

Interchangeability of Biosimilars: A European Perspective

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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

only be marketed following expiry of the data and patent protection of the reference product [1].

The quality, safety, and efficacy profiles of biosimilars are comparable to those of their reference product. Thus, they are therapeutic alternatives that can be used instead of the reference products. Most best-selling biological products are intended for long-term use in chronic diseases. In this case, most patients who would be eligible for biosimilars are receiving long-term treatment with the reference products. Whether patients can be switched from a reference product to the corresponding biosimilar product is of major importance both in containing pharmacotherapy costs and in promoting patients' access to current and future biologicals [2–4]. The interchangeability of biosimilars is controversial [5–9], and the pharmaceutical industry is fueling the discussion [10]. Therefore, it is important to critically evaluate the potential risks of switching from a reference biological product to a corresponding biosimilar product.

In this article, 'interchangeability' means the 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. The decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent in a given patient is referred to as 'switching' [1].

This article does not deal with the automatic substitution of biosimilars, which is a practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [1].

2 Comparability in the Context of Manufacturing Changes

The manufacturing process of each biotechnological medicinal product undergoes several changes during its life cycle [11]. Changes in the manufacturing process may have a substantial impact on the product because they give rise to a new version of the product. Therefore, the new and previous versions need to be compared by appropriate tests, usually physico-chemical, structural, and in vitro functional tests, before a change in the manufacturing process can be approved [12].

The demonstration of comparability does not mean that the pre-change and post-change product are identical but that they are highly similar and that the existing knowledge is sufficient to conclude that the observed differences have no adverse impact upon safety or efficacy of the medicinal product. When differences in physico-chemical and structural properties between the pre- and post-change products

are observed and their clinical impact remains unknown, additional non-clinical and/or clinical studies need to be conducted.

The comparability approach has successfully been applied for more than 2 decades in hundreds of manufacturing changes [11]. When comparability has been demonstrated, the new version can be introduced to the market without informing prescribers, pharmacists, or patients.

3 Comparability in the Context of Biosimilarity

From the regulatory and scientific viewpoints, a biosimilar and its reference product contain different versions of the same active substance [13]. Just as comparability needs to be demonstrated in the context of manufacturing changes, the development of biosimilars is based on a comparability exercise with the biosimilar and the reference product.

This comparability exercise is built on thorough physico-chemical and structural analyses and in vitro functional tests complemented with clinical studies that are specifically designed to address remaining uncertainties after the preceding analyses and tests [13]. The practical difference between the development of a new version of the same product and the development of a biosimilar product is the much larger scale of comparisons, including clinical data, in the biosimilar scenario, because a biosimilar is developed by a different manufacturer using a different manufacturing process.

The long experience with manufacturing changes of marketed biological products in general, and of the reference products in particular, are very useful in the assessment of the potential clinical implications of differences and the magnitude of risks associated with transition from one version of the biological to another.

4 Considerations for Interchangeability

Experience with manufacturing changes of biological medicines suggests that switching from pre- to post-manufacturing change versions will very rarely trigger adverse reactions [11]. In addition, switches from one biological to another biological product that is structurally clearly different but has the same therapeutic intent, are common in healthcare [14].

Prescribers should not be misled by publications that do not distinguish biosimilars developed according to the strict requirements of the EU from other less defined copies of biological products used elsewhere [15, 16].

4.1 Switches between Comparable Products: Pharmacokinetics and Pharmacodynamics

Biosimilars and their reference products have the same mechanism of action; highly similar physico-chemical, structural, and in vitro functional properties; and comparable pharmacokinetics/pharmacodynamics, safety, and efficacy, as summarized in the respective European Public Assessment Reports (EPARs) [17]. Therefore, it is unlikely that they would behave differently in a single patient. Suggestions that two comparable versions of the same active substance with comparable pharmacokinetic profiles at the population level would have different pharmacokinetics in individual subjects are theoretical. The scientific situation in this respect is similar to that of generics where, based on demonstrated bioequivalence at the population level, individual patients can be switched between the generic and the respective reference product, even without consultation of the prescriber. The goal of pharmacokinetic studies in the context of a comparability exercise is the detection of potential product-related differences (e.g., due to differences in formulation) and should be distinguished from patient-related factors such as day-to-day intra-subject variability. There are no studies on sources of variance in comparative studies investigating biosimilars and their reference products. However, it seems likely that, as for generics, intra-subject variability rather than product-related variation plays a crucial and decisive role in the variation of drug exposure [18].

4.2 Immunogenicity

Manufacturing changes of biotechnology-derived proteins have not, except for very rare cases, triggered significant immune responses (see the following sections). The current EMA regulatory guideline for immunogenicity assessment of a biotechnology-derived protein, including biosimilars, requires that immunogenicity will always be investigated pre-approval using validated state-of-the-art methods to measure the incidence, titer, neutralizing capacity, and persistence of anti-drug antibodies (ADAs) and their correlations with drug exposure, safety, and efficacy outcomes [19].

It is expected that the immune system will recognize most therapeutic proteins [20]. However, the recognition rarely leads to harmful immune responses [21]. Biosimilars are highly similar to their reference products, and the active substance of most currently approved biosimilars mimic closely or at least partly endogenous substances of the body to which there is an immunological tolerance. Therefore, it is not unexpected that the licensed biosimilars were shown to exhibit immunogenicity comparable with their reference products.

4.2.1 Switching between Immunogenic Products

Nevertheless, some reference products are immunogenic, and an immune response might theoretically evolve towards a class switch of ADAs to immunoglobulin E (IgE). IgE-class antibodies to therapeutic proteins may lead to acute hypersensitivity [22]. Another type of evolution is epitope spreading and subsequently enhanced antibody production, leading to cross-reactive neutralizing ADAs that also target the natural counterpart of the therapeutic protein, such as erythropoietin, as has been observed in patients treated with epoetins [23].

In both cases, T-cell help is required for an enhanced immune reaction after the product switch. T-cell activation is not expected to result from a switch between comparable products since the active substances of the reference and biosimilar products have an identical amino acid sequence and because the T-cell epitopes are linear peptides. For example, infliximab antibodies against the reference product are suggested to recognize the same epitopes in the biosimilar infliximab [24, 25]. In the absence of other T-cell stimulation, aggregates and impurities might be able to bypass T cells and generate activation (danger) signals to B cells [26–29]. This possibility is well known, and the current quality standards exclude products with an unfavorable profile of product- and process-derived impurities and aggregates.

4.2.2 Immunogenicity Cannot be Excluded for Biologicals

Harmful immunogenicity is not expected to be triggered by a switch unless the new version of the reference product, after a manufacturing change or creation of a biosimilar, is of inferior quality, i.e., is not truly comparable. This risk is built into all biological medicinal products because they typically undergo several manufacturing changes during their life cycle [11, 30]. The most prominent example of a rare immunological problem is anti-epoetin antibody-induced pure red cell aplasia (PRCA) in more than 200 patients with chronic kidney disease who were switched from a previous to a new version of epoetin alfa (Eprex®) after a simultaneous change in the product formulation and the administration route [23].

Neutralizing cross-reactive anti-epoetin antibodies were also demonstrated during the clinical development of a biosimilar epoetin alfa in two patients with chronic kidney disease [31]. The antibodies evolved into neutralizing antibodies with subsequent development of PRCA-type clinical findings in one patient. It was shown that the patients had received a product containing increased amounts of aggregates due to tungsten that migrated from the syringe into the product and that mediated unfolding and aggregation of epoetin alfa [32].

Thus, both developers of biosimilars and regulators can avoid the entry of an inferior product to the market by clinical comparability studies and by learning from past experience gained with the reference product. Interestingly, the current examples of switch-related immunological adverse drug reactions were found to be caused by differences between drug formulations [23, 32] as well as by improper storage and transport conditions [33] but not by differences in active substances as often suggested in the public discussion on interchangeability and risk of immunogenicity.

Thus, an enhanced immune reaction after a switch between products containing different versions of the same active substance is unlikely but may occur very rarely towards new versions of biological products, including biosimilars.

4.2.3 Switch-Related Immunogenicity: Case Studies

Induction of an immune reaction after a switch to a biosimilar will require a difference in antigenicity between the products and lack of immunological tolerance in the host. Switches between non-comparable products provide an exaggerated model for switch-related immunogenicity. In this respect, hemophilia A may represent the worst case scenario. The development of neutralizing ADAs (inhibitors) is a serious and relatively common problem in the treatment of hemophilia A with coagulation factor products. In this situation, immunogenicity is not surprising because the patients lack the immunological tolerance to normal coagulation factor VIII (FVIII) and to coagulation factor analogs. The structures of recombinant FVIII products may be very different, but they still contain elements shared by the normal endogenous FVIII. Switching from one product to another is discouraged to avoid 'inhibitors', i.e., neutralizing ADAs. However, recent clinical studies suggest that the risk of neutralizing ADAs is not significantly increased upon switching between different coagulation factor products [34, 35].

Another example of a potential switch-related risk is that of interferon (IFN)- β -1b and IFN- β -1a in patients with multiple sclerosis [36]. These two proteins have different amino acid sequences, post-translational modification profiles, and administration routes. In a small study, patients with pre-existing neutralizing IFN- β antibodies were randomized to be switched from subcutaneous administration of IFN- β -1b or IFN- β -1a to either receive intramuscular IFN- β -1a or to continue receiving subcutaneous therapy. Neutralizing antibody titers did not change upon the switch compared with in those who did not switch.

Similarly, switching treatment from intravenous to subcutaneous formulations may be viewed as a risky

scenario because of anticipated increased immunogenicity. A study investigated switching between the intravenous and subcutaneous formulations of trastuzumab (Herceptin[®]) in patients with breast cancer. The switch was associated with an increased incidence of ADAs but not adverse events [37].

It has been stated that ADA-positive patients should not switch to a biosimilar [24]. However, clinical studies of ADA-positive patients suggest that the switch from the reference product to the biosimilar has no impact on the incidence of ADAs or the clinical outcome [25, 38–40]. Thus, a switch between comparable versions of the same active substance (as with biosimilars) does not appear to be problematic in clinically stable ADA-positive patients.

In conclusion, the observations that switching between products containing structurally different active substances, even between high-risk products, or in ADA-positive/susceptible patients did not enhance immune responses suggest that the risk of exaggerated immune reactions as a result of switching between a biosimilar and its reference products is substantially overrated.

5 Experience from Sequential Use of Biologicals

Ebbers et al. [14] reviewed the literature for studies in which patients were switched from a biological product either to a new version of the product (e.g., a new formulation) or to a related product by another manufacturer. The studies involved more than 11,000 patients. Most of the studies did not report any switch-related adverse effects, except for increased or decreased injection site reactions in two studies.

The sequential use of biological products is not uncommon in clinical practice. Switches have been reported in more than 20% of patients receiving epoetins and about 10% receiving granulocyte colony-stimulating factors (G-CSFs) in less than 2 years. Switches may involve competing products from different manufacturers or the original and modified second-generation products from the same manufacturer [14].

5.1 Switching From a Reference Product to its Biosimilar Version

The development programs of some biosimilars included studies that involved switches from the reference product to the biosimilar and vice versa. The EPARs available on the EMA website describe the development programs of the authorized biosimilars and provide substantial evidence for the safety of a switch [17].

5.1.1 Omnitrope® (Somatropin)

During development of the first version of the biosimilar, 44 patients treated with the reference product and 45 patients treated with the biosimilar were compared in a clinical trial. The efficacy and safety of the products were comparable, but the biosimilar was more immunogenic because of impurities. In the next part of the study, the same patients were switched to new improved versions of the biosimilar. No changes in efficacy or safety were observed, and ADAs continuously decreased after the switch to the improved biosimilar.

5.1.2 Epoetin Alfa Hexal®, Binocrit®, Abseamed® (Epoetin Alfa, HX575)

In a randomized pivotal efficacy and safety study, 314 patients with renal anemia treated with the reference product intravenously were switched to the HX575 biosimilar and followed for 54 weeks. Additionally 117 patients were later switched from the reference product to the biosimilar and followed for 26 weeks. Overall, no differences in safety, immunogenicity, or efficacy profiles were demonstrated following the switches.

5.1.3 Silapo®, Retacrit® (Epoetin Alfa, SB309)

A randomized crossover phase III trial in 313 patients with renal anemia found similar safety, immunogenicity, and efficacy profiles between the biosimilar and the reference product. In this study, half of the study population was switched twice: at randomization and again at crossover.

5.1.4 Zarzio® (Filgrastim)

Two pharmacokinetic and pharmacodynamic crossover studies of subcutaneous administration involved 96 healthy volunteers; two pharmacokinetic and pharmacodynamic studies with single administration and crossover studies involved 50 patients. The biosimilar and the reference products had similar safety, immunogenicity, and efficacy profiles after switching.

5.1.5 Nivestim® (Filgrastim)

A randomized, multiple-dose, active comparator-controlled, two-way crossover study was conducted. Subjects ($n = 24$) received five doses of subcutaneous filgrastim during each treatment cycle. The pharmacokinetic, pharmacodynamic, and safety profiles were not dependent on the treatment sequence.

5.1.6 Abasaglar® (Insulin Glargine)

The phase III study in type I diabetes mellitus compared the biosimilar insulin glargine against the reference product in 536 adult patients in combination with mealtime insulin lispro. In total, 85% of the patients were receiving the reference product before randomization into the biosimilar or the reference product arms. In this subgroup, no relevant differences in efficacy, safety, or immunogenicity were observed between the switch-to-biosimilar group and the reference group.

5.2 Other Data for Switches Involving Biosimilars

5.2.1 Omnitrope® (Somatropin)

Flodmark et al. [41] studied 98 children who switched to biosimilar somatropin (Omnitrope®) from its reference product. The switch was not associated with deviation from the expected height velocity during the monitored period as predicted by modelling. There were no serious or unexpected adverse events following the switch. Similar results were reported by Romer et al. [42] and Rashid et al. [43].

5.2.2 Erythropoiesis-Stimulating Agents

The efficacy of treatment with erythropoiesis-stimulating agents (ESA) is monitored and the treatment adjusted according to response. On the basis of a population analysis in patients with renal anemia, it was concluded that ESA consumption and persistence with treatment was not affected following a switch from the reference product to a biosimilar, indicating that efficacy and tolerability was similar for biosimilar and reference ESAs [44].

5.2.3 Remsima®, Inflectra® (Infliximab)

Two randomized parallel-group studies were conducted, one in patients with ankylosing spondylitis and the other in patients with rheumatoid arthritis. The long-term extension included a switch from the reference product to the biosimilar. Preliminary results at week 52 of the long-term follow-up studies (until week 102) for those who switched from the reference to the biosimilar suggest that safety, efficacy, and immunogenicity were comparable in the biosimilar maintenance and the biosimilar switch (from reference to biosimilar) groups [45, 46]. Small prospective and retrospective clinical studies have explored the safety and efficacy of switching from a reference product to biosimilar infliximab products in a mixed rheumatological cohort [47], in those with ankylosing spondylitis [39] or

psoriasis [48] and in pediatric [49] and adult patients [38, 50, 51] with inflammatory bowel disease (IBD). Results of these studies do not raise concerns about the safety or feasibility of switching.

A large controlled switch study of biosimilar infliximab (NOR-SWITCH) with a primary endpoint of disease worsening at 52 weeks involved 481 adult patients with rheumatism, psoriasis, or IBD on stable treatment with reference infliximab. Disease worsening occurred in 26.2 and 29.6% in the reference and biosimilar arms, respectively. The adverse event profiles were comparable [52].

5.2.4 Flixabi[®] (Infliximab)

Phase III results of the second biosimilar infliximab have been reported as a poster [53]. After 54 weeks, 94 patients treated with the reference product (Remicade[®]) were switched to SB2 (Flixabi[®]), while 101 patients continued treatment with the reference product and 201 patients continued SB2 treatment until week 78. The efficacy and safety profiles as well as the incidence of ADAs were comparable in the treatment arms during the switch period.

5.2.5 Emerging Interchangeability Data on Etanercept and Adalimumab

Controlled data on switching back and forth between original etanercept (Enbrel[®]) and biosimilar etanercept (GP2015) as well as data on switching from original adalimumab (Humira[®]) to a biosimilar adalimumab (ABP 501) were presented at the US FDA arthritis advisory committee meeting in July 2016 [54]. The data did not give cause for concern. These biosimilars have not been licensed in the EU at the time of the writing of this article.

5.2.6 European Database for Suspected Serious Adverse Reactions

Ebbers et al. [14] reviewed the EudraVigilance database, which covers suspected serious adverse drug reactions reported to the regulatory authorities in the EU, Norway, and Iceland. The EU has a very good signal-detection system via the EudraVigilance database. Search for possible switch-related serious adverse reactions produced only three reports of possible adverse effects in which both an originator and a biosimilar product were used in a patient. The lack of safety signals provides further

reassurance of the safety of switching between the reference medicinal product and the biosimilar.

6 Discussion

6.1 Interchangeability Studies

In the USA, interchangeability is defined in the legislation and corresponds to automatic substitution in the EU terminology, where interchangeability means 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 [1]. Thus, the European type of interchangeability is not a legal but a scientific and medical term.

For the time being, there are no plans at the EU level to introduce new legal or regulatory requirements for interchangeability studies and thus create two classes of biosimilars. Nevertheless, there is ongoing discussion on the need for specific interchangeability studies in the EU. Proponents of interchangeability studies claim that two independently developed biologicals cannot be classified as interchangeable without specific studies evaluating multiple switches between the reference product and the biosimilar in comparison with a group not undergoing switches. In the absence of data on interchangeability between biosimilars of the same reference product, such biosimilars are also deemed not interchangeable [8, 55]. Unfortunately, there are no detailed descriptions of the proposed interchangeability studies of biosimilars since there are major scientific and practical challenges.

The considerations and switch data presented in previous sections suggest the potential impact, if any, of a switch is subtle or rare. Therefore, and because of confounding factors, such as the fluctuating course of chronic diseases, varying intra-patient pharmacokinetics, intra- and inter-observer variability in assessing disease activity, concomitant diseases and/or medications, and batch-to-batch variation, specific interchangeability studies would need to be of substantial size [3, 56]. In our opinion, the feasibility and benefit of such studies is questionable but they might discourage biosimilar development. Instead, we believe that interchangeability can be supported adequately by state-of-the-art physico-chemical, structural, and in vitro functional testing complemented by clinical equivalency in a representative therapeutic indication at the population level. In addition, active post-marketing surveillance of switch-related adverse events by registries and by improved adverse event reporting and analysis will provide the necessary safety net. Such an approach will require action not only by developers and regulators but also by prescribers.

6.2 Practical Aspects of Interchangeability

Clinically significant differences in efficacy between the biosimilar and its reference product are ruled out with reasonable certainty by the comparability exercise. Thus, no change in dosage or dosing regimen is warranted when a patient is switched from a reference product to its biosimilar. In chronic diseases in which biosimilar use is anticipated, patients are already monitored regularly, supporting a safe switch between a biosimilar and the reference product. Patients should receive information about the switch in the same way as for any new medication. Patient education would be needed for different administration devices, such as autoinjectors.

In the EU, physicians and/or pharmacists should always document the specific biological medicinal products they prescribe for or dispense to their patients, including trade name, international nonproprietary name (INN), and batch number. This also applies to the reporting of adverse events to allow for proper root cause analysis. Traceability of biosimilar products based on trade name has been reported as very good in the EU [57], whereas recording of batch numbers was poor for biologicals in general and should be improved.

Switching between biological medicinal products is common in routine healthcare [14]. There are recommendations on switches between non-biosimilar biological products, including those targeting the same antigen/receptor [58–60], whereas several position papers of medical societies do not regard current biosimilars as interchangeable. However, the latter view is changing with improved understanding of the biosimilarity concept among prescribers and with the increasing experience in switching [61].

There is no official position on interchangeability of a biosimilar at the EU level. Instead, several national regulatory authorities, including the Dutch Medicines Evaluation Board (MEB), the Finnish Medicines Agency Fimea, Healthcare Improvement Scotland, the Irish Health Products Regulatory Authority, and Paul Ehrlich Institute in Germany, have already taken national positions to endorse the interchangeability of biosimilars under the supervision of the prescriber [62–66].

7 Conclusions

The analysis of the theoretical grounds of potential switch-related adverse effects, data on switching between non-biosimilar biological products, and experience with switches between biosimilars and their reference products suggests that the potential risks have been exaggerated. In the EU, specific switching studies are required neither by

legislation nor by regulatory guidelines. Attempts to provide proof of lack of any switch-related changes in efficacy or safety, including immunogenicity, by specific interchangeability studies would be very demanding and likely still unable to provide definite answers. Our conclusion is that a state-of-the-art demonstration of biosimilarity, together with intensified post-marketing surveillance, is a sufficient and realistic way of ensuring interchangeability of EU-approved biosimilars under supervision of the prescriber. In the authors' opinion, biosimilars licensed in the EU are interchangeable if the patient is clinically monitored, will receive the necessary information, and, if needed, training on the administration of the new product.

Acknowledgements The authors thank Drs. Meenu Wadhwa and Christian Schneider for their valuable expert comments during the preparation of the manuscript. The generous help of Ms. Mira Juppi is also gratefully acknowledged.

Author contributions PK conceptualized the idea for the study. The manuscript was written by PK, LvA, EW-H, TG, VS, and MW.

Compliance with Ethical Standards

Conflict of interest PK, LvA, EW-H, TG, VS, and MW have no conflicts of interest. They are employees of national regulatory agencies. However, the opinions expressed in this article represent the personal opinions of the authors.

Funding No funding was received for the preparation of this manuscript.

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