



European Stakeholder Learnings Regarding Biosimilars: Part II—Improving Biosimilar Use in Clinical Practice

Liese Barbier¹ · Steven Simoens¹ · Arnold G. Vulto^{1,2} · Isabelle Huys¹

Published online: 15 October 2020
© The Author(s) 2020

Abstract

Background Despite the benefits biosimilars offer in terms of cost savings and patient access, healthcare professionals and patients have been reluctant to use them. Next to insufficient understanding of and trust in biosimilars, healthcare professionals and patients have questions about switching and the nocebo effect when using biosimilars in clinical practice. In addition, clear motivation to use biosimilars may be lacking among these stakeholders.

Objective This study aims to provide recommendations on how to improve biosimilar use on both a clinical and a practical level based on insights from healthcare professionals (physicians, hospital pharmacists, nurses), patients (or their representatives), and regulators across Europe.

Methods We conducted 44 semi-structured interviews with experts from five stakeholder groups across Europe: physicians, hospital pharmacists, nurses, regulators, and patients/representatives. Interviews were transcribed ad verbatim and transcripts analysed according to the thematic framework method.

Results Based on the insights and considerations of the experts interviewed, we identified a number of recommendations to improve the use of biosimilars in clinical practice. Regarding switch implementation, the experts voiced support for the following actions: (1) disseminate evidence from and experience with (multiple) switching; (2) provide clear, one-voice regulatory guidance about the interchangeability of biosimilars and their reference product; (3) apply a multi-stakeholder implementation and communication protocol to guide switching in clinical practice; (4) apply a pragmatic approach when taking switch decisions; and (5) avoid mandated switching, allowing stakeholder communication and alignment. When discussing approaches to increase the willingness of stakeholders to use biosimilars, we concluded that actions should be centred on (1) communicating the benefits provided by biosimilars and the introduction of market competition, (2) increasing awareness among stakeholders about medicine prices and their societal responsibility to use medicines in a cost-effective manner, (3) transparent reporting about the allocation of savings, (4) sharing biosimilar usage data among hospitals and prescribers to allow peer-to-peer benchmarking, and (5) applying a balanced combination of tangible and non-tangible incentives that can be tailored to offset the time and effort expended by stakeholders when switching to a biosimilar.

Conclusions This study proposes a number of strategic, practical, and overarching recommendations to support healthcare professionals and inform decision makers to improve the clinical use of biosimilars and the willingness of stakeholders to use them. The proposed solutions to fully realise the potential of biosimilars for healthcare systems and patients include developing practical switch guidance, being transparent about the gains from biosimilar use (and how savings are allocated), and developing a combination of non-tangible and tangible incentives for involved stakeholders.

Arnold G. Vulto and Isabelle Huys contributed equally to this work.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40259-020-00440-z>) contains supplementary material, which is available to authorized users.

✉ Arnold G. Vulto
a.vulto@gmail.com

¹ Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

² Hospital Pharmacy, Erasmus University Medical Center, Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

1 Introduction

With the patent protection and other exclusivity rights of an increasing number of original biological medicines (also called reference products) expiring, interest in the development and commercialization of biosimilars has soared [1]. Biosimilars can reduce treatment costs by introducing market competition and thus relieve increasing budgetary pressure on healthcare systems. In addition to having an impact on pharmaceutical spending, biosimilar market entry has also been shown to increase patient access to these formerly expensive biologicals [1, 2].

Key Points

Despite the benefits offered by biosimilars, they are not being widely adopted and prescribed. Healthcare professionals and patients have questions regarding the use of biosimilars, particularly regarding switching and the nocebo effect. In addition, prescribers may lack a clear motivation to use biosimilars.

This study proposes several strategic, practical, and overarching recommendations to support healthcare professionals and inform decision makers to improve the clinical use of biosimilars and encourage stakeholders to use them.

Developing practical switch guidance, transparently communicating the gains from biosimilar use (and how savings are allocated), and developing a combination of tangible and non-tangible incentives for involved stakeholders will contribute to realizing the full potential of biosimilars.

Since the first biosimilar approval in Europe in 2006, more than 55 biosimilars have received marketing authorization in Europe [3]. So far, rates of biosimilar use have varied across member states and product classes and in some cases have been limited [1, 4]. The differences in uptake across European countries and regions may partly be explained by varying biosimilar (market entry) policies [1, 5]. Furthermore, despite the potential of biosimilars to positively impact expenditure and patient access, biosimilar adoption may be hampered by reluctance on the part of both healthcare professionals (HCPs) and patients to use biosimilars because of a lack of trust in and understanding of them [6, 7]. In the first article of this series on biosimilar multi-stakeholder insights, we provided recommendations on how to improve HCP and patient biosimilar understanding in Europe [8].

In clinical practice, HCPs are faced with questions regarding the use of biosimilars. As biological medicines are often used in chronic treatment settings, use of a biosimilar may involve switching a patient from a reference product to a biosimilar. Since their introduction in Europe, and especially with the introduction of monoclonal antibody biosimilars, the safety of switching a patient between highly similar but non-identical products has been questioned [9], and this has left HCPs uncertain about using biosimilars [6]. Several randomized, controlled and real-world studies have evaluated the efficacy, safety, and immunogenicity of switching from reference products to biosimilars. Overall,

the vast majority of studies did not indicate any major safety, efficacy, or immunogenicity issues associated with this [10, 11]. However, a number of real-world studies have reported a relatively high therapy discontinuation rate among patients after switching, which was mostly attributed to the occurrence of the nocebo effect [10]. The nocebo effect is defined as a negative impact on the patient's perceived treatment outcome resulting from the patient's negative expectation about the (change in) therapy [12, 13]. To support HCPs and patients in their use of biosimilars, guidance on switch implementation and mitigation of the nocebo effect is required.

In addition, biosimilar use may be hampered by a lack of motivation among HCPs and patients, as stakeholders are unlikely to change behaviour without an incentive [6, 7]. Although several European countries are testing gainsharing models, where savings generated from biosimilar competition are shared among stakeholders [5], experience with these arrangements remains fairly new [14]. Insights into the willingness of stakeholders to use biosimilars and the design of appropriate incentives may help decision makers improve biosimilar policy making.

This article is the second part of a study on European multi-stakeholder lessons regarding biosimilars. It aims to provide recommendations—based on insights from physicians, hospital pharmacists, nurses, patients (or their representatives), and regulators across Europe—on how to improve biosimilar use, both clinically (e.g. how to implement a switch) and practically (e.g. how to organize stakeholder incentives).

2 Methods

This study consisted of 44 semi-structured interviews [described elsewhere [8] and included in the electronic supplementary material (ESM) 1] with biosimilar experts across five stakeholder groups (physicians, hospital pharmacists, nurses, patients, and regulators) to gain insights about how to improve the clinical and practical use of biosimilars in Europe.

3 Results

In total, 44 interviews were carried out. Participant characteristics are shown in ESM 1.

3.1 Towards Improved Biosimilar Use in Clinical Practice

Stakeholder challenges and proposals to improve biosimilar switch implementation are shown in Fig. 1.

3.1.1 What to Consider When Deciding to Switch

Most physicians, pharmacists, and nurses found that patients may be switched safely and felt reassured by the available data regarding switching. Although some patients also felt reassured by the available data, several remained hesitant about switching. Some patients requested studies over a longer timeframe to better evaluate the long-term effects of switching. Furthermore, the willingness to switch could depend on the product's complexity. Several interviewees argued that the uncertainty surrounding switching mostly resulted from misinformation from the pharmaceutical industry.

Several HCPs advocated for a pragmatic approach when deciding whether to switch. Initiating only bio-naïve patients with a biosimilar in certain cases, such as shorter treatment periods, was preferred: "It would be a lot of hassle and time investment to switch a patient in the last four months of [their] treatment." Also, several patients favoured only starting new patients with a biosimilar, regardless of the treatment setting (acute vs. chronic).

Forcing a switch was believed to be counterproductive and could result in distrust of biosimilars. Across stakeholders, most interviewees felt that the physician should remain

in control of treatment decisions and be able to decide whether to switch based on individual patient circumstances. It was believed that giving patients the option to return to the reference product would reassure patients.

Several interviewees argued for continued monitoring and ensuring product traceability when switching.

3.1.2 How to Implement a Switch and Minimize the Nocebo Effect

Almost all interviewees indicated that switching should follow a structured process that is agreed upon and carried out by an aligned HCP team. Several pharmacists explained that the switch should follow a stepwise approach. First, a discussion about the switch should be organized among the relevant stakeholders, allowing for shared decision making. Second, the patient should be informed that a switch will be organized at the next administration. Some interviewees referred to the Dutch Association of Hospital Pharmacists (NVZA) toolbox [15] as a supporting tool to implement a structured switch. Careful planning was considered necessary: "building trust takes a lot of time, and only one incident to dissolve [it] again."

How to overcome stakeholder hurdles related to switching in clinical practice	
Stakeholder challenges	Stakeholder aligned recommendations
<ul style="list-style-type: none"> • Uncertainty about the safety of switching, partly due to misinformation and industry influence leading to a lack of stakeholder confidence 	<ul style="list-style-type: none"> • Educate about and disseminate clinical switch data • Share positive switch experiences
<ul style="list-style-type: none"> • Fear of losing control of treatment and traceability with (multiple) switching 	<ul style="list-style-type: none"> • Involve physicians in the switch decision and avoid mandated/top-down organized switching • Avoid frequent switches • Provide the opportunity for motivated exceptions • In some cases, it may be more pragmatic to only start bio-naïve patients with the biosimilar (e.g. short treatment duration)
<ul style="list-style-type: none"> • Guidance lacking or unclear about <ul style="list-style-type: none"> • Switch implementation strategies • Nocebo effect management • Switching and interchangeability (no overarching EU position, incomplete patchwork of position statements on national level) 	<ul style="list-style-type: none"> • Develop and provide guidance about switching (protocol) <ul style="list-style-type: none"> • How to organize a structured switch approach • How to effectively communicate to the patient, circumventing a possible nocebo effect • Develop one-voice regulatory interchangeability and switching guidance <ul style="list-style-type: none"> • Increase collaboration between authorities and HCPs • Translate regulatory guidance into practical stakeholder info
<ul style="list-style-type: none"> • HCP time and effort threshold to switch a patient • A lack of motivation ("what's in it for me?") 	<ul style="list-style-type: none"> • Design and implement a stakeholder incentive to lower threshold <ul style="list-style-type: none"> • Involve a specialized nurse to support the switch process
<ul style="list-style-type: none"> • Possible additional investment and time-to-market hurdle for developers to conduct additional switch studies beyond licensing requirements as response to stakeholder uncertainty 	<ul style="list-style-type: none"> • Create stakeholder confidence about biosimilars to reduce the stakeholder need for additional data generation

Fig. 1 How to overcome stakeholder hurdles related to switching in clinical practice—proposed multi-stakeholder actions. *HCPs* healthcare professionals

Several interviewees contended that the HCP team must be well informed and educated to coherently communicate and transfer confidence to the patient. Informing patients with an aligned, unified message was deemed essential. Verbal and non-verbal signals from HCPs could also impact the patient's perception: "If the nurse looks unsure and cannot respond satisfactorily to questions, it doesn't build patient's trust." Several interviewees believed that the physician's confidence is key to minimizing a nocebo effect, as "the patient is confident when the physician is confident." Moreover, a specialized nurse may help to guide the switch process more smoothly.

Several interviewees voiced that patient concerns and possible nocebo effects need to be taken seriously: "To patients, those effects feel very real" and "Switching them from an active drug that induced remission of a previously very impactful disease is very sensitive." One patient remarked that distinguishing between a nocebo-related and true side effect may prove challenging. Several interviewees mentioned that communication should be fully transparent to build trust between patient and provider.

Almost all interviewees mentioned that starting a dialogue with the patient and informing them about the switch is important. Several nurses, physicians, and regulators considered that dedicating time to explain the change to the patient was a necessity. Although interviewees generally agreed that patients should be informed about the switch, they disagreed about exactly how to involve them, with most believing that patients should not be involved in the decision making and others arguing that patients should be involved to reduce reluctance, avoid nocebo effects, and build trust in their HCPs.

There was no consensus over the level of detail that patients should receive about biosimilar concepts. One nurse argued, "If the HCP tells the patient that the medicine is good, it is not very interesting for the patient if it is an original drug or a biosimilar." Several nurses voiced that patient communication should not be overcomplicated: "Now we said 'Well, we don't have the original product, so we treat everybody with the biosimilar', and I haven't heard any problems." One nurse questioned the need to inform patients about biosimilars altogether: "It is an ethical problem. Must you inform patients when in fact there is no difference for them as far as you expect?" Another interviewee mentioned that no questions were asked when they switched to a filgrastim biosimilar: "Everybody called it another type of growth factor. As it was communicated that the product had all the same side effects and the same precautions were needed, there was no big deal about it." Several interviewees considered that striking a balance between the amount and type of information to provide to patients is challenging: "A patient might be triggered to think that there is something wrong if a lot of emphasis is put on the switch."

Most interviewees mentioned that patients need to be informed as to why a switch is being made and about its positive impact. Some interviewees counter-argued that not all patients are interested in the cost benefit. Furthermore, it was argued that it should be made clear to the patient that less expensive does not equal inferior when discussing the financial benefits of the switch.

Generally, it was believed that information should be centred on explaining that the biosimilar is equally as safe and effective as the reference product and that patients may expect the same outcomes. Both nurses and patients considered that reassurance regarding safety was important. Some regulators claimed that the nocebo effect may be minimized if HCPs and patients were informed that biosimilars are only authorized if their efficacy and safety profiles are shown to be equal to those of the reference product.

Several interviewees across the groups advised that information should include the practical implications for the patient: "what does the switch mean for the patient." It was mentioned that patients should be provided with a contact in case they have questions or experience adverse effects. Other patient-communication aspects that were deemed important were to inform patients in a timely manner, provide multiple opportunities to discuss the switch, and provide follow-up after the switch. Some patients mentioned that additional follow-ups could serve as opportunities to monitor for side effects.

It was stated that patient information should be understandable, readable, and concise. Layman's terms (such as those used in the patient biosimilar question & answer brochure from the European Commission [EC] [16] or the Dutch Medicines Evaluation Board biosimilar booklet [17], repeatedly mentioned as examples) should be used, and materials should be available in the patient's first language. Providing written information that patients can read and re-read was considered important. Several interviewees argued that there is no one-size-fits-all approach for good patient communication and that tailoring the communication strategy and level of detail to the needs and wishes of the patient is important.

Several interviewees mentioned that special consideration should be given to patients who self-administer their therapy, as they may need to receive training about the injection device.

One physician argued that patient communication should focus on the medicine's international nonproprietary name, as this requires a less active mindset shift among patients when switching as physicians are able to maintain their treatment terminology.

Several HCPs and one patient mentioned that the patient's treatment outcome expectations should be managed, as response to treatment may naturally wane over time for certain types of medicines. Patient trust in the HCP may be negatively affected if this were to coincide with the timing

of the switch: “It would only take one patient treated with infliximab that reached tolerance at the same time as the switch to undermine our complete programme.”

Furthermore, interviewees mentioned that objectively assessing any changes before and after the switch by monitoring specific disease parameters for certain product types and patients may help to reassure patients and HCPs throughout the switch process.

In summary, the general opinion was that a switching operation should be set up as a multi-stakeholder project, with clear decision lines, education for a unified approach, and a well-planned implementation and follow-up procedure.

Figure 2 provides a structured overview of key steps regarding switch management.

3.1.3 Multiple Switching, Switching Between Biosimilars of the Same Reference Product, and Switching Between Administration Routes

Several HCPs and patients had reservations about multiple switching and indicated that constant changes should be avoided. It was argued that more information and data were needed because of a lack of experience with this. Some interviewees mentioned that data on multiple switches are increasingly being generated. Several physicians contended

that multiple switching discussions are misused to “bring noise to the discussion,” as it suggests that the physician could lose control over the process. Overall, most physicians and nurses maintained that frequent switches should be avoided because it could lead to traceability issues and confusion among the HCPs and patients involved. It was mentioned that agreements about multiple switching should be made with the payer or hospital: “Now we decide that we can switch everyone, but that we cannot switch again within the first years. This is not based on evidence, it’s based on distrust, thinking that there are long-term effects. Over the next years, a discussion about multiple switching is needed.” Questions arose about what would be considered an acceptable interval between switches. Furthermore, several interviewees argued that a pragmatic approach should be taken to avoid multiple switching of patients receiving chronic treatment: “Patients cannot be switched all the time.” Also, some reasoned that the cost savings of a second switch could be limited.

Most physicians and pharmacists considered switching between biosimilars of the same reference product acceptable: “For me it is the same as switching between reference product and biosimilar. You have again a high level of similarity.” It was not deemed necessary to provide confirmatory

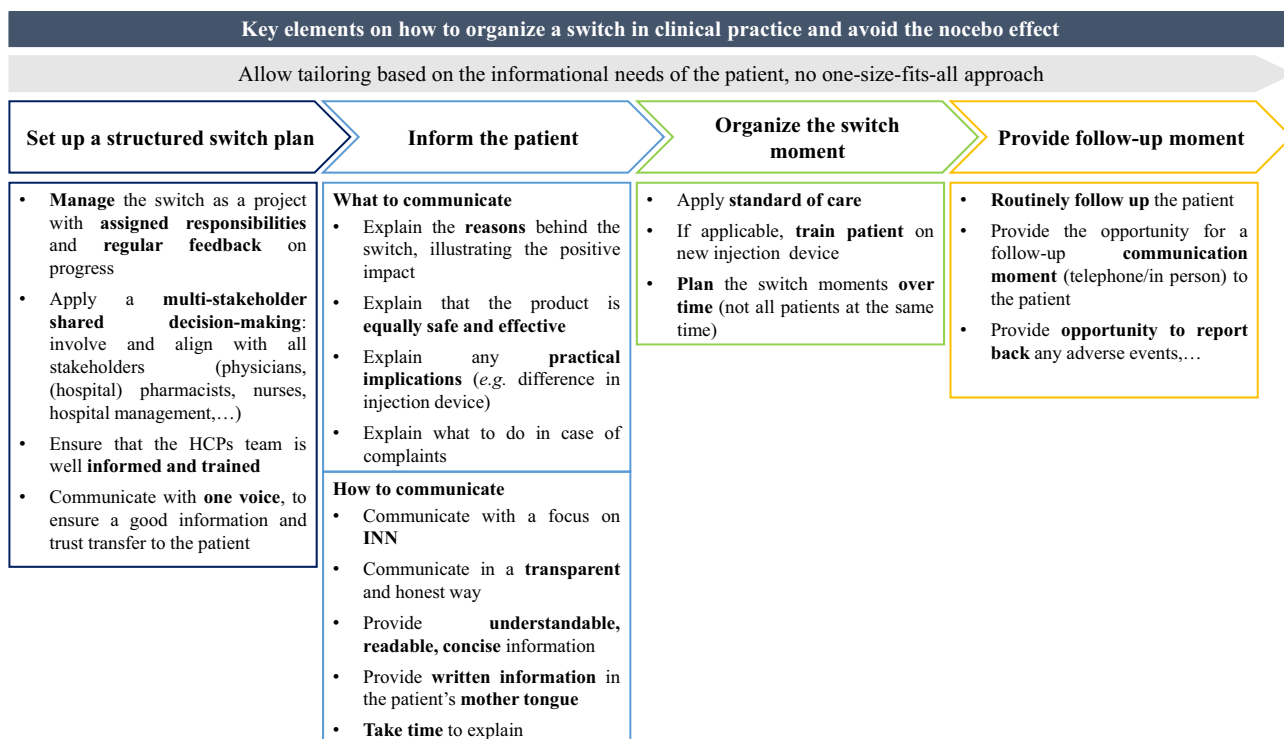


Fig. 2 Key elements on how to organize a switch in clinical practice and avoid the nocebo effect—multi-stakeholder insights. HCPs healthcare professionals, INN international nonproprietary name

data in this regard. Sharing experiences and registries of biosimilar-to-biosimilar switches was considered informative for stakeholders. Some regulators doubted that developers would be interested in investing in biosimilar-to-biosimilar switch studies. Most nurses were hesitant about biosimilar-to-biosimilar switching because of a lack of practical experience with this.

It was argued that switching between different administration routes (i.e. from subcutaneous to intravenous products or vice versa) occurred often in clinical practice and that physicians considered it clinically unproblematic. However, changes at organizational and logistical levels would be required. In addition to these practical considerations, it was suggested that the patient's preference should be considered, as the change could have an impact on the patient's life (e.g. home vs. hospital administration, or the level of contact with HCPs). Most interviewees would prefer to maintain patients receiving subcutaneous treatments on their current treatment but start treatment-naïve patients with the lower-priced intravenous formulation. In contrast, one pharmacist argued that it would be fair to ask patients to switch back to intravenous administration if it would allow more patients to be treated. Participants also argued that, depending on the hospital's organisation, any discounts provided by biosimilar competition for intravenous products would need to offset the possible increase in day clinic costs.

3.1.4 Stakeholder Opinions Regarding Substitution for Biologicals

Overall, most physicians and pharmacists were not against pharmacist substitution per se, provided that the physician is informed about the change, stressing the importance of physicians remaining in control over the treatment. Several patients also emphasized that the patient should be informed about any change. Physicians strongly opposed automatic substitution (i.e. change by the pharmacist without informing the physician), as this would lead to a loss of control and possibly to multiple subsequent transitions. Most nurses did not object to substitution as they deemed it a physician/pharmacist decision and responsibility: "If we agree that biosimilars are as safe and effective as the originator, and we can treat more people and reduce the cost for the healthcare system, why shouldn't we do automatic substitution?"

Overall, several interviewees considered that substitution practices for biologicals would likely evolve over time and perhaps be introduced in the future. Most interviewees emphasized that introducing substitution for [monoclonal antibody (mAb)] biologicals would be premature, as the level of trust in biosimilars is still considered too fragile: "Everyone is still learning about biosimilars." Enforcing or prematurely introducing substitution could negatively affect the acceptance of biosimilars. Most pharmacists compared

the discussions about substituting biologicals with those at the time of generic market entry. Similarly, the debate was considered to stem from fears that the patient would not respond as well to the treatment and that there would be problems tracking which product the patient receives. Another pharmacist argued that, as the originator also changes over time because of manufacturing changes, the patient is already exposed to different versions over time.

In addition to psychological considerations, several regulators and pharmacists explained that organizational and policy barriers exist: "Substitution could be done, but the conditions need to be appropriate." An information system that allows good pharmacist-physician communication is necessary. Furthermore, some pharmacists mentioned that a clear mandate from national authorities is required. Several interviewees also stated that an adequate system for reporting adverse reactions is essential. Pharmacists should also be trained to educate patients about a possible (change in) injection device. Alternatively, specialized pharmacies could be nominated to carry out substitution.

Furthermore, interviewees also noted that differentiation between therapeutic areas and product types could be applied (proportionality of risk) and physicians should be allowed to veto a substitution if appropriately motivated. For example, where product effects are known to possibly wane over time, development of tolerance at the time of substitution could adversely affect the patient-HCP relationship.

Stakeholder considerations regarding substitution for biologicals are shown in Fig. 3.

3.2 Towards Improved Stakeholder Willingness to Use Biosimilars: Biosimilar Value Proposition and Stakeholder Incentives

Stakeholder-specific considerations are presented in Figs. 4 and 5.

3.2.1 Reasons to Use Biosimilars and Possible Differentiators Between Products

Generally, the lower price of biosimilars was recognized as the most important benefit, with some viewing it as the only benefit. Several interviewees acknowledged that, with the introduction of market competition, savings could also be derived from reduced prices for reference products. Some interviewees argued that biosimilars should not be favoured per se over the reference product, as the price of the reference product will generally also decrease.

Interviewees often mentioned that lower treatment prices could translate to improved patient outcomes as more patients could be treated within the same budget or patients could be treated earlier in the treatment pathway as it becomes more cost effective to do so.

Stakeholder considerations about (automatic) substitution	
Stakeholder considerations about current context	Outlook on possible future substitution
<ul style="list-style-type: none"> • Emotional barriers <ul style="list-style-type: none"> • More trust and experience with biosimilars may need to be gained by stakeholders before introduction of substitution • Physicians fear to lose control over treatment • Current landscape considered too fragile • Practical barriers <ul style="list-style-type: none"> • Pharmacists and systems (e.g. physician-pharmacist communication systems outside of the hospitals) may be insufficiently prepared • In most European countries, no mandate given to pharmacists to substitute biologicals 	<ul style="list-style-type: none"> • Could be considered in future years when practical and emotional barriers are addressed • Elements on how to organize: <ul style="list-style-type: none"> • Always inform the physician: no automatic substitution • Allow motivated exceptions for specific products or patients • Clear mandate from the National Competent Authority • Practical communication system between physician and pharmacist • Reliable system for reporting of adverse events • Patient counseling by pharmacist in case of change in injection device

Fig. 3 Stakeholder considerations about (automatic) substitution

What are advantages offered by biosimilars according to stakeholders?			
Depending on the region/country, the value offered by biosimilars (balance between benefits) may be different			
Towards savings	Towards the patient/care		Towards innovation
<p>Lowered treatment costs</p> <ul style="list-style-type: none"> • Lower priced biosimilar • Price competition upon biosimilar market entry <ul style="list-style-type: none"> • Lower priced reference product • Lowered prices in broader therapeutic class* 	<p>Increased patient access to biological treatment</p> <ul style="list-style-type: none"> • More patients treated within the same budget • Earlier treatment of patients with a biological due to improved cost-effectiveness (advancing therapy to an earlier treatment-line) 	<p>Improved delivery of care</p> <ul style="list-style-type: none"> • Support from specialized nurse • Differentiation and improvements in injection device • Value-added services (e.g. disease programs to enhance patient adherence)** 	<p>Reinvestment of savings in reimbursement of innovative medicines</p>
	<p>Lowered patient co-payment</p>	<p>Plurality in suppliers, beneficial in case of shortages</p>	<p>Innovation in biologicals development (product differentiation)</p> <ul style="list-style-type: none"> • New administration routes • New indications • New formulations*** • Next-generation biologics***

Fig. 4 What are the advantages offered by biosimilars according to stakeholders? Asterisks indicate possible benefits from biosimilars mentioned in the literature that were not mentioned during the expert interviews. *QuintilesIMS [32]; **Simoens and Cheung [33]; ***Dutta et al. [34]

Some interviewees reasoned that biosimilar savings could create budgetary headroom for the reimbursement of innovative medicines. Some mentioned increased freedom for physicians to prescribe new therapies as a benefit.

Some interviewees argued that reasons to use biosimilars will vary regionally. In regions with good access to biological therapies, savings derived from biosimilar use are expected to be reinvested in the reimbursement of innovative medicines, whereas in regions with limited access, biosimilar entry could translate to increased patient access.

Several physicians and regulators indicated that biosimilars could also improve delivery of care, including improvements in the administration device or by providing

administration routes that do not (yet) exist with the reference product. Furthermore, packaging differences can potentially impact positively on patient co-payments (e.g. introducing more units per package while retaining the same out-of-pocket cost). Respondents thought these differentiation strategies could stimulate originator companies to also introduce extra services, and one patient mentioned that the availability of different products could positively impact the patient’s product choice.

Some pharmacists mentioned that the availability of biosimilars (i.e. the presence of different suppliers of the product) could also be beneficial to secure supply in case of shortages.

How to motivate stakeholders – a balanced combination of non-tangible and tangible incentives	
Non-tangible incentives	Tangible incentives/gainsharing
<ul style="list-style-type: none"> • Creating HCP awareness about treatment costs • Calling on/enforcing the societal responsibility to prescribe in a cost-effective manner <ul style="list-style-type: none"> • Stimulate the “what is best for society” perspective • Reinvest savings derived from biosimilar use (predominantly) in the healthcare system • Correct application and transparent organization of tender procedures • Reporting transparently about the gains from biosimilar introduction <ul style="list-style-type: none"> • Visualize and report about benefits • Communicate about allocation of savings • Reporting usage data to allow peer-to-peer benchmarking and monitoring of purchasing/prescribing <ul style="list-style-type: none"> • Among prescribers (prescribing behaviour) • Among hospitals (purchasing behaviour) • Can simultaneously instil HCP trust 	<ul style="list-style-type: none"> • Providing a tangible incentive to compensate for switch effort <ul style="list-style-type: none"> • Incentive towards improving care rather than a personal financial benefit <ul style="list-style-type: none"> • In terms of extra HCP staff • Financial benefit for hospital unit • Tailoring of incentive proportional to required effort <ul style="list-style-type: none"> • Effort to switch SC products may be larger due to possible differences in injection device (training of patients) • Threshold may be higher for products dispensed outside the hospital (less structural support and no tender driving the decision)

Fig. 5 How to motivate stakeholders: a balance between non-tangible and tangible incentives (as identified from expert interviews). *HCP* healthcare professional, *SC* subcutaneous

Several interviewees remarked that more effort is required to ensure that the market becomes or remains sufficiently attractive, ensuring continued investment in the development of new and market presence of already approved biosimilars. A few interviewees mentioned that decreased interest in the biosimilar segment and subsequent competition may lead to shortages. “If prices are driven down too much, some players will go out of the market, certainly in smaller markets, putting such markets at risk of drug shortages.”

Most interviewees identified price as the main, or sole, differentiator between the reference product and its biosimilar(s), as they perform equally in terms of efficacy and safety. Some interviewees considered factors beyond price when choosing between products. These included supply reliability, value-added services such as information support, and the delivery device and injection material for subcutaneous products. Some nurses argued that the patient friendliness of the product and its ease of use should be assessed together with the patient. The presentation of different concentrations was mentioned by a few pharmacists as another possible differentiator.

It was argued that additional services should be considered as a bonus and should not trump price differences. Some interviewees questioned the value of some differentiators, such as the citrate-free formulation for some adalimumab products: “How much weight do we want to award to these, sometimes, low impact differences?” Several pharmacists advocated for transparent award criteria to assess differentiators.

3.2.2 Motivating Stakeholders to Use Biosimilars

3.2.2.1 Creating Awareness About Medicine Prices and Calling Upon Stakeholders’ Societal Responsibility

Some interviewees expressed the need for increased awareness of medicine prices among HCPs and the public. Several regulators and physicians argued that it is the duty of the physician to prescribe and that of the society to use medicines in a cost-effective manner: “As a society, we have the obligation to look at the economic aspects once the product is considered equal.” Some physicians and regulators argued that decisions should be made from a common good perspective (“what is best for society”) and that the stakeholders involved should not expect compensation. As a Danish nurse mentioned, “It is money for the Danish people, it is not for our hospital to gain money. It is not the Danish way to gain something. Savings should go towards the society.” Most pharmacists agreed because they considered biosimilar implementation to be part of the job. Some physicians mentioned that discounts should be sufficiently substantial to offset the effort invested in biosimilar implementation. Some argued that the government should take a more active role in guiding which product(s) to use.

3.2.2.2 Raising Awareness About Biosimilar Benefits and Reporting Usage Data

Several physicians and pharmacists felt that information about the benefits derived from biosimilar use was often lacking but was an important motivational factor for biosimilar use. One regulator mentioned

that a powerful incentive for patients to use biosimilars would be increased patient access, but some nurses asserted that such arguments are not always convincing for patients: “You should treat patients at patient level and not tell them, ‘You create access for many other patients worldwide.’ It’s not convincing.” Several patients and nurses explained that it is difficult to persuade patients who are satisfied with their current treatment to switch. In contrast, one physician indicated that a few patients asked to be treated with the biosimilar. Earlier treatment access when using a biosimilar might be a more convincing incentive, as it could lead to a personal benefit for a patient. Overall, several interviewees across groups considered that the benefits derived from biosimilar use should be communicated more clearly: “As sustainability of healthcare is for all of us, we should try to stimulate education about the impact of biosimilars as much as possible.”

Several patients mentioned that there is no tangible incentive for patients to use biosimilars when treatment is fully reimbursed and that the willingness to switch may be greater in settings where these medicines are only partly reimbursed. Furthermore, with regard to motivating patients, one Dutch interviewee mentioned that lowering the patient’s ‘own risk’ insurance payment when agreeing to switch has been effective in the Netherlands.

Apart from improving awareness about biosimilar benefits, some physicians believed another stimulus for biosimilar use would be to transparently report biosimilar usage data among prescribers and hospitals, as this provides useful insights into colleague prescriber behaviour and, subsequently, gives confidence to less experienced stakeholders.

3.2.2.3 Allocation of Savings: Balancing Societal and Stakeholder Benefits and the Need for Transparency Some HCPs and patients felt that the savings should (partially) remain at the departmental level or within the therapeutic area that helped to realize the savings. Others were indifferent to the allocation level as long as savings were reinvested in healthcare. Some interviewees expressed concerns that savings would be reinvested towards structural or practical improvements (e.g. hospital infrastructure) and not towards patient care per se. Some argued that the government should decide on how to allocate savings. Overall, interviewees asked for transparency regarding the allocation of money saved.

3.2.2.4 Providing Tangible Incentives When Switching: Applying a Gainsharing Model Most physicians and nurses and some regulators considered that a tangible incentive would be appropriate to compensate stakeholders when biosimilar use requires significant HCP effort in terms of planning and time, i.e. when switching. Several regulators and HCPs considered that physicians lack the motivation to

invest energy and time in a switch if the impact is solely on an overarching, more abstract, financial level. Furthermore, it was argued that the incentive should be proportional to the effort (e.g. a larger incentive for switching to a subcutaneous product, as this may require more time for injection device training). Most interviewees considered direct financial benefits on an individual level to be inappropriate but considered that allocating part of the realized savings to improving patient care, such as financial support for the hospital ward or hiring new staff (i.e. gainsharing), would be an adequate and acceptable stimulus. An additional nurse may help balance the extra workload and enable more active follow-up of the switch. Reinvesting some savings in increased monitoring to reassure patients was mentioned as another gainsharing example. Some physicians mentioned that publication opportunities may also be a motivator.

3.2.2.5 Considerations for Incentive Design in Hospital vs. Ambulatory Care Settings Several physicians highlighted that defining incentives for biosimilar implementation in ambulatory care, particularly in countries where these are not part of the hospital budget, can be challenging. Some interviewees deemed that in the hospital context, a tender would be a satisfactory lever, lessening the need for accompanying incentives. As some pharmacists explained, introducing a negative incentive by lowering the product reimbursement level (e.g. 80% of list price) by payers (such as in Belgium) motivated hospitals to organize competitive tenders, ensuring product acquisition costs below the lowered reimbursement limit.

4 Discussion

This article is the second part of a study on European multi-stakeholder learnings about biosimilars. The article outlines the considerations of various stakeholders as to how to implement biosimilar switching and design incentives to stimulate biosimilar use and translates them into practical, overarching, and strategic recommendations (as shown in Table 1). The results of this study may support HCPs and policy makers when planning to improve biosimilar use in healthcare systems. We propose that actions be centred around the 11 key recommendations outlined in Table 1.

It is important to recognize that most of the expert considerations were related to their experience with anti-tumour necrosis factor products. Strategies should ideally be tailored to the treatment setting (hospital vs. ambulatory care, chronic vs. shorter-term treatment), product type (more simple biologicals vs. more complex mAbs), and patient needs. The other strengths and limitations of this study are described elsewhere [8].

Table 1 Multi-stakeholder recommendations—key points for decision makers and healthcare professionals in Europe**Practical recommendations addressing acute/shorter-term HCP needs regarding switching, supporting HCP biosimilar use**

1. Communicating about results from RCTs, real-world studies, and clinical experiences regarding (multiple) switching
2. Providing a clear, one-voice EU overarching regulatory position regarding the interchangeability of biosimilars
3. Developing a multi-stakeholder implementation and communication protocol to guide switching in clinical practice
 - a. Guidance development on how to structurally organize a switch with involved stakeholders
 - b. Guidance development on communication strategies towards patients, limiting bias and mitigating a possible nocebo effect
 - c. Possibility to allow tailoring of strategies to the context of the treatment setting, product type, and individual patient needs (more detailed information provided in Fig. 2)
4. Developing and applying a balanced combination of non-tangible and tangible incentives for physicians and other stakeholders to use biosimilars
 - a. Proportional tailoring of incentives to offset the stakeholder effort invested in biosimilar implementation (i.e. effort may be higher when switching subcutaneous products because of possible differences between injection devices)
 - b. Application of a gainsharing agreement, reinvesting a part of the savings towards improving care and lowering the time and effort threshold associated with a switch by, for example, hiring additional staff

Overarching recommendations regarding switching decisions

5. Applying a pragmatic switch approach, considering the potential gains vs. longevity of treatment
6. Avoiding top-down organized switching, allowing and organizing stakeholder involvement, communication, and alignment

Strategic recommendations towards long-term sustainable competition with biosimilar presence

7. Raising awareness about medicine prices and stakeholders' societal responsibility to use and prescribe medicines in a cost-effective manner
8. Communicating publicly and actively about savings/advantages resulting from biosimilar use
9. Sharing of biosimilar uptake and prescribing data among hospitals and prescribers to allow peer-to-peer benchmarking
10. Reporting transparently about the allocation of savings resulting from biosimilar use
11. Developing policies with a long-term vision, beyond realizing short-term savings and with a focus towards creating a sustainable market with presence and competition of multiple suppliers

Tailoring of strategies to the specific treatment setting, the product type, and stakeholder needs is desirable

HCPs healthcare professionals, RCTs randomized controlled trials

In line with findings from the considerable number of switch studies conducted over recent years [10, 11], the interviewed experts largely considered switching from a reference product to a biosimilar to be a part of clinical care. However, stakeholders indicated a need for guidance regarding multiple switching, as regulatory guidance predominantly focusses on a single switch from a reference product to a biosimilar, and a harmonized regulatory position about interchangeability across Europe is lacking [10, 11, 18]. A clear Europe-wide one-voice regulatory position about interchangeability and switching is required to support stakeholders faced with switch decisions in Europe. Such a European position will require an active request by and collaboration between the national regulatory agencies, the EC, and the European Medicines Agency (EMA), and could be taken up by the Heads of Medicines Agencies. Also, data regarding multiple switching between reference products and biosimilars, and between biosimilars of the same reference product, have been reported [19–25] and are likely to accumulate with increasing experience, which can further support stakeholders.

There was strong desire for the adoption of a structured and collaborative approach to implementing a switch. Furthermore, several switch experiences in clinical practice showed the benefits of using a managed switch programme in terms

of cost savings while maintaining similar patient-reported outcomes [26, 27]. Opinions on how to involve the patient varied, and finding an appropriate balance for sharing information was deemed challenging. Overall, tailoring communication to the individual patient was considered important.

As also mentioned in previous publications [28–31], this study found that stakeholders are concerned about mandated switching, as this may result in worse patient-perceived treatment outcomes because of a possible nocebo effect. Involving and aligning HCPs and patients when making switch decisions can positively affect acceptance and limit nocebo effects. Other strategies to mitigate a possible nocebo effect include delivering balanced information, focussing on treatment equality, explaining the reasons for and the benefits of a switch, and conveying the physician's trust in the biosimilar to the patient. As discussed in the first article of this series, disseminating switch experiences may translate into increased HCP and patient trust [8].

Several strategies to increase stakeholder willingness to use biosimilars emerged from the interviews. Although opinions on how to design incentives diverged (and were also culturally influenced), incentives to offset the work associated with a switch were generally deemed necessary. A combination of non-tangible incentives (e.g. calling upon

societal responsibility and transparent reporting about savings allocation) and tangible incentives (e.g. extra staff) could be applied and tailored to the level of effort required in the local and societal context. Gainsharing agreements emerged as the preferred way to motivate stakeholders, as savings could partially serve to improve local clinical care. Visualizing and communicating clearly and transparently about biosimilar-related savings and how these are then allocated could improve stakeholder motivation.

As the learnings from this study primarily apply to the hospital context, future research could focus on switch and incentive approaches tailored to the ambulatory care setting.

5 Conclusion

This study proposes practical and strategic measures to improve biosimilar implementation practices and increase the willingness of stakeholders to use biosimilars based on insights from different stakeholder groups (patients, physicians, pharmacists, nurses, and regulators). Suggested solutions included applying a structured switch and communication strategy, implementing a combination of non-tangible and tangible stakeholder incentives, and actively providing information regarding the benefits of biosimilar use. The recommendations from this study can support HCPs with biosimilar use and decision makers with designing biosimilar policies and stakeholder incentives.

Acknowledgements The authors thank the interviewees for their willingness to participate and share their insights. The authors would also like to thank S. Ozcicek, S. Pinoy, L. Stragier, and C. Vanneste for their help with conducting and processing interviews.

Author contributions All authors contributed to the study conception and design. LB conducted the structured literature review. LB and four pharmacy students conducted and coded the interviews. LB analysed the literature and interview data and prepared the first draft of the manuscript. All authors reviewed and commented on the manuscript. All authors read and approved the final manuscript. No data, figures, or tables have been published previously, and the manuscript is not under consideration elsewhere.

Declarations

Funding This manuscript was funded by the KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity (MABEL Fund).

Conflict of interest IH, SS, and AGV are founders of the MABEL Fund. AGV is involved in consulting, advisory work, and speaking engagements for a number of companies, including AbbVie, Accord, Amgen, Biogen, Fresenius/Kabi, Medicines for Europe, Pfizer/Hospira, Mundipharma, Roche, Novartis, Sandoz, and Boehringer Ingelheim. SS was involved in a stakeholder roundtable on biologics and

biosimilars sponsored by Amgen, Pfizer, and MSD. He has participated in advisory board meetings for Pfizer and Amgen and contributed to studies on biologics and biosimilars for Hospira, Celltrion, Mundipharma, and Pfizer. IH and LB have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Ethics approval was obtained from the Education-Guidance Committee for Medical Ethics in delegation of the Ethics Committee of UZ/KU Leuven (MP001375, Belgium).

Consent to participate All interviewees provided their written informed consent to participate in the study.

Consent for publication All interviewees provided their written informed consent for us to use the coded data of their interview for publication in scientific journals.

Data availability The interview data are not publicly available as they contain information that could compromise interviewees' privacy and consent.

Code availability Not applicable.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. IQVIA. Advancing biosimilar sustainability in Europe—a multi-stakeholder assessment. 2018. <https://www.iqvia.com/insights/the-iqvia-institute/reports/advancing-biosimilar-sustainability-in-europe>.
2. IQVIA. The impact of biosimilar competition in Europe. 2018. <https://ec.europa.eu/docsroom/documents/31642/attachments/1/translations/en/renditions/native>.
3. European Medicines Agency. Biosimilar medicines. https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/field_ema_med_status/authorised-36/ema_medicine_types/field_ema_med_biosimilar/search_api_aggregation_ema_medicine_types/field_ema_med_biosim. Accessed 12 Jun 2020.
4. IQVIA. The impact of biosimilar competition in Europe. 2019. <https://ec.europa.eu/docsroom/documents/38461/attachments/1/translations/en/renditions/native>.
5. Simon Kucher & Partners. Payers' price & market access policies supporting a sustainable biosimilar medicines market. 2016. https://www.medicinesforeurope.com/wp-content/uploads/2016/09/Simon-Kucher-2016-Policy-requirements-for-a-sustainable-biosimilar-market-FINAL-report_for-publication2.pdf.

6. Dylst P, Vulto A, Simoens S. Barriers to the uptake of biosimilars and possible solutions: a Belgian case study. *Pharmacoeconomics*. 2014;32:681–91.
7. Lepage-Nefkens I, Gerkens S, Vinck I, Piérart J, Hulstaert F, Farfan-Portet M. Barriers and opportunities for the uptake of biosimilar medicines. 2013. https://kce.fgov.be/sites/default/files/page_documents/KCE_199Cs_Biosimilars_syntheseENG_0.pdf.
8. Barbier L, Simoens S, Vulto AG, Huys I. European Stakeholder Learnings Regarding Biosimilars: Part I - Improving Biosimilar Understanding and Adoption. *BioDrugs*. 2020. <https://doi.org/10.1007/s40259-020-00452-9>.
9. Faccin F, Tebbey P, Alexander E, Wang X, Cui L, Albuquerque T. The design of clinical trials to support the switching and alternation of biosimilars. *Expert Opin Biol Ther*. 2016;16:1445–533.
10. 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.
11. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G, et al. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. *Drugs*. 2018;78:463–78.
12. Colloca L, Panaccione R, Murphy TK. The clinical implications of nocebo effects for biosimilar therapy. *Front Pharmacol*. 2019;10:1–11.
13. 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;32:397–404.
14. Simoens S, Le PC, Boone N, Breedveld F, Celano A, Llombart-Cussac A, et al. How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers. *Generics Biosimilars Initiat J (GaBI J)*. 2018;7:70–4.
15. NVZA. NVZA Toolbox Biosimilars—Een praktische handleiding voor succesvolle implementatie van biosimilars in de medisch specialistische zorg. 2017. https://nvza.nl/wp-content/uploads/2017/04/NVZA-Toolbox-biosimilars_7-april-2017.pdf.
16. European Commission. Biosimilar medicines—information for patients. 2016. <https://ec.europa.eu/docsroom/documents/26643>.
17. Medicines Evaluation Board. Antwoorden op vragen over biologische medicijnen Krijgt u biologische medicijnen. 2018. <https://www.cbg-meb.nl/onderwerpen/medicijninformatie-originele-biologische-medicijnen-en-biosimilars/documenten/brochures/2020/01/01/biologische-medicijnen>.
18. European Medicines Agency. Biosimilars in the EU—information guide for healthcare professionals. 2017. https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf.
19. Wizemann V, Rutkowski B, Baldamus C, Scigalla P, Koytchev R. Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anaemia treatment. *Curr Med Res Opin*. 2008;24:625–37.
20. Gerdes S, Thaçi D, Griffiths CEM, Arenberger P, Poetzl J, Wuerth G, et al. Multiple switches between GP2015, an etanercept biosimilar, with originator product do not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis: 30-week results from the phase 3, confirmatory EGALITY study. *J Eur Acad Dermatol Venereol*. 2018;32:420–7.
21. Sigurdardottir V, Husmark T, Svard A. Switching from reference product etanercept to the biosimilar SB4 in a real-life setting: follow-up of 147 patients. *Ann Rheum Dis*. 2017;76:835.
22. Blauvelt A, Lacour J-P, Fowler J, Schuck E, Jauch-Lembach J, Balfour A, et al. Long-term efficacy, safety, and immunogenicity data from a phase III confirmatory study comparing gp2017, a proposed biosimilar, with reference adalimumab. *Am Coll Gastroenterol*. 2017;112:S419.
23. Genovese M, Glover J, Matsunaga N, Chisholm D, Alten R, et al. Efficacy, safety and immunogenicity in randomized, double-blind (DB) and open-label extension (OLE) studies comparing FKB327, an adalimumab biosimilar, with the adalimumab reference product (humira®; rp) in patients (PTS) with active rheumatoid arthritis. *Arthritis Rheumatol*. 2017;69(Supplement 10):ACR abstract number 2799.
24. Blackwell K, Semiglazov V, Krasnozhan D, Davidenko I, Nelyubina L, Nakov R, et al. Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. *Ann Oncol*. 2015;26:1948–53.
25. Macaluso FS, Fries W, Viola A, Centritto A, Cappello M, Giuffrida E, et al. The SPOSIB SB2 sicilian cohort: safety and effectiveness of infliximab biosimilar SB2 in inflammatory bowel diseases, including multiple switches. *Inflamm Bowel Dis*. 2020. <https://doi.org/10.1093/ibd/izaa036>.
26. Razanskaite V, Bettey M, Downey L, Wright J, Callaghan J, Rush M, et al. Biosimilar infliximab in inflammatory bowel disease: outcomes of a managed switching programme. *J Crohns Colitis*. 2017;11:690–6.
27. Chan A, Kitchen J, Scott A, Pollock D, Marshall R, Herdman L. Implementing and delivering a successful biosimilar switch programme—the Berkshire West experience. *Futur Healthc J*. 2019;6:143–5.
28. Ighani A, Wang JY, Manolson MF. Biosimilar viewpoints from the perspective of psoriasis patients who use either biologic or systemic treatments. *J Am Acad Dermatol*. 2018;79(Supplement 1):AB57.
29. Robinson K, Esgro R. Revealing and addressing knowledge gaps regarding biosimilars in rheumatology practice with targeted continuing education and patient surveys. *Arthritis Rheumatol*. 2018;70(Supplement 9):2808–9.
30. Karateev D, Belokoneva N. Evaluation of physicians' knowledge and attitudes towards biosimilars in Russia and issues associated with their prescribing. *Biomolecules*. 2019;9:57.
31. Karki C, Baskett A, Baynton E, Lu Y, Shah-Manek B. Perceptions of cost pressure associated with biosimilars among physicians in Europe. *Value Heal*. 2018;21(Supplement 1):S253.
32. QuintilesIMS. The impact of biosimilar competition in Europe. London: QuintilesIMS; 2017.
33. Simoens S, Cheung R. Tendering and biosimilars: what role for value-added services? *J Mark Access Health Policy*. 2020;8(1):1705120.
34. Dutta B, Huys I, Vulto AG, et al. Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! *BioDrugs*. 2020;34:159–70.