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Are we ready to close the discussion on the interchangeability of biosimilars?

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Since the introduction of the first biosimilar the discussion about their interchangeability has persisted. The body of evidence gathered for biosimilars provides reassurance that they are approved based on a rigorous comparability exercise and do not show clinically meaningful differences to their reference products. There are no data suggesting that the risk of switching to a biosimilar in terms of increased immunogenicity is greater than switching between two batches of any biologic. The key concern around switching biosimilars is the nocebo effect, which reinforces the need for physician involvement when switching. Whereas this might argue against automatic substitution of biosimilars, it is not a biosimilars-specific concern. To increase physician confidence in biosimilars, regulators should acknowledge that biosimilars are interchangeable.

Introduction

Biosimilars are competing versions of biologic products where patent protection and marketing exclusivity have expired. They are authorized on the basis of a comprehensive biosimilar comparability exercise, demonstrating similarity in terms of quality, nonclinical and clinical parameters. The first biosimilar was introduced in the EU in 2006, as of 1 st May 2019, there are 54 authorized products in the EU and 19 in the USA (Fig. 1). In Europe, biosimilars have become a reality, with some biosimilars achieving market share of >90% [1]. In the USA, the uptake of biosimilars has been modest thus far. As experience with biosimilars has accumulated, the debate surrounding the use of these products has evolved from questioning the validity of the biosimilar comparability exercise as a paradigm for approving products to questioning the possibility of extrapolating clinical data to indications not studied in randomized controlled trials [2,3]. Although the debate on approving biosimilars and extrapolating indications has waned, concerns about switching patients from a reference product to a biosimilar, or between biosimilars, remain [4].

Interchangeability is a product characteristic that means that a medicine can be exchanged for another with the same clinical effect. There are different ways of interchanging. Switching is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent, whereas (automatic) substitution is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [5]. Here, we discuss regulatory approaches toward interchangeability with a focus on the FDA and European Medicines Agency (EMA) and provide our perspective on concerns about interchanging biosimilars.

Current regulatory situation regarding interchangeability

Only the USA distinguishes between interchangeable products and biosimilars, which is laid down in the Biologics Price Competition and Innovation Act of 2009. The FDA has the authority to designate biologics to be interchangeable and thus substitutable, if permitted by state laws. In May 2019, the FDA released its finalized guidance that describes requirements to establish interchangeability covering four major topics [6]:

- Data and information needed to support a demonstration of interchangeability.
- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability.

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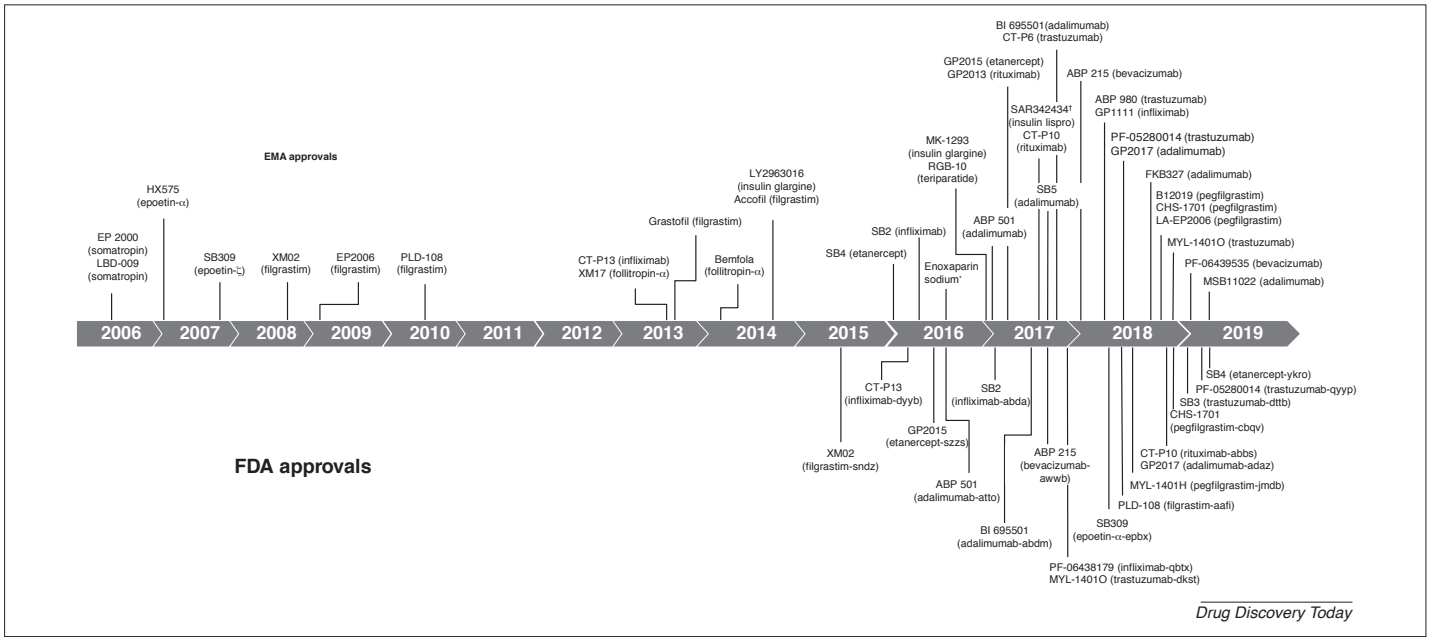

FIGURE 1

Timeline of biosimilar therapeutic approvals by the European Medicines Agency (EMA) (top) and FDA (bottom) up to April 30th, 2019. Developmental drug name followed by international nonproprietary name (INN) in parentheses (brand names were added where development names could not be identified). One version of an active substance can be registered under multiple brand names. For the US-approved products, the four-letter suffix was added for each product.
*Not considered a biosimilar by the FDA; but approved on the basis of an abbreviated new drug approval (ANDA).
†Approved on the basis of a new drug approval (NDA) in the USA.

- Considerations regarding the comparator product in a switching study or studies.
- Abbreviated considerations for developing presentations, container closure systems and delivery device constituent parts for proposed interchangeable products.

The EMA does not make a distinction between biosimilars and interchangeable products and has abstained from taking an official position on the interchangeability of biosimilars, because prescribing practices and advice to prescribers fall under the responsibility of member states [7]. However, individual members of the Biosimilar Medicinal Products Working Party (BMWP) have commented that products should be interchangeable [8]. Several European countries, including The Netherlands, Finland, Germany and Italy, have released statements declaring that biosimilars can be interchanged under the supervision of the treating physician, provided that patients are well informed and adequately followed up, and traceability is ensured [9]. Substitution on the level of the pharmacist, without involvement of the prescriber, is not allowed in most European countries. To date, no interchangeable products have been approved in the USA. Australia has mostly adopted EU guidance for the development of biosimilars and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) has designated several biosimilars (e.g., etanercept, adalimumab and infliximab) to be interchangeable/substitutable without the need for additional studies [10]. Health Canada has stated that the decision to switch a patient being treated with a reference biologic drug (innovator product) to a biosimilar should be made by the treating physician; the authority to declare a product to be interchangeable lies with the provinces [11].

Is immunogenicity a concern when interchanging?

The FDA considers that the risk of increased immunogenicity following repeated switching is a key concern when establishing interchangeability; unlike the EMA, which states that there is 'no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines' [7].

The immunogenicity of biopharmaceuticals has been extensively studied in the past 15 years and there are no data in the >16 000 papers published about the immunogenicity of biopharmaceuticals that suggest an association between immunogenicity and switching between biologics. As far as a risk of switching does exist, it is unlikely to be greater than the risk of switching between two different batches of a biological. In the pre-biosimilar era physicians were switching between biopharmaceuticals such as growth hormones, epoetins, interferons and factor VIIIs without problems in terms of immunogenicity. An often-used study concerned the development of antibodies in factor VIII users after being switched between different originator products. In this case, loss of efficacy was attributed to neutralizing antibodies. This study, however, was in a small number of patients who differed in their factor VIII gene defect, which influences the sensitivity for immunogenicity in hemophilia patients and later studies could not confirm this observation [12]. Measures have been taken to ensure proper traceability of biologics and no product-specific safety concerns have been identified for a biosimilar, providing ample reassurance that any potential safety concern can be attributed to the correct product [13].

Two recently published systematic reviews that evaluated all available data on switching to biosimilars did not identify any study that reported clinically relevant increased immunogenicity following a switch to a biosimilar [14,15]. It must be noted that most real-world data on switching were derived from studies investigating the biosimilar infliximab and less data are available for other products, for example in oncology. McKinnon *et al.* conclude that sufficiently powered and appropriately designed clinical studies are needed to facilitate decision making on biosimilar interchangeability. To perform dedicated studies to exclude risks

for rare or long-term safety events for products that are shown to be very similar in the lab and in the clinic would require very large patient numbers. The costs of such studies would probably affect the price discounts that can be offered by biosimilars. Although most of these studies were not designed to identify differences in rare events, the combined data reassure that no unexpected immunogenicity has occurred after switching. Data from several studies have also confirmed that the immunodominant epitopes that are recognized by anti-drug antibodies (ADAs) against infliximab and adalimumab are the same for the innovator and biosimilars [16–18]. Taken together, current data do not indicate any differences in incidence and specificity of antibodies against biosimilars and reference products.

Is there a need for dedicated switch studies?

A major element of the FDA guidance is the need to provide clinical data in the form of alternating studies to support a designation of interchangeability. Such studies need to include a comparison of patients that receive continuous treatment versus patients whose treatment is alternated (i.e., contain at least three consecutive switches) as is mandated by the Biologics Price Competition and Innovation Act. The Guidance states that the endpoint for interchangeability studies should assess clinical pharmacokinetics (PK) and pharmacodynamics (PD), because these assessments are generally most likely to be sensitive to changes in exposure and/or activity, as well as immunogenicity. Although there have been no published studies to date that have performed intensive PK sampling during alternating, as is proposed by the FDA, data from randomized controlled trials (RCTs) and real-world switches have thus far not reported any change or significant differences in PK parameters following a switch to a biosimilar [19–21]. Furthermore, the alternating design in biologic-naive patients, which have been applied in clinical studies to support the authorization of biosimilars might not be representative for patient populations that are switched in real life. For example, alternating data obtained from a group of biologic-naive psoriasis patients (initiated on an adalimumab biosimilar candidate) who are switched three times within an 18-week time frame might not address clinician concerns about switching patients that have been on stable treatment for several years – an interchange scenario that is more likely to occur in a real-life clinical setting.

Currently, no dedicated interchanging trials are required in the EU. Members of the BMWP questioned the feasibility and benefit of such studies. Given the need to demonstrate similarity using state-of-the-art methods, any residual uncertainty will be very small, a fact that would take very large studies to address. Instead, they state that interchangeability can be supported adequately by the current data required to establish biosimilarity, supplemented by active post-marketing surveillance of switch-related adverse events, by registries and by improved adverse event reporting and analysis, as a safety net [8].

Sourcing of a comparator product

FDA guidance recommends alternating studies to be performed using US-licensed reference products, arguing that there could be subtle differences between the US-licensed reference product and the non-US-licensed comparator product that might not lead to identifiable differences in a head-to-head comparison of patients continuously treated with the biosimilar candidate or reference product but, could lead to immunological reactions following multiple exposures to the two products [6]. Although the use of a non-US-licensed reference product is allowed it might require extensive bridging data. What is not addressed in the FDA guidance is that biosimilars and their products have independent lifecycles, meaning that following manufacturing changes no comparison between two products is required [15]. This could imply that clinical studies confirming continued interchangeability could be required following manufacturing changes that affect quality attributes. Such differences have been observed for several originator biologics, including etanercept, rituximab and trastuzumab, but have never raised questions about interchangeability [22,23]. Also, the question remains how to deal with other biosimilar or interchangeable products, would there be a need to do comparative clinical studies with them too? FDA guidance is limited to establishing interchangeability to a reference product, leaving the question of interchangeability between interchangeable biosimilars unanswered. In Europe, several national regulatory agencies have released statements declaring that switching among biosimilars is permitted under the guidance of the treating physician, whereas Australia has deemed several different biosimilars of the same active substance interchangeable and substitutable.

There is at this moment little clinical evidence comparing the switching of multiple biosimilars, but preliminary data from infliximab biosimilar-to-biosimilar switch experiences do not raise any safety or efficacy concerns [24]. Direct comparisons of physicochemical properties and biological activity could also be supportive in excluding relevant differences between multiple products, as has been shown for infliximab [25].

Differences in administration devices for self-administered biosimilars

Products can be available in different presentations to their reference products, which, without proper guidance from a healthcare provider, could lead to inappropriate use by patients or caregivers. FDA guidance requires sponsors to provide data and information supporting the appropriate use and performance testing of the delivery device constituent part of the proposed interchangeable product [6]. This point has been largely ignored in European discussions on interchangeability but can be an important determinant for the safe and effective use of products administered by patients themselves or their caregivers. The fact that in Europe it is mostly recommended that switching takes place under the supervision of the prescriber could make this less of a concern, as compared with a situation where products are substituted at the level of the pharmacy. The Australian PBAC also noted differences in injection devices for etanercept and adalimumab products, but stated that these are 'likely to be minor and can be managed through the regular patient education and counselling on the use of the devices that is provided to patients by prescribers and pharmacists' [10]. Although concerns about different administration devices are valid, these are not specific for biosimilars.

Current evidence on switching points to nocebo effects as a driver for differences in discontinuation rates

Several recent comprehensive reviews on the accumulated experience of switching biosimilars concluded that switching from the reference product to a biosimilar in the blinded controlled setting did not identify any relevant differences in terms of safety, efficacy or discontinuation rates between biosimilars and their reference products [14,15]. However, some safety concerns have been observed in open-label (extension) studies and observational studies. Several recent observational studies reported that patients switching to biosimilar etanercept discontinued treatment more frequently compared with the reference product [26–28]. Differences in discontinuation rates were mainly due to unspecific adverse events and changes to subjective outcomes, which could not be corroborated with objective

clinical or laboratory results. Nikiphorou *et al.* noted that several patients who were switched to CT-P13 from reference infliximab switched back without objective deterioration of disease, potentially owing to negative expectations of the biosimilar being perceived as a 'cheap copy' [27]. An observational study using data obtained from the Danish DANBIO registry showed that rheumatoid arthritis patients who were initially switched to the biosimilar etanercept SB4, but switched back to reference etanercept for efficacy reasons, had significantly lower (self-reported) patient global assessment scores, but demonstrated no change in objective parameters such as C-reactive protein levels and swollen joint counts [28]. Two studies investigating CT-P13 and SB4 also observed differences in subjective health complaints, but not in objective health complaints that could be verified by the investigators [26,29]. The view that nocebo effects are the main determinant for the higher-reported discontinuation rates in biosimilars is strengthened by the observation from the German RABBIT Registry that stated in naive patients starting SB4 there were no observed differences in discontinuations compared to the reference product [30]. These examples suggest that nocebo effects explain most of the observed differences in discontinuation rates in patients that are switched to a biosimilar.

Concluding remarks

We believe that there is now sufficient evidence to conclude on the robustness of the way biosimilars are developed and approved by regulatory agencies. Based on currently available data, there is no reason to doubt that biosimilars are interchangeable and that the risk of increased immunogenicity of switching to a biosimilar is no greater than switching between two batches of any biologic. We argue that the default should be that biosimilars are interchangeable, unless there is compelling evidence otherwise. The FDA's position to require blinded interchangeability studies aimed at identifying differences in PK and/or clinical parameters is not likely to provide the definitive clinical evidence on switching in clinical practice. A wealth of data from blinded RCTs that has accumulated in the past 12 years has provided assurance that switching to a biosimilar does not lead to loss of efficacy or an increase in adverse events [14,15]. Although open-label and observational studies have reported safety concerns in certain cases, these mostly point to nocebo effects as the driver of observed safety issues when switching.

Does this then mean that biosimilars should thus be automatically substituted without the involvement of the prescriber? There could be reasons to limit substitution; however, none of these is unique to biosimilars. Differences in devices could lead to the inappropriate use of medication, which highlights the need for physician involvement when switching to explain the proper use of the administration device. Nocebo effects are valid symptoms associated with all kinds of medication use that need to be given serious attention because they could lead to unnecessary discontinuation of treatment in some patients, which could be driven by a lack of healthcare professional confidence in biosimilars. The EMA, as the expert authority on medicinal products in the EU, should take an official position on the interchangeability of biosimilars. A harmonized regulatory position that there are no differences between biosimilars that preclude interchanging would allow the discussion to focus on questions that are most relevant when switching to biosimilars, such as ways to reduce nocebo effects. For biosimilars to deliver on the promise of cost savings, patients and physicians should be confident that they can be safely and effectively switched.

Conflicts of interest

Hans Ebbers is an employee of Biogen, and therefore receives a salary and may own Biogen stock. Huub Schellekens has no competing interests to declare.

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