Scientific rationale for interchangeability of biosimilars in the EU

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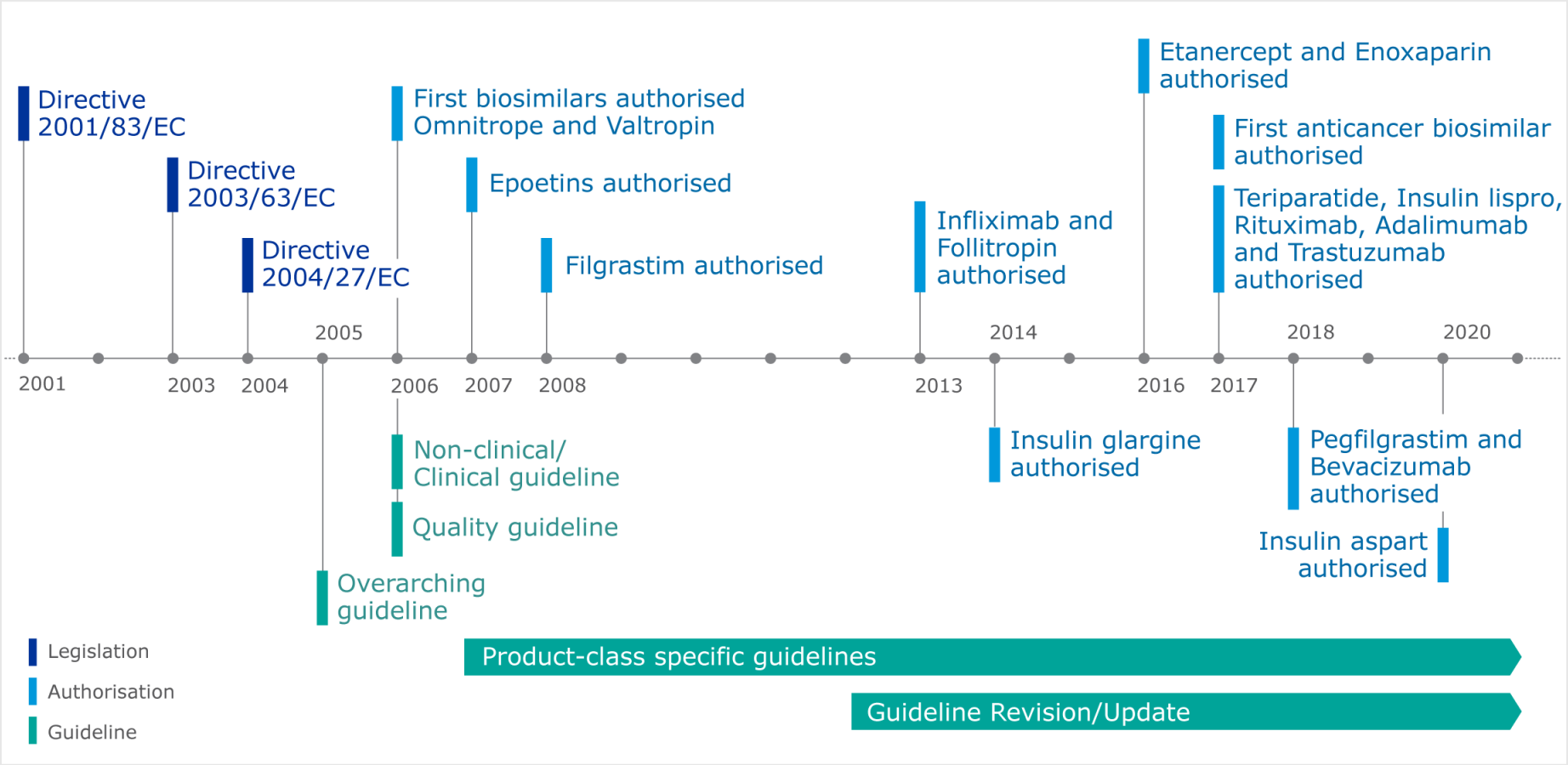
The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut or EMA.

An agency of the European Union

Evolution of Biosimilars in the EU/EEA



Biosimilars in Europe (end February 2023)*

117 **MAAs reviewed**

132 **MAAs submitted incl.duplicates**

15 **MAAs under review**

- Aflibercept (1)
- Bevacizumab (1)
- Eculizumab (2)
- Filgrastim (1)
- Insulin (1)
- Natalizumab (1)
- Pegfilgrastim (2)
- Ranibizumab (1)
- Tocilizumab (3)
- Trastuzumab (1)
- Ustekinumab (1)

2 Negative / refused

- Insulin (1); interferon alfa 2a (1)

25 Withdrawn (*pre-approval*)

- Insulin (6)
- Bevacizumab (1)
- Epoetin (1)
- Eptacog alfa (1)
- Rituximab (2)
- Pegfilgrastim (6, 2 resubmitted)
- Trastuzumab (4)
- Adalimumab (1)
- Infliximab (1)
- Teriparatide (2)

90 **Positive opinions = MA**

74

- Somatropin (1)
- Epoetin (5)
- Filgrastim (7)
- Infliximab (4)
- Follitropin alfa (2)
- Etanercept (3)
- Bevacizumab (8)
- Insulin aspart (3)
- Insulin human (1)
- Insulin glargine (2)
- Insulin lispro (1)
- Enoxaparin (1)
- Teriparatide (4)
- Rituximab (5)
- Adalimumab (10)
- Trastuzumab (6)
- Pegfilgrastim (8)
- Ranibizumab (3)

EMA scientific committees and working parties

1 Awaiting EC decision
teriparatide (1)

15 Withdrawn (*post-approval*)

- Filgrastim (2)
- Somatropin (1)
- Insulin glargine (1)
- Adalimumab (4)
- Rituximab (2)
- Enoxaparin (1)
- Pegfilgrastim (1)
- Teriparatide (1)
- Bevacizumab (2)

* Information from SIAMED

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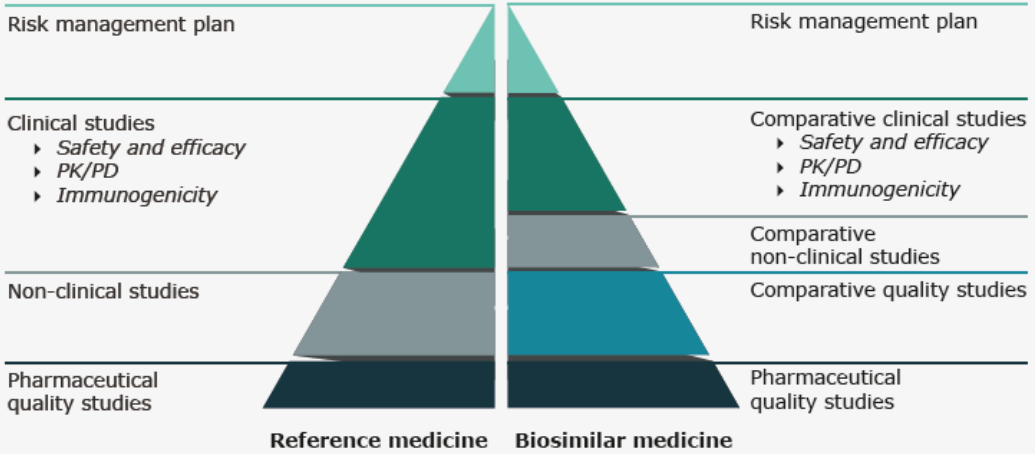
Biosimilars in the EU

Information guide for healthcare professionals

Prepared jointly by the European Medicines Agency
and the European Commission

Comparison of data requirements for approval of a biosimilar versus the reference medicine



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Manufacturing changes authorized by EMA

(EPARs of 29 mabs: Total manufacturing changes = 404)

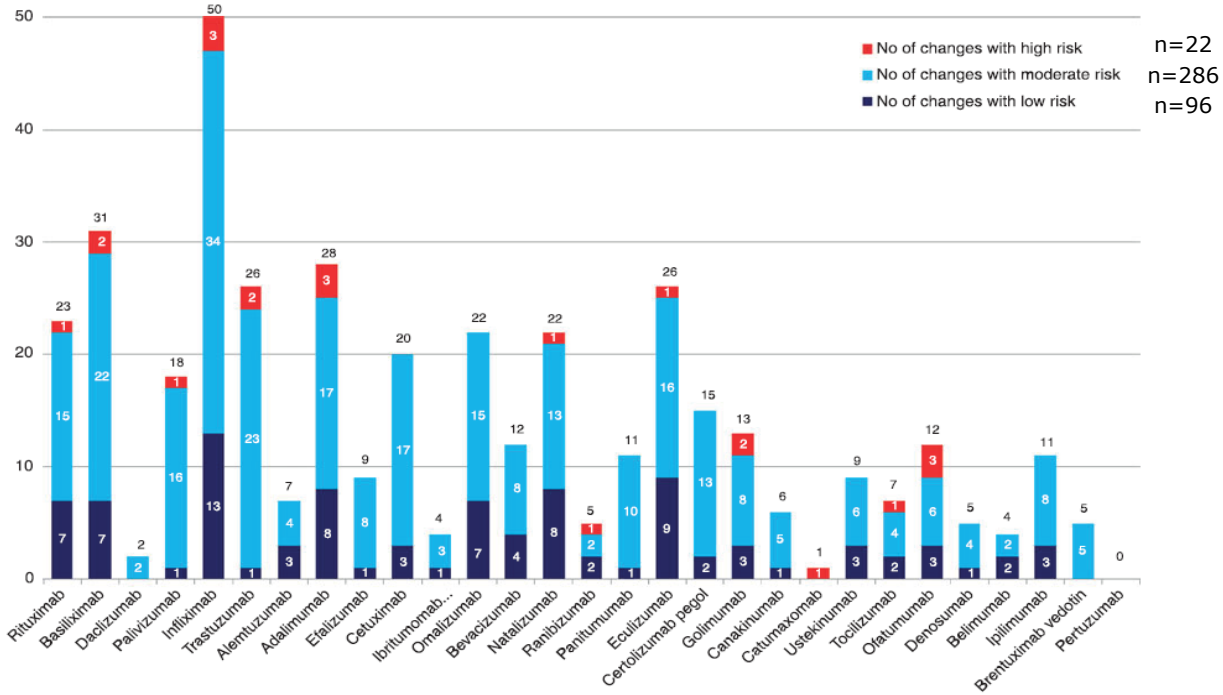

Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

*v*ezér B, Buzás Zs, Sebeszta M, Zrubka Z.: Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016 May;32(5):829-34

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Terminology so far

1. Switching
The decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent in patients who are undergoing treatment.

Interchangeability
Medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient, on the initiative, or with the agreement of the prescriber.

2. Substitution
practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber. There is no "substitutability determination" at EU level

3. Automatic Substitution (EU)
practice whereby a pharmacist is obliged to dispense one medicine instead of another equivalent and interchangeable medicine due to national or localrequirements (without consulting the prescriber)

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NOR-SWITCH study

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

Kristin K Jørgensen*, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk†, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group

Lancet 2017; 389: 2304-16
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This online publication has been corrected. The corrected version first appeared at thelancet.com on May 23, 2017
See Editorial page 2263
See Comment page 2266

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Summary

Background TNF inhibitors have improved treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, but are expensive therapies. The aim of NOR-SWITCH was to examine switching from originator infliximab to the less expensive biosimilar CT-P13 regarding efficacy, safety, and immunogenicity.

Methods The study is a randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up. Adult patients on stable treatment with infliximab originator treated in a hospital setting for at least 6 months were eligible for participation. Patients with informed consent were randomised in a 1:1 ratio to either continued infliximab originator or to switch to CT-P13 treatment, with unchanged dosing regimen. Data were collected at infusion visits in 40 Norwegian study centres. Patients, assessors, and patient care providers were masked to treatment allocation. The primary endpoint was disease worsening during 52-week follow-up. 394 patients in the primary per-protocol set were needed to show a non-inferiority margin of 15%, assuming 30% disease worsening in each group. This trial is registered with ClinicalTrials.gov, number NCT02148640.

Findings Between Oct 24, 2014, and July 8, 2015, 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group). 155 (32%) patients in the full analysis set had Crohn's disease, 93 (19%) had ulcerative colitis, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference −4·4%, 95% CI −12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for infliximab originator *vs* 21 [9%] for CT-P13; for overall adverse events, 168 [70%] *vs* 164 [68%]; and for adverse events leading to discontinuation, nine [4%] *vs* eight [3%], respectively).

Interpretation The NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. The study was not powered to show non-inferiority in individual diseases.

Funding Norwegian Ministry of Health and Care Services.

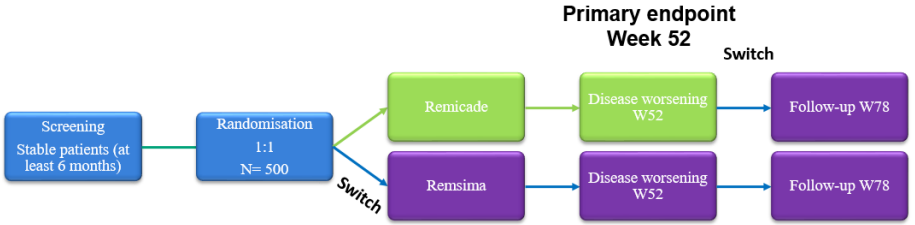
Introduction

Infliximab is a chimeric IgG1 antibody approved for treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. Across all these indications, infliximab and other tumour necrosis factor (TNF) inhibitors have substantially improved disease management.[1] However, access to TNF inhibitors varies and is inversely related to socioeconomic conditions in each country.[2] The patent for the infliximab originator (Remicade; Janssen Biologics, The Netherlands) expired in 2015 in Europe and in many other parts of the world.

The biosimilar infliximab CT-P13 was approved by the European Medicines Agency in 2013 and by the US Food and Drug Administration in 2016.

Randomised controlled trials in patients who have not previously received TNF inhibitors, comparing infliximab originator with CT-P13, have been done in ankylosing spondylitis (PLANETAS,[3] a phase 1 study) and rheumatoid arthritis (PLANETRA,[4] a phase 3 study). However, according to guidance for regulatory approval of biosimilars, CT-P13 has been approved for all six relevant indications.[5-7] This extrapolation of indication has been debated in clinical communities, especially gastroenterology,[8,9] because the mechanisms of action for infliximab might differ between indications.[10,11] Several other TNF inhibitor biosimilars have been approved or are under regulatory review and will be available for therapeutic use in the coming years.[6,12]

In Norway, an annual tender system for TNF inhibitors and related biological drugs was established in 2007.



Patients with rheumatoid arthritis, spondylarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis

→ The NOR-SWITCH trial demonstrated that switch from INX to CT-P13 was not inferior to continued treatment with INX.

Jørgensen K. et al , Lancet 2017; 389: 2304–16

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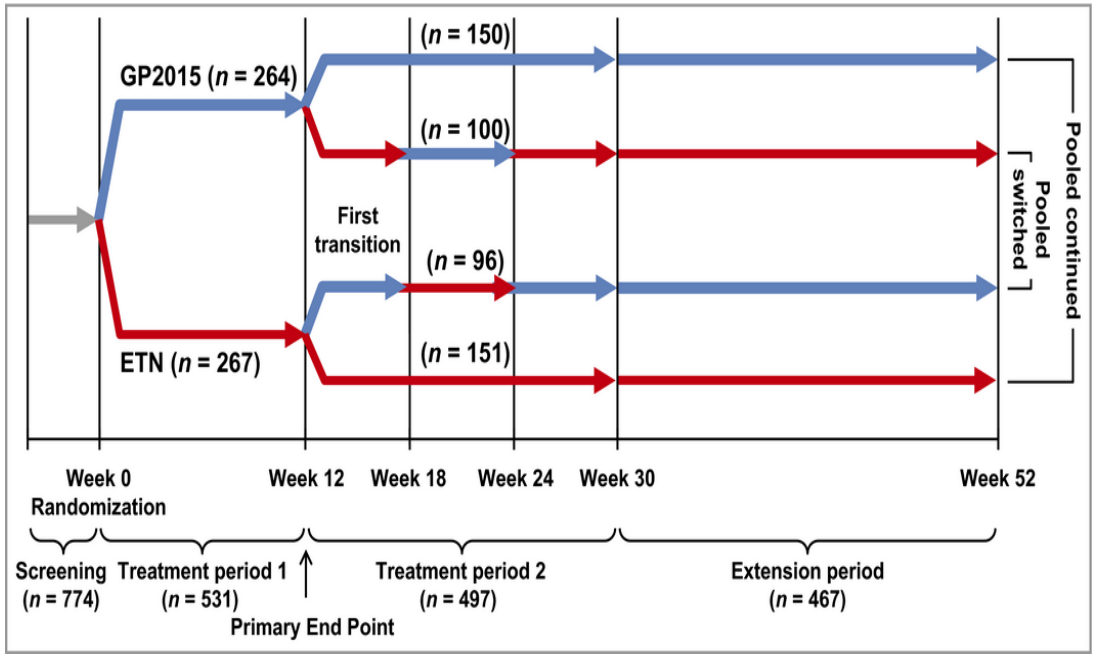
Egality study



Short Half life etanercept: T1/2= 115 hr

Phase III randomized study of the proposed etanercept biosimilar in patients with psoriasis demonstrated equivalent efficacy and comparable safety and immunogenicity of GP2015 and ETN

→ Switching treatments 3 times did not impact efficacy, safety or immunogenicity

Griffiths et al; British Journal of Dermatology (2017) 176, pp928–938

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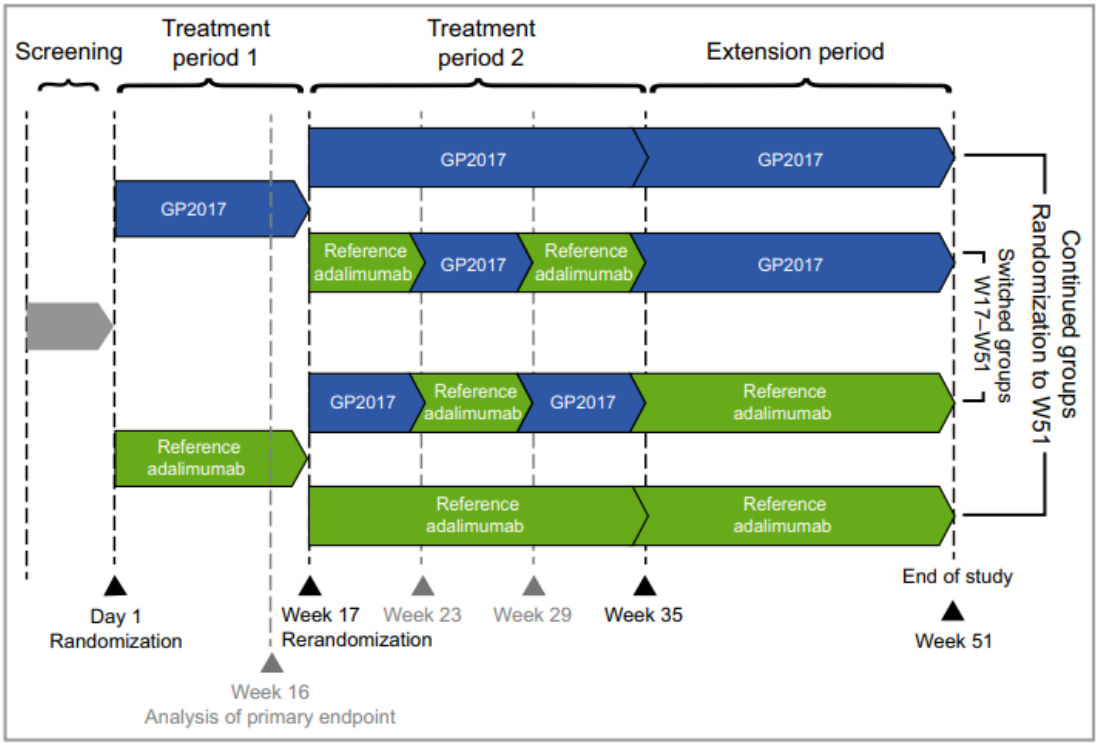
ADACCESS-Study



Phase III randomized study of the proposed adalimumab biosimilar in patients with psoriasis

→ Switching up to four times between GP2017 and ref-ADMB had no detectable impact on efficacy, safety or immunogenicity.

Blauvelt et al, Br J Dermatology; 2018 Sep;179(3)

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Ebbers et al 2012

EXPERT OPINION

1. Introduction
2. Analysis of the literature
3. Safety database
4. Current knowledge about switching
5. Discussion
6. Expert opinion

informa healthcare

Review

The safety of switching between therapeutic proteins

Hans C Ebbers, Michael Muenzberg & Huub Schellekens†
†Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutics, TB Utrecht, The Netherlands

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.

Keywords: biopharmaceuticals, biosimilars, erythropoietin, filgrastim, growth hormone, G-CSF, safety, switch, switching

Expert Opin. Biol. Ther. (2012) 12(11):1473-1485

1. Introduction

The generic approach allows copies of small molecule drugs on the market after patent expiration and loss of data protection. Because of their complexity, heterogeneity, and the lack of analytical tools to fully characterize mixtures of therapeutic proteins, competing products containing these molecules can never be produced to be fully identical to the original product. For these reasons in many parts of the world regulatory pathways for the marketing of copies of therapeutic proteins were introduced based on the principle of similarity [1]. In the past years, various terms have been applied to describe these products, including follow-on biologics, subsequent-entry biologicals, and similar biotherapeutic products; however the term accepted by both European Regulators and US regulators is "similar biological products" or biosimilars [2]. To obtain a marketing authorization the manufacturer of a competing product needs to show similarity in quality, safety and efficacy. This similarity exercise includes comparative clinical data, the extent of which is product dependent. If a product meets the similarity criteria, it may be marketed as a biosimilar. After authorization, the clinical safety of biosimilars must be monitored closely on an ongoing basis during the post-approval phase. Therefore, risk management plans need to be submitted along the marketing authorization for all biosimilars [3].

The biosimilar regulatory pathway was pioneered by the European Medicine Agency (EMA) and its scientific committee (CHMP) and has become the world standard for the authorization of copy versions of biologicals by adaption of the principles by WHO. The EMA was the first regulatory agency issuing guidelines based on the EU legislation which became effective in November 2005. Currently, seven biosimilar products, sold under 13 different brand names, are approved in the

Review of 58 clinical trials

Pharmacovigilence data bases, literature, clinical trial data bases

(HGH:13, EPO 35, Filgrastim 10)

AE Reports Summaries for safety of switching

→ **No evidence that switching to and from different biopharmaceuticals leads to safety concerns**

Ebbers, H. et al; Expert Opin. Biol. Ther. (2012) 12(11)

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Interchangeability of Biosimilars: A European Perspective

Pekka Kurki, Leon van Aerts, Elena Wolff-Holz, Thijs Giezen, Venke Skibeli & Martina Weise

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CURRENT OPINION

Interchangeability of Biosimilars: A European Perspective

Pekka Kurki[1] · Leon van Aerts[2] · Elena Wolff-Holz[3] · Thijs Giezen[4] · Venke Skibeli[5] · Martina Weise[6]

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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.

Key Points

Biosimilars are copy versions of an already existing biological medicinal product. They are high-quality products and as efficacious and safe as the original biological medicines.

Because of the high similarity, there is no reason to believe that the body's immune system would react differently to the biosimilar compared with the original biological upon a switch. This view is supported by the current experience with biosimilars on the market and by literature data.

In our opinion, switching patients from the original to a biosimilar medicine or vice versa can be considered safe.

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1 Introduction

A biological medicine can be developed to be highly similar to an existing originator biological medicine (the reference product) according to EU legislation and guidelines issued by the European Medicines Agency (EMA). Similar biological medicinal products (biosimilars) can

Kurki, P.; et al, BioDrugs (2017) 31:83-91

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- Switches between biological products with same therapeutic intent are common
- Licensed biosimilars exhibit immunogenicity comparable with their reference products which is in line with theoretical considerations
- Review of published data: epoetin, filgrastim, insulin glargine, HGH, Remsima

→ In the authors' opinion, biosimilars licensed in the EU are interchangeable if the patient is clinically monitored and receives necessary information /training on the administration of the new product.

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DANBIO-Registry

Krankheitsaktivität	3 Monate vor Switch	Switch	3 Monate nach Switch	p-Wert*
rheumatoide Arthritis, n = 933				
Anzahl Patienten	639	745	568	
DAS28	1,9	2,1	2,1	0,8
Psoriasis-Arthritis, n = 351				
Anzahl Patienten	223	253	197	
DAS28	1,8	2,0	2,1	0,1
axiale Spondyloarthritis, n = 337				
Anzahl Patienten	187	217	243	
ASDAS	1,9	1,9	1,9	0,8

→ **The study shows no effects of switches on the disease acticity**

Glintborg B, Sorensen IJ, Loft AG et al.:
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. Ann Rheum Dis 2017; 76: 1426-1431

Glintborg B, Loft AG, Omerovic E et al.:
To switch or not to switch: results of a nationwide guideline of mandatory swit-ching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. Ann Rheum Dis 2019; 78: 192-200.

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Kurki et al 2021

Drugs
https://doi.org/10.1007/s40265-021-01601-2

ORIGINAL RESEARCH ARTICLE

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

Pekka Kurki[1] · Sean Barry[2] · Ingrid Bourges[3] · Panagiota Tsantili[4] · Elena Wolff-Holz[5]

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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.

Prelicensing and Long-term

Safety

Immunogenicity and

Interchangeability

Data of all 23 biosimilar mAbs and fusion proteins

- Highly similar and interchangeable
- In line with theoretical considerations
- Concerns regarding immunogenicity upon switches are unfounded

→ Systematic switch studies are not needed

Kurki P et al; https://doi.org/10.1007/s40265-021-01601-2

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→ Interchangeability of EU-licensed biosimilars has been demonstrated.

→ Substitution should be tailored to the local circumstances, including consideration of

- methods for traceability
- need for training of patients and pharmacy personnel
- switch protocol, timing of/interval between switches
- different presentation forms
- price differences triggering a substitution

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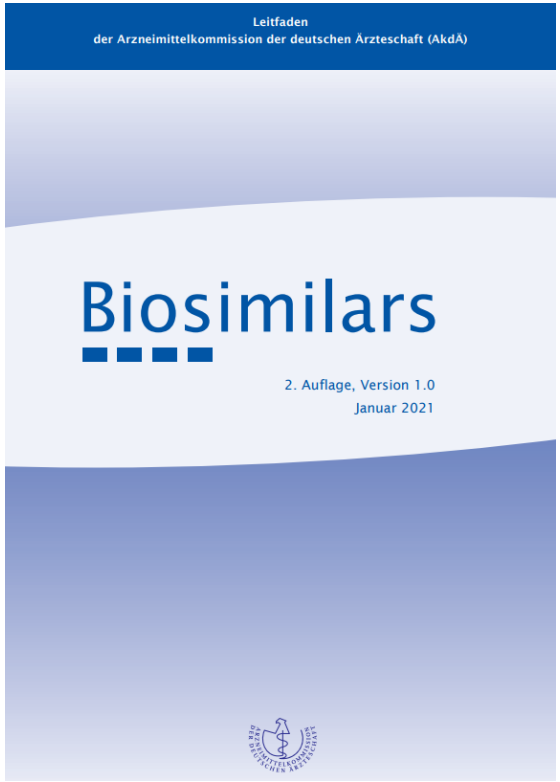
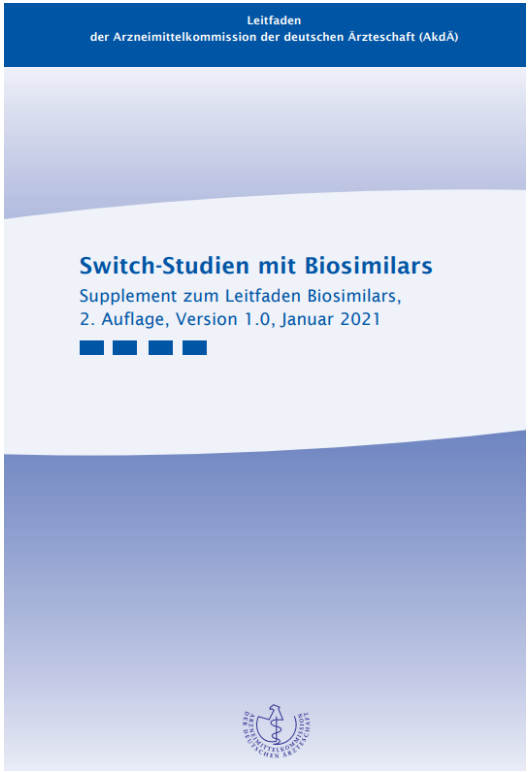
The German Physician´s perspective:





https://www.akdae.de/arzneimitteltherapie/lf/biosimilars

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The German Physician´s perspective:

There is sufficient evidence that Biosimilars

- are considered equivalent with regard to therapeutic efficacy and safety
- can be administered to patients de novo and after switch from originator
- All biologics need proper pharmacovigilance monitoring, identification by
  - relevant brand name
  - batch number
  - in addition to the active substance
- The most economical treatment option shall be chosen
- Individualized patient counseling is viewed as necessary to reduce nocebo effect. Therefore automatic substitution is currently not supported

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See websites for contact details

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