Drugs (2021) 81:1897–1903
https://doi.org/10.1007/s40265-021-01629-4

COMMENTARY

Interchangeability of Biosimilars: Overcoming the Final Hurdles

Liese Barbier[1] · Arnold G. Vulto[1,2]

Published online: 2 November 2021

1 Introduction

April 2021 marked the 15th anniversary of the first biosimilar approval in Europe and, by extension, worldwide. In the US, the first biosimilar approval followed in 2015. Biosimilars are highly similar versions of originator biological medicines, which are approved according to the same standards of pharmaceutical quality and have comparable efficacy and safety in patients. Biosimilars offer important benefits to society as their market introduction has been shown to reduce costs and increase patient access to important and often expensive biological therapies. Currently, biological medicines account for approximately 40% of total pharmaceutical expenditure in Europe, and this share is projected to further rise over coming years [1]. As such, the introduction of biosimilars to the market is an essential and necessary way to manage this growing segment and improve the affordability and accessibility of biological medicines for patients and our healthcare systems.

2 Biosimilars: A Science-Driven Development that has been Met with Reluctance

While biosimilars are similar to an original biological medicine, they should be regarded as a real science-driven innovation in drug development. Biosimilars are based on the principles of reverse engineering, and the emphasis of their development lies in analytical and functional testing through sophisticated technology. However, both the biosimilar development model and the applied underlying science are not part of the knowledge world or expertise field of most physicians. Moreover, clinical trials, traditionally a gold standard for the demonstration of efficacy and safety of originator medicines in patients, play only a confirmatory role in the similarity exercise that underpins the development and evaluation of biosimilars. Rather than demonstrating de novo efficacy or safety, the biosimilarity exercise aims to show a highly similar product with comparable efficacy and safety to the originator biological medicine (the so-called reference product). Bringing these elements together, it is understandable that many physicians had difficulties accepting the biosimilar development paradigm. This may have been aggravated by the fact that many physicians have a rather poor understanding of biological medicines in general. Conversely, it may be argued that there is a certain dichotomy between the generally swift embracement of innovative medicines—for which the available evidence is in some cases limited at the time of approval—and the reluctance among prescribers towards biosimilars, despite their development and evaluation being science driven and grounded in the knowledge of and experience with the reference product for a decade or more. One would expect that the academically trained medical community would embrace a new development paradigm if it were shown to be scientifically robust. Already in 2007, Moors [2] described five key challenging factors for the adoption of innovations in medicine, and biosimilars in particular:

- Relative advantage: What is the advantage of the innovation over the existing therapy?
- Compatibility: To what degree is the innovation perceived as compatible with the experience and knowledge of the potential adopter?
- Complexity: To what degree is the innovation perceived as complex to integrate in clinical practice?
- Trialability: To what degree can the innovation be experimented with before adoption?

✉ Arnold G. Vulto
a.vulto@erasmusmc.nl; a.vulto@gmail.com

Liese Barbier
liese.barbier@kuleuven.be

[1] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, 3000 Leuven, Belgium

[2] Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

- Observability: To what degree are the advantages of the innovation clearly observable by the adopter?

Still, 15 years after the first biosimilar approval, many physicians (and therefore also patients) remain reluctant to use biosimilars, especially when doing so involves switching patients from the reference product to a biosimilar. While considerable experience has been gained with biosimilars—both with their evaluation and with their safe use in clinical practice—doubts remain, particularly about their interchangeability with the originator biological. As defined by the European Medicines Agency (EMA), interchangeability refers to the possibility of exchanging one medicine for another that is expected to have the same clinical effect. This could mean replacing an originator biological with a biosimilar or vice versa or replacing one biosimilar with another [3]. Such a replacement can be done either by switching (done by the prescriber) or by substitution (at the pharmacy level). The interchangeable use of biosimilars is especially relevant for more complex monoclonal antibody (mAb) biosimilars, as these are often used in chronic treatment. Furthermore, questions regarding switching multiple times and between biosimilars of the same reference product are pertinent for clinicians given the evolving and increasingly complex biosimilar landscape, which includes the availability of often multiple biosimilars per reference product. While the evaluation and approval of biosimilars generally takes place at the centralized European level through the EMA, guidance on and decisions regarding their interchangeable use, switching, and substitution are a national matter, i.e., up to the individual EU member states.

Although the uptake of biosimilars has been challenged—resulting in slow and variable uptake across European countries—their societal value has been clearly established over past years [4]. Biosimilars offer a lower-cost alternative for often very expensive biological originator medicines. Furthermore, competition in the market reduces the prices of originators and other competitors also. The lower treatment cost means more patients can be treated with biologicals and possibly also in earlier phases of their disease. In addition, budget is freed for reimbursement of new innovative medicines. Hence, biosimilars offer much-needed advantages for healthcare systems, payers, patients, and stakeholders alike and, as such, offer the opportunity to improve the sustainability of healthcare budgets. The latest IQVIA report on biosimilar competition in Europe estimated that biosimilar competition now offers, on average, around 10% savings on the overall pharmaceutical budget in the European market [1].

There are many reasons why physicians remain reluctant to prescribe biosimilars and switch their patients from an originator biological to an equally safe and effective alternative at considerably lower costs. The term biosimilar indicates that these medicines are not identical but "only" similar to the reference product. This "similar but not identical" paradigm has triggered questions about their sameness in terms of patient outcomes. Furthermore as explained, the evidence underpinning their similarity is largely based on technology that the average physician has little knowledge of. European regulators have made considerable efforts over recent years to convey the science behind biosimilar development and evaluation to healthcare professionals and patients; however, somehow, much of the published evidence and developed information material, from regulators and others, seems to have not reached prescribers and patients/patient organizations sufficiently. Barbier et al. [5] recently found that—despite strong EU-level guidance on biosimilars—the websites of the national medicines agencies in about half the European countries included no or limited information and guidance on biosimilars and their use. In 2019, Cohen and McCabe [6] reported that innovative companies use this situation to spread misinformation and disparaging statements about biosimilars, exacerbating the knowledge gap and undermining trust in their safety. The stakes for originator pharmaceutical companies are high, as biosimilars often introduce competition for multibillion dollar products. To add to the confusion, the regulatory landscape regarding biosimilar interchangeability significantly varies between the EU and the USA. The FDA introduced a dedicated regulatory pathway for interchangeability designation, which may be misunderstood by some as a higher standard for biosimilarity. While the interchangeability designation in the USA regulates the automatic substitution of biosimilars at the pharmacy level (in accordance with state laws), it may have led to a general impression in the healthcare community that "ordinary" biosimilars may not be suitable for interchanging by the prescriber.

3 Fifteen Years of Evolution in the Debate Around Biosimilars

The debate on biosimilars and their appropriate use in clinical practice has evolved considerably over the past 15 years. In the early days, skeptical prescribers did not trust the quality of these "cheaper" (sic) alternatives. Next, there was mistrust in their efficacy and safety, as biosimilar development is not based on the traditional large efficacy and safety clinical trials that many doctors are accustomed to seeing. The debate continued around extrapolation of indications: how acceptable is it to use a medicine for an indication in which a patient trial is not at hand? With the first approval of a complex mAb biosimilar in 2013 in Europe, discussion sparked on potential safety risks associated with switching a patient from an originator biological to a biosimilar. The fear was that switching between nonidentical but highly similar

biologicals could induce immune reactions, with loss of efficacy and worsened disease outcomes or adverse events. There was a serious problem of loss aversion among prescribers to use biosimilars without clinical data on switching being available. In recent years, several reviews have evaluated the safety of switching from originator biologicals to biosimilars. Barbier et al. [7] published a systematic review of 178 switch studies, encompassing over 20,000 switched patients, reporting no signs that switching from an originator biological to its biosimilar is associated with loss of efficacy or increased rates of side effects. The currently available peer-reviewed literature contains no evidence to substantiate an inherent risk with switching between original biologicals and biosimilars. However, attention should be paid to mitigating possible nocebo effects when switching [7, 8]. To this end, healthcare professionals should be trained and follow structured switch protocols to avoid negative perceptions among patients regarding their biosimilar treatment. With a large body of clinical studies on switching available, the question arises: when will the clinical data be enough to convince the medical community of the efficacy and safety of biosimilars developed and evaluated according to robust regulatory requirements? In 2019, Ebbers and Schellekens [9] argued that sufficient experience and data have been gathered regarding biosimilar evaluation and their use in clinical practice and called upon stakeholders to close the discussion on their interchangeability.

In this issue of *Drugs*, Kurki et al. [10] and Mysler et al. [11] present two unique papers that address the topic of biosimilar interchangeability and provide important findings to inform and drive the debate to a conclusion. While both papers investigate the topic of interchangeable biosimilar use from different perspectives—regulatory and clinical—and do so through different approaches, they arrive at similar conclusions. Kurki et al. [10] provide insights from the EU regulatory perspective on interchangeability, and Mysler et al. [11] focus on biosimilar-to-biosimilar switching from the clinical perspective. In this commentary, we discuss both papers, mainly from a European perspective. The US landscape around biosimilars is more hostile and is complicated by the typical US claim culture. Moreover, as discussed, the regulatory landscape in terms of interchangeability in the US differs from the approach taken in Europe.

4 Biosimilar Interchangeability: The Regulatory Perspective

Regulators have an essential role in providing clear and trustworthy information about biosimilars to the medical community and the public in general. In Europe, regulators have built a strong tradition of actively communicating their scientific reasoning regarding biosimilars in the peer-reviewed literature [12– 16], starting with Weise et al. [12] in 2012. Now, in this issue, a new and insightful open access contribution from a team of European regulators on the safety, immunogenicity, and interchangeability of biosimilars has been added to this armamentarium of regulatory-authored biosimilar papers.

In the first paper in this issue of *Drugs*, Kurki and colleagues [10] joined forces to address the concerns of prescribers regarding the (interchangeable) use of biosimilars. To this end, they conducted a comprehensive analysis of safety, immunogenicity, and switching data of EU-approved biosimilars available in regulatory reports, with a specific focus on the more complex biosimilars (all mAbs and fusion protein biosimilars that were approved in Europe up to July 2020 [10]). Importantly, the analysis comprised both prelicensing and longer-term data. For this, the authors reviewed both European public assessment reports (EPARs) and EMA postmarketing surveillance reports of authorized biosimilar mAbs and fusion proteins and their reference products. To provide some context on the former, EPARs are publicly available on the EMA website and contain detailed information on the assessment of the quality, efficacy, and safety of medicinal products that have been granted or refused a marketing authorization through the centralized (i.e., through the EMA) authorization procedure. In the case of biosimilars, EPARs provide insight on the similarity exercise that has been executed for that particular product. For the longer-term data, periodic safety update reports and other safety reports submitted to the EMA were reviewed. This combined in-depth analysis is a key strength of the paper and makes it the first to extensively analyze the postmarketing surveillance data used by regulators to continuously evaluate mAb biosimilars after market entry. Given that the main concerns of prescribers center on the safety, immunogenicity, and interchangeability of biosimilars, Kurki et al. [10] reviewed these regulatory documents layer by layer, considering safety, administration devices and presentations, immunogenicity, and interchangeability at a product-specific level. The paper and its supplementary materials contain detailed comparative numerical data on immunogenicity (e.g., drug antibodies) for all products. They pay special attention to the perceived higher drug-antibody titers as seen with biosimilars compared with historical data from the reference products. This is another example of advances in science, as modern assays display sensitivity magnitudes higher than that of assays from 15 to 25 years ago.

The analysis by Kurki et al. [10] underscores the excellent safety record of EU-approved biosimilars. Their analysis of postmarketing surveillance data, including up to 7 years of follow-up, revealed no biosimilar-specific (i.e., not known for the reference product) adverse effects, despite the patient-treatment years totaling over 1 million. While clinical switch trials are not requested for regulatory

approval requirements in Europe, and the EMA does not conclude on biosimilar interchangeability, clinical switch data are often provided in regulatory submissions under the form of extensions of pivotal comparative efficacy and safety studies and are, as such, reported in the EPAR. The analysis of EPAR-included switch data showed that, as expected and in line with published reviews on clinical switch studies, single or multiple switches between originators and biosimilars did not have a negative impact on efficacy, safety, or immunogenicity.

Since recent biosimilar approvals also included products that are administered subcutaneously by patients themselves (e.g., adalimumab and etanercept), Kurki et al. [10] also included an analysis of administration devices. This analysis exemplified that biosimilars may add new administration devices and also new presentations compared with the reference product, which adds to patient and healthcare provider choice when using/selecting a biological. Furthermore, the analysis reassuringly demonstrated the feasibility of self-administration of biosimilars with different administration devices. As such, differences in administration devices should, if done with proper patient guidance, not preclude switching.

Kurki et al. [10] conclude by stating that biosimilars approved according to the EMA's stringent regulatory requirements, can be considered interchangeable with their reference products. Based on the theoretical considerations and the clinical switch data available from both controlled studies and real-world settings, they argue that additional systematic switch studies are unnecessary to support switching patients in clinical practice. Furthermore, these studies may be considered ethically questionable since they draw from limited clinical resources. The findings presented by Kurki et al. [10] further strengthen the rationale put forward in an earlier Kurki-authored paper in 2017 [14] on biosimilar switching and interchangeability, where they argued that biosimilars licensed in the EU could be considered interchangeable.

Although Kurki et al. [14] did not broach the topic of automatic substitution (i.e., the exchange of a biosimilar at the pharmacy level) in their 2017 publication, the landscape has been evolving over the past few years, and regulators now conclude that automatic substitution at the pharmacy level could, in principle, be possible. To allow pharmacy-level substitution, community pharmacists should naturally receive the necessary training to enable them to adequately counsel patients about their treatment and possible changes in injection device. Although automatic substitution for biologicals is generally not allowed or practiced across Europe, a few countries have made or are preparing legislative changes to implement it. Australia is an example of how substitution for biologicals may be implemented. There, the Pharmaceutical Benefits Advisory Committee conducts a product-by-product evaluation to assess the possibility to allow for product exchange at the pharmacy level.

In the second paper in this issue, Mysler et al. [11] stress the importance of clinical decision making at the individual patient level, taking patient and disease variables into account on a case-by-case basis. While this may appear more challenging in a healthcare setting where substitution is introduced, the prescriber could annotate the prescription if necessary (e.g., "dispense as written"). Before substitution of biologicals in Europe becomes a reality, several political, organizational, and practical hurdles likely need to be overcome [17, 18].

While the analysis by Kurki et al. [10] and their conclusions are reassuring and an important message for stakeholders about biosimilar use in practice, this message needs to effectively reach the medical and policy-making community. The authors also acknowledge this: "Learned societies, regulators, and policymakers should act swiftly to create a common European position on interchangeability to promote rational use of biologicals." The recently established Heads of Medicine (HMA) biosimilar working group, comprising representatives of several national medicines agencies across member states and an EMA representative, will undoubtedly be an important step forward in this regard.

5 Biosimilar-to-Biosimilar Switching: The Clinical Perspective

In the second paper we discuss in this commentary, Mysler et al. [11] approached the question of the interchangeable use of biosimilars from a clinical perspective. The team of eight co-authors (notably, half are employed by Pfizer, an important player in both the originator biological and the biosimilar market) wrote an extensively documented review article, discussing virtually every angle related to the interchangeable use of biosimilars in clinical practice. Based on a review of the literature up to January 2021, the authors provide a timely and comprehensive insight into the current landscape of switch decision-making contexts and biosimilar-to-biosimilar switching from a clinical perspective. Although the review focuses on patients with inflammatory diseases as an example, the authors' reasoning is well beyond that example. The paper underwent thorough peer review, and we believe it is an important addition to the scientific literature for clinicians.

While a single switch from reference to biosimilar is accepted practice in most health systems and well-documented in both controlled clinical switch studies and real-world switch data [7], multiple switching and biosimilar-to-biosimilar switching is met with uncertainty. With an increasing number of biosimilars for a single reference product, biosimilar-to-biosimilar transitioning—which

Mysler et al. [11] refer to as "cross-switching"—is becoming a reality for prescribers to decide upon. While Kurki et al. [10] present an exhaustive analysis and reassuring evidence from a regulatory perspective on biosimilar interchangeability, in Europe, decisions as to whether a patient can be switched between biosimilars are generally left to prescribers. Alongside the lack of official regulatory positions on switching (including multiple and cross-switching) in several European member states [5], Mysler et al. [11] highlight that clinical guidelines for individual prescribers to rely on in the context of biosimilar-to-biosimilar switching are also largely absent.

Similarly to physicians' uncertainties regarding switching in general, questions about cross-switching center around the fear of inducing immunogenicity and/or loss of efficacy, although no such phenomena have been documented in well-validated articles. Head-to-head clinical trials between biosimilars of the same reference product are unlikely, as pharmaceutical companies have no commercial interest in conducting them or clear incentive to do so. Furthermore, to make such clinical trials scientifically meaningful—as any differences between products are likely to be very small—large numbers of patients would need to be included, making them unaffordable. Kurki et al. [10] argue that systematic switch trials may be regarded as unethical and a waste of scarce clinical resources, as mentioned earlier in this commentary.

Reasons to cross-switch are usually financial: the alternative better fits the payer (and thus in the end also the patient, as argued earlier). While switching for medical reasons aims to optimize the clinical benefit for the patient, the goal of reference-product-to-biosimilar or biosimilar-to-biosimilar switching is to increase the affordability of care and the sustainability of the health budget.

As the major theoretical argument against switching is inducing unwanted immunogenicity, the authors pay a lot of attention to this. They argue that, by nature of the similarity exercise there should be a large overlap between immune epitopes of the biosimilar and the reference product. What are the chances of a large divergence in epitopes between biosimilars of the same reference product? A number of researchers, particularly Ben Horin [19], Ruiz-Argüello [20], Fiorino [21], and Goncalves, have worked out a robust methodology to investigate this ex vivo, particularly for infliximab [22, 23], and Mysler et al. [11] discuss this work extensively. These results are supported by the emerging real-world clinical data on switching between biosimilars that the authors identify and discuss in detail. These data point in the same direction: no unexpected safety findings or reported loss of efficacy were found in a frequency higher than would occur with the reference product.

6 Conclusion

Both papers in this issue provide support for the interchangeable use of biosimilars. Their conclusions may support clinicians and stakeholders alike with the implementation of biosimilars in clinical practice and address ongoing uncertainties in the debate. While attention should be paid to the nocebo effect, and healthcare providers should be properly trained to guide patients with biosimilar use, there are no signs to indicate that switching between reference products and biosimilars or between biosimilars is associated with an increased risk of (induced) immunogenicity. We concur with Kurki et al. [10] that requesting more and especially systematic switch studies may be considered ethically questionable and wasteful. A robust post-marketing surveillance system is in place to monitor any switch-related adverse events and to identify rare immune reactions that can only be detected after long follow-up periods in large patient numbers.

To bridge the gap to the clinical community, the next essential stop is to effectively communicate these scientific insights to prescribers. Here, scientific medical associations such as the European Alliance of Associations for Rheumatology, the European Society for Medical Oncology, and the European Crohn's and Colitis Organisation, among others, hold a crucial role. Treatment guidelines and position statements should be updated regularly to reflect the evolving regulatory and clinical experience with biosimilars. As noted, national medicines agencies should update their websites and provide clear statements on biosimilars and their use to support not only medical associations and prescribers but also decision makers with appropriate policy making. Clear regulatory one-voice messaging on biosimilar interchangeability is an essential remaining piece of the puzzle to bridge the final gap. A strong science-based and homogeneous EU position from regulators is key to combating the confusion among prescribers, which is otherwise likely to continue for years to come. After 15 years of biosimilars in Europe, with advancing science and mature experience, there is timely and much-needed momentum to create a common European scientific position on interchangeability. By doing so, healthcare systems can capture the societal benefits offered through biosimilar competition. With over 2 billion patient-treatment days with EU-approved biosimilars reported without any serious adverse events [24], and an analysis of more than 1 million patient-treatment years of safety data raising no safety concerns, as presented by Kurki et al. [10], ample clinical experience with biosimilars supports this approach.

We conclude that the science has helped to overcome the final hurdles for a wider implementation of biosimilars

that are developed and assessed according to robust regulatory requirements. This will be a major step forward in ensuring the sustainability of the drug budget and the access of patients to these expensive and sometimes unaffordable biological medicines.

Declarations

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflict of interest AGV is one of the founders of the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL Fund). AGV is involved in consulting, educational work, and speaking engagements, i.e., AbbVie, Accord, Amgen, Biogen, Effik, Pfizer/Hospira, Fresenius-Kabi, Mundipharma, Roche, Novartis, Sandoz, and Boehringer Ingelheim. LB's research is supported by the KU Leuven and the MABEL Fund. LB has no commercial or financial relationship that could be perceived as a potential conflict of interest. AGV or LB were not involved in the Kurki or Mysler papers.

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Availability of data and material Not applicable

Code availability Not applicable

Authors' contributions AGV and LB wrote, revised, and approved this commentary.

References

1. IQVIA. The Impact of Biosimilar Competition in Europe. 2020. Available from https://www.iqvia.com/library/white-papers/the-impact-of-biosimilar-competition-in-europe. Accessed 12 Oct 2021.
2. Moors EHM. Challenges for the adoption of future biosimilars. Eur J Hosp Pharm Pract. 2007;2007(13):57–8.
3. European Medicines Agency and the European Commission. Biosimilars in the EU—Information guide for healthcare professionals. 2017.
4. Dutta B, Huys I, Vulto AG, Simoens S. Identifying key benefits in European off–patent biologics and biosimilar markets : it is not only about price! BioDrugs. 2020;34(2):159–70.
5. Barbier L, Mbuaki A, Simoens S, Vulto A, Huys I. PNS151 the role of regulatory guidance and information dissemination for biosimilar medicines—the perspective of healthcare professionals and industry. Value Health. 2019;1(22):S786–7.
6. Cohen HP, McCabe D. The importance of countering biosimilar disparagement and misinformation. BioDrugs. 2020;34(4):407–14.
7. Barbier L, Ebbers H, Declerck P, Simoens S, Vulto A, Huys I. The efficacy, safety and immunogenicity of switching between reference biopharmaceuticals and biosimilars: a systematic review. Clin Pharmacol Ther. 2020;108(4):734–55.
8. Kristensen LE, Alten R, Puig L, Philipp S, Kvien TK, Antonia M, et al. Non-pharmacological effects in switching medication : the Nocebo effect in switching from originator to biosimilar agent. BioDrugs. 2018;32(5):397–404.
9. Ebbers HC, Schellekens H. Are we ready to close the discussion on the interchangeability of biosimilars? Drug Discov Today. 2019;24(10):1963–7.
10. Kurki P, Barry S, Bourges I, Tsantili P, Wolff-Holz E. Safety, immunogenicity and interchangeability of biosimilar monoclonal antibodies and fusion proteins: a regulatory perspective. Drugs. 2021. https://doi.org/10.1007/s40265-021-01601-2.
11. Mysler E, Azevedo VF, Danese S, Alvarez D, Noriko I, Ingram B, et al. Biosimilar-to-biosimilar switching: what is the rationale and current experience? Drugs. 2021. https://doi.org/10.1007/s40265-021-01610-1.
12. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. Blood. 2012;120(26):5111–7.
13. Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. Blood. 2014;124(22):3191–6.
14. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M, et al. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017;31(2):83–91.
15. Wolff-Holz E, Tiitso K, Vleminckx C, Weise M. Evolution of the EU biosimilar framework: past and future. BioDrugs. 2019;33(6):621–34.
16. Pinheiro LC, Giezen TJ, Wolff-Holz E, Weise M, Laslop A, Hidalgo-Simon A. Identifiability of biologicals: an analysis using the EMA adverse drug reaction database, EudraVigilance. Clin Pharmacol Ther. 2021. https://doi.org/10.1002/cpt.2411.
17. Tolonen HM, Airaksinen MSA, Ruokoniemi P, Hämeen-anttila K, Shermock KM, Kurki P. Medication safety risks to be managed in national implementation of automatic substitution of biological medicines: a qualitative study. BMJ Open. 2019;9:e032892.
18. Barbier L, Simoens S, Vulto AG, Huys I. European stakeholder learnings regarding biosimilars: part II—improving biosimilar use in clinical practice. BioDrugs. 2020;34:797–808.
19. Ben-Horin S, Yavzori M, Benhar I, Ella Fudim E, Picard O, Ungar B, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut. 2016;65(7):1132–8.
20. Ruiz-Argüello M, Maguregui A, Ruiz Del Agua A, Pascual-Salcedo D, Martínez-Feito A, Jurado T, et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. Ann Rheum Dis. 2016;75(9):1693–6.
21. Fiorino G, Begona Ruiz-Arguello M, Maguregui A, Nagore D, Correale C, Radice S, et al. Full interchangeability in regard to immunogenicity between the infliximab reference biologic and biosimilars CT-P13 and SB2 in inflammatory bowel disease. Inflamm Bowel Dis. 2018;24(3):601–6.

22. Goncalves J, Santos M, Acurcio R, Iria I, Gouveia L, Matos Brito P, et al. Antigenic response to CT-P13 and infliximab originator in inflammatory bowel disease patients shows similar epitope recognition. Aliment Pharmacol Ther. 2018;48(5):507–22.
23. Pouillon L, Allocca M, Peyrin-Biroulet L. Editorial: antigenic response to CT-P13 and infliximab originator in IBD shows similar epitope recognition—evidence from basic science supports safe switching to biosimilars. Aliment Pharmacol Ther. 2018;48(5):574–5.
24. Medicines for Europe. The total clinical experience with biosimilar medicines exceeds 2 billion patient treatment days. 2020. [cited 2021 Sep 1]. https://www.medicinesforeurope.com/2020/12/16/the-total-clinical-experience-with-biosimilar-medicines-exceeds-2-billion-patient-treatment-days/. Accessed 12 Oct 2021.