly dependent on local organization of the healthcare system. Countries are willing to include biosimilars for reimbursement, but for commercial reasons they are not always marketed. In two thirds of countries, originator and biosimilar products may be subjected to internal reference pricing systems. Few countries have implemented specific incentives targeting physicians. Several countries are implementing pharmacist substitution; however, the scope and rules governing such substitution tend to vary between these countries. Reported educational policies tend to target primarily physicians, whereas fewer initiatives were reported for patients. Recommendations as proposed by the different country experts ranged from the need for information and communication on biosimilars to competitive pricing, more support for switching and guidance on substitution.

Conclusions: Most countries have put in place specific supply-side policies for promoting access to biosimilars. To supplement these measures, we propose that investments should be made to clearly communicate on biosimilars and educate stakeholders. Especially physicians need to be informed on the entry and use of biosimilars in order to

create trust. When physicians are well-informed on the treatment options, further incentives should be offered to prescribe biosimilars. Gainsharing can be used as an incentive to prescribe, dispense or use biosimilars. This approach, in combination with binding quota, may support a sustainable biosimilar market.

Other relevant publications

- **The impact of biosimilar competition in Europe**
  Whitepaper by IQVIA (2021, new version published annually)
  Full text available here
- **Spotlight on Biosimilars: Optimising the sustainability of healthcare systems.**
  Whitepaper by IQVIA
  This report highlights examples of the benefits biosimilar competition can create as well as how these benefits can be unlocked through optimisation.
  Full text available here
- **Off-Patent Biologicals and Biosimilars Tendering in Europe—A Proposal towards More Sustainable Practices**
  Barbier, L. *et al* Pharmaceuticals 2021 ; 14(6), 499
  Full text available here
- **A review on biosimilar infliximab, CT-P13, in the treatment of inflammatory bowel disease.**
  Farkas K. and Molnár T. Immunotherapy. 2018; 10(2):107-117.
  Full text available here
- **Policy practices to maximise the social benefit from biosimilars**
  Inotai A. et al. Journal of Bioequivalence & Bioavailability 2017;9(4):467-472
  Full text available here (open access)
- **Impact of Infliximab and Etanercept Biosimilars on Biological Disease-Modifying Antirheumatic Drugs Utilisation and NHS Budget in the UK**
  Aladul MI et al. BioDrugs. 2017; 31(6):533-544.
  Full text available here
- **Biosimilar infliximab in inflammatory bowel disease: Outcomes of a managed switching programme**
  Razanskaite V et al. Journal of Crohn's and Colitis 2017
  Full text available here
- **Biosimilars: How can payers get long-term savings**
  Mestre-Ferrandiz J et al. PharmacoEconomics 2016
  Full text available here

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