Biosimilar Uptake: The Importance of Healthcare Provider Education

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Abstract

From peptide hormones to monoclonal antibodies, advances in biotherapeutic medicines, or biologics, have brought incalculable benefits to patients, especially for conditions where previous classes of therapy were ineffective or non-existent. At the same time, the development of biologics has been accompanied by questions of access and cost. The advent of biosimilars, molecules highly similar to their reference biologics, has offered the promise of ameliorating cost and access challenges. However, issues regarding biosimilar uptake remain. Multiple factors impact the utilization of biosimilars by healthcare providers and perhaps the best recognized of these is education. This paper discusses the importance of education to biosimilar adoption and lists action-items that various stakeholders in healthcare can adopt to improve the overall understanding of this important class of therapeutics.

Key Points

- Education is an important factor to the acceptance and adoption of biosimilars.
- Action-items related to the promotion and improvement of biosimilars education are presented.

1 Introduction

From antibiotics to statins, small molecules dominated the twentieth century armamentarium and remain a formidable category of medicines today. However, if current innovation and spending trends continue, then the future is more likely to belong to biologics—complex molecules produced from living organisms and/or tissues. The development of biosimilars, molecules highly similar to their reference biologics, will further transform the biologic landscape. The promise of biosimilars rests on the twin pillars of affordability and accessibility. Much as generics did for small molecules, it is hoped that widespread availability and adoption of biosimilars will increase the affordability and accessibility of biologics. Of course, the potential success of biosimilars is intimately tied to their uptake by healthcare providers. Biosimilars education is a key component of promoting this uptake, as recognized by the US Food and Drug Administration (FDA) in its Biosimilars Action Plan [1]. The aim of this article is two-fold: (i) to highlight key aspects of the ongoing discussion about the importance of education to the adoption of biosimilars and (ii) to offer actionable items for various stakeholders to consider in what should be a common goal of a more informed healthcare provider population, confident in the growing array of biosimilar tools at their disposal.

2 Importance of Education

The first biosimilar to receive regulatory approval anywhere was the human growth hormone somatropin, in 2006, by the European Medicines Agency (EMA). As a biologic that serves an arguably smaller patient population, it wasn’t until the approval of the world’s first monoclonal antibody biosimilars in 2013 (to infliximab), also by the EMA, that the importance of biosimilar education began to come to the forefront. Initial attempts to gauge the perception of biosimilars among clinicians indicated that uptake would be heavily dependent on prescriber comfort with the new medicines. For example, a very early survey of randomly selected
members of the European Crohn’s and Colitis Organization (ECCO), carried out in the fall of 2013, only weeks after the approval of infliximab biosimilar, indicated that 61% of responding clinicians had little or no confidence in using biosimilars in everyday clinical practice; only 5% were totally confident, with the remaining falling in between [2]. This view was not isolated to practitioners in Europe as a February 2014 survey of members of the Canadian Rheumatology Association (CRA) revealed similar results. When faced with a scenario where a treatment-naïve patient is an ideal candidate for a biologic, and where cost was not an issue, 72% of clinicians would be unlikely, or very unlikely, to select a biosimilar as initial therapy [3]. These early market insights revealed commonalities amongst providers with hesitation to be early adopters of biosimilars. The lack of knowledge or confidence regarding biosimilars among some healthcare providers, continues to serve as a barrier to adoption—a situation that is further compounded by the presence of misinformation and disparagement [4]. In order to overcome any potential hesitation with biosimilars from a scientific or clinical standpoint, education will need to be at the forefront.

This article is not intended to be a systematic review of the literature about familiarity with, and acceptance of, biosimilars by healthcare providers. For an in-depth summary of various surveys and studies carried out during the early days of biosimilars (2014–2017) the reader is directed to a comprehensive analysis and references therein [5]. Instead, this article summarizes the knowledge gaps that have been identified, and that contribute to greater provider hesitancies with biosimilars. The studies reviewed by Leonard et al. [5] pointed to the following areas where additional education was needed.

### 2.1 Immunogenicity, Safety, and Efficacy

When it comes to biologic treatments in general, the most common and significant safety concern is related to immunogenicity, or the propensity of the biologic to provoke an immune response to itself and/or to other related proteins. Given the highly sensitive nature of biologics, any change in manufacturing process has the potential to result in a clinical consequence of an altered immunogenicity profile [6]. Yet manufacturing changes often occur with biologic drugs; as an example, originator infliximab has undergone over 3 dozen manufacturing changes since its approval [7]. The FDA has an established evaluation processes to review manufacturing changes and their potential impact on the performance of a product [8]. Furthermore, the risk of immunogenicity with switching to a biosimilar has not been shown to be any greater than switching between two batches of any biologic [9]. A systematic literature review of 178 studies (both randomized controlled trials and real-world evidence), which included approximately 21,000 patients, concluded that switching from a reference biologic to a biosimilar was not related to any major efficacy, safety, or immunogenicity issues [10]. Nevertheless, despite the growth in data and evidence supporting safe use of biosimilars, continued education on the inherent variability associated with biologics and their manufacturing process, in addition to the FDA’s rigorous processes for reviewing biosimilar applications, will go a long way to address potential provider concerns with biosimilar immunogenicity, safety and efficacy.

### 2.2 Regulatory Pathways

Using the FDA’s 351(k) regulatory approval pathway as an example, biosimilars undergo rigorous scientific evaluations to ensure a high level of similarity in structure, pharmacokinetics (and pharmacodynamics), clinical efficacy, and safety to the reference biologic [11]. The goal of the biosimilar approval pathway is to establish a high level of similarity with the originator biologic, which results in the greatest regulatory weight being placed on the physiochemical characterization of the molecule. With the regulatory emphasis on ensuring a high level of analytical “sameness” with the originator biologic, versus establishing independent safety and efficacy, the role of clinical studies in the approval pathway is to address any residual uncertainty remaining after analytical studies are completed. In fact, as a result of the UK’s robust scientific and regulatory experience with biosimilars since the first approval in 2006, the Medicines and Healthcare products Regulatory Agency (MHRA) updated its regulatory guidance for biosimilar approvals, stating that comparative efficacy trials may unnecessary if the approach is supported by sound scientific rationale [12]. The reliance on the totality of data for biosimilars serves as a paradigm shift for healthcare providers who traditionally rely on robust, Phase III clinical studies in multiple indications to inform their opinion on the safety and efficacy of a drug. Therefore, education on the scientific rigor behind the biosimilar regulatory approval pathways, as well as experiences gathered over the past 15 years, is critical to strengthen provider confidence in evaluating and adopting biosimilars.

### 2.3 Extrapolation

Studies have revealed greater provider hesitation with biosimilar utilization in indications that were granted via extrapolation, citing the concept as a barrier to biosimilar adoption [13–15]. Extrapolation refers to the process by which a biosimilar is approved for use in an indication held by the reference product, without the need to conduct clinical trials in that indication. An example of this is the approval of the first infliximab biosimilar in the USA for all indications held by the originator (including inflammatory bowel
disease (IBD)) based on an application containing clinical study data for ankylosing spondylitis (AxSpA) and rheumatoid arthritis (RA) only. The FDA, for example, utilizes the totality of data to approve indications via extrapolation for biosimilars which includes: all available data in the biosimilar application, previous findings of safety and efficacy for other approved indications for the reference biologic, and knowledge and considerations of various scientific factors for each indication. This process is one of the key scientific principles that allows biosimilars to enter the market quicker and with less developmental costs associated with conducting additional clinical trials. Education on how extrapolated indications are granted by regulatory bodies, and the critical quality attributes needed to establish scientific justification, is important to ensure provider confidence exists with all indications approved for a biosimilar.

### 2.4 Interchangeability

With a regulatory designation unique to the USA, the topic of interchangeability continues to be one of the most commonly referenced knowledge gaps amongst providers [5, 16, 17]. An interchangeable biosimilar, according to the FDA, is expected to produce the same clinical result as the reference product in any given patient and can be automatically substituted for the reference biologic at the pharmacist level, per individual state laws [18]. It is important to note that interchangeability is a regulatory designation, not a clinical one. Given the implications of the designation, interchangeability is most relevant for biosimilars that will be reimbursed under the pharmacy benefit. However, the perception of what it represents can create barriers to adoption when providers associate the designation with clinical performance of the product. As of June 2021, there are no interchangeable biosimilars available on the US market1. Education is critical to close knowledge gaps associated with the regulatory definition and implications of interchangeability, especially when it contributes to provider hesitation with biosimilar utilization.

### 3 Do Increases in Uptake Mirror Gains in Education?

In the previous section, areas of concern that were repeatedly identified by clinicians during the early days of biosimilar market availability were summarized. It is instructive to take a look at provider acceptance of biosimilars over time, and how educational efforts may have played a role in adoption rates. While any insight gained from analyzing survey-based data is, at best, strictly correlative, it can nevertheless be useful in capturing trends.

To assess changes in gastroenterologists’ perceptions, and the potential role of education in evolving perceptions, ECCO surveyed its members in 2013 (as mentioned earlier) and 2015 to allow a comparative analysis [2, 19]. The earlier survey revealed a much more hesitant perspective with biosimilars amongst European gastroenterologists, with majority of respondents having little or no confidence about the use of biosimilars. However, following the entrance of infliximab biosimilars in the European market in 2013, drastic changes in provider attitudes towards biosimilars were identified by 2015. As revealed in the surveys, 47% of respondents felt either totally or very confident with biosimilars in 2015 (compared to only 13% in 2013) and an additional 34% respondents were “confident enough”. Moreover, the 2015 survey revealed more than a 50% reduction in safety concerns with immunogenicity associated with biosimilars. The authors of the study attributed the significant changes in attitudes to increased biosimilar knowledge from extensive educational efforts in the EU on biosimilars including postgraduate education, as well as published evidence from clinical practice [19]. Along with enhanced familiarity and confidence in biosimilars, market adoption of infliximab biosimilars in the EU grew over 10% in 2015, with a rapidly increasing rate of adoption resulting in over 50% market share by 2017 [20].

By contrast, continued knowledge gaps identified through market research studies with US rheumatologists may reveal contributing factors to the limited adoption of infliximab biosimilars in the USA. A survey conducted in December 2016 with 102 US physicians, primarily rheumatologists, revealed only 38% of respondents were extremely familiar with the FDA’s definition of biosimilars [13]. Perhaps tellingly, 21% of respondents indicated they were extremely likely or likely to switch to a biosimilar if the patient was failing on the originator. Given that a biosimilar has no clinically meaningful differences from the originator in terms of safety, purity, and potency, such a decision to switch to a biosimilar after treatment failure on the reference biologic would also be expected to have undesirable outcomes. In fact, evidence-based guidelines on medical switching of biologics for multiple conditions, including RA and IBD, recommend switching patients who experience inadequate response or an adverse event with a biologic to an entirely different class of biologic or treatment option [21, 22]. Taken together, these findings indicated significant educational needs to address knowledge gaps associated with biosimilars. In a similar study conducted in 2019 with 320 US rheumatologists seeking to understand beliefs and knowledge about biosimilars, there was significant improvement in the level of familiarity with biosimilars, with 83% of respondents being very familiar with the FDA definition of a biosimilar.

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1 While this article was in production, the FDA granted its first interchangeability designation to a biosimilar of insulin-glargine.
biosimilar [23]. However, 34% still responded that they were very likely or likely to switch a patient who was not doing well on the reference product to a biosimilar. Even allowing for a possibly non-representative sample of US rheumatologists in this web-based survey (320 respondents out of 9050 invitees), this result still suggests that a not-insignificant number of US rheumatologists still have knowledge gaps on the concept of biosimilarity. On the one hand, these findings underscore the continued need for education amongst US rheumatologists, despite marked improvements with biosimilar familiarity. On the other hand, they signal the likelihood of additional contributing factors that will explain the limited market adoption (< 20% by January 2021) of infliximab biosimilars in the USA, despite having been available since 2016 (see also “Sect. 6” below).

Given the vast differences in years and patients days of biosimilar experience between various global markets, significant opportunities exist for countries with less biosimilar experience, such as the USA, to learn from more mature markets as seen across Europe. In addition to utilization and outcomes data, lessons can be learned from educational efforts and programs that have been deemed more successful or impactful in driving biosimilar confidence and utilization, such as Germany’s significant investment in physician education or the European Specialists Nurses Organisation (ESNO) creation of nurse-specific education to support patients switching to biosimilars (see [24] and references therein).

4 Patient Education and the Nocebo Effect

An essential, and at times underappreciated, aspect to improving biosimilar uptake is the importance of educating the patient population. In one of the earliest international surveys of patient perspectives on biosimilars, only 38% of nearly 1200 patients with irritable bowel disease (IBD) had heard of biosimilars; and of those, less than one-third would be fully confident in taking a biosimilar even if their physician explained and prescribed it to them [25]. Besides the obvious hesitancy to consent to treatment, thereby directly impacting uptake, a non-confident patient population can present an indirect hurdle to the uptake of biosimilars: the nocebo effect. This effect is believed to be responsible for negative treatment outcomes that arise because of a patient’s negative perceptions (or expectations) of the treatment and not because of the action of the treatment itself. The magnitude of this effect is not fully understood and could vary with disease state, but several recent studies on infliximab and etanercept biosimilars suggest an effect on the magnitude of 1 in 8 patients [26–28].

Regardless of the actual magnitude, the nocebo effect is not insignificant and, if not mitigated, can negatively impact the perception of biosimilar safety and efficacy among patients and clinicians alike. In the case of the former, this becomes self-reinforcing, i.e., a negative perception about biosimilars treatment results in (subjectively) a perceived negative outcome of the treatment thereby further reinforcing the negative perception and eroding confidence in, and adherence to, this class of treatments as a whole. In the case of the latter, this can make the outcomes of switching studies (which are used to help inform treatment decisions) appear more unfavorable toward the biosimilar than is warranted. Either way, this lowered perception of biosimilars caused by the nocebo effect can only negatively impact their uptake.

Fortunately, the nocebo effect has gained recent prominence in biosimilars therapy [29, 30]. The importance of patient education to mitigating the effect has also been recognized [30] and researchers are beginning to be able to measure its impact [31]. Patient education should be a two-pronged strategy. The first, and obvious, piece is education of the patients themselves by providing the necessary information and delivering it in an appropriate manner. The second piece is continued education of all healthcare providers (physicians, nurses, pharmacists, etc.) to ensure accurate, consistent, and coordinated messaging to patients along their care journeys. Patients place incredible levels of trust in those who treat them, and if a clinician harbors uncertainty about biosimilars (perhaps because they are not fully familiar, or comfortable, with the molecules) that lack of confidence can be internalized by the patient. After all, if the provider is not confident about a biosimilar, why should the patient be? There needs to be a uniform message across all categories of healthcare providers as discordant misinformation, for example between provider types, can lead to biosimilar rejection by the patient [32]. The path towards greater understanding and confidence in biosimilars, and ultimately to enhanced acceptance and increased uptake, is discussed in the next section.

5 The Path Forward

Education initiatives aimed at improving understanding of biosimilars should be viewed as the responsibility of all stakeholders in healthcare: these include healthcare providers; researchers and academics; pharmaceutical companies; industry associations; payers; regulatory bodies; patients and patient advocacy groups, etc. While coordination across all these diverse groups is hardly feasible, cooperation and collaboration are encouraged whenever possible. To conclude our discussion, a number of action-items are summarized the implementation of which will continue to improve understanding and acceptance of this important class of therapeutics. Some (such as continued research) are obvious, others less so. And while not all the stakeholders listed will be
able to partake in the entire list (e.g., patients will not con-
duct research), concerted efforts by stakeholders in parallel
will continue to improve understanding and acceptance of
biosimilars.

5.1 Continue Research

Data are always the best argument and continued evidence
generation is rightfully at the top of the list of action-items.
Indeed, the other items on this list will not be successful
unless they can build upon a solid foundation of ongoing
research. The good news is that with 15 years of biosimi-
lar use (and nearly a decade of biosimilar monoclonal anti-
body use) and over 2 billion patient days with biosimilars
treatment in the EU alone, the body of data regarding the
safety and efficacy of biosimilars has been largely positive.
In fact, in 2019, the EMA concluded that the “EU moni-
toring system for safety concerns had not identified any
relevant difference in the nature, severity or frequency of
adverse effects between biosimilars and their reference
medicines” [33]. However, it goes without saying that addi-
tional research, from randomized clinical trials to benchmark
switching studies like the NOR-SWITCH study, which set
a standard for studies comparing originator to biosimilars
[34], will continue to allay any continued concerns about
clinical parameters of safety, efficacy, and immunogenicity.
Pharmacovigilance studies looking at long-term biosimilar
use will also be needed, as the very first surveys of clinicians
in the biosimilar era revealed concerns about durability of
response beyond the 30- to 52-week follow-up period typical
of many clinical trials [3]. Finally, more real-world studies
will be required to account for the variability in patient char-
acteristics (not just medical, but financial and behavioral)
that are not covered in strictly controlled clinical trials, and
to account for the increasing reality of multiple switches,
which can occur for medical, or non-medical reasons (and
which are also relevant to understanding and minimizing,
the nocebo effect).

5.2 Build Treatment Standards (and Confidence)

In a survey of over 1200 US physicians across multiple
specialties, physician peers (64%) were the most trusted
source of biosimilar information, after peer reviewed litera-
ture (88%) and regulatory agencies (73%), such as the FDA
[16]. More recently, the importance of social influence was
demonstrated in a large network analysis showing subse-
quent uptake of bevacizumab being associated with peer-
to-peer connections to early adopters of the treatment [35].
Therefore, there is considerable opportunity for clinicians
to educate and influence their fellow practitioners regard-
ing biosimilars, thereby impacting uptake. One approach is
for clinicians to develop standardized treatment guidelines
for biosimilars. For a recent example of the development of
treatment algorithms and decision trees for various clini-
cal scenarios, consider the review article by Reinsch et al
on the use of infliximab and adalimumab biosimilars in
the treatment of moderate-to-severe Crohn’s disease [36].
Greater standardization has the benefit of reducing negative
outcomes from variance introduced by treatment setting and
clinician experience/expertise. Treatment standards will also
benefit real-world studies, which will be a lot easier to evalu-
ate if the input data (i.e., treatment regimens) are compara-
bale. A second approach is for clinicians to integrate biosimi-
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which are also relevant to understanding and minimizing,
the nocebo effect).

5.3 Account for Clinician Variance

While survey data regarding healthcare provider percep-
tion, and use, of biosimilars are helpful, it is important to
remember that they represent the aggregate. Clinicians are
not a monolith and there may be surprising differences in the
factors that associate with differences in prescriber comfort
with biosimilars. For example, a very recent switching study
from France followed a population of patients with inflam-
matory rheumatic disease that was eligible for a switch from
originator etanercept to biosimilar etanercept [39]. Rather
than the traditional switching studies whereby patients are
randomized to biosimilar or originator, or whereby patients
are switched entirely to biosimilar and compared to a
matched cohort, this study did not assign patients. Instead, physicians were given information about biosimilars and were then invited to propose a switch to their patients. The study then measured which factors were associated with whether or not a switch was made. Interestingly, a switch to biosimilar was significantly more likely with an older physician than a younger one, and with a physician who held a full-time academic position versus one who did not [39]. Impact of physician age was already apparent in the early days of biosimilars; the February 2014 survey of CRA members referenced above also indicated that physicians with >20 years of practice were significantly more likely to be familiar with biosimilars than those with < 10, or even 10–20, years of experience [3]. These types of data points suggest implications for biosimilars education. First, future survey designers should consider ways they can broaden their analysis to better understand physician characteristics that associate with biosimilar education/use. The more that can be understood regarding factors correlated with clinician prescribing behavior, the better designed educational interventions can be. Second, those developing educational materials, for example pharmaceutical companies training their medical science liaisons, should consider moving away from a one-size-fits-all approach. The results of the French and Canadian studies above suggest that messaging needed to allay the concerns of one sub-population of physician, may not be the same messaging for a different sub-population. In addition to physician characteristics, regional and cultural differences are also likely to affect healthcare provider response to education initiatives and, consequently, prescribing behavior.

5.4 Start Education Early

Additional data would definitely be required to further probe the apparent older-younger physician dichotomy in biosimilar familiarity and use suggested by the two studies referenced in the previous section. Nevertheless, the results raise an interesting question: how well are we educating our physicians (and pharmacists, and nurses, and so on) on biosimilars? It is possible that some of the clinician differences observed in those two studies could be diminished with more formal biosimilar education during their professional school programs. Although there is no formal across-the-board curriculum requirement for biosimilars education, the types of content that would be useful for professional schools to cover can be found in an example of an educational framework proposing to integrate biosimilars into the pharmacy curriculum [40]. Medical schools and pharmacy schools do offer courses on managed care as part of their curriculum. Integrating biosimilars into managed-care courses, perhaps as case studies, could be a natural fit and would serve a dual purpose. It would (i) build the foundation of knowledge that will be needed for future providers regarding this important class of medicines; and (ii) place biosimilars in the context of many of the other managed-care issues, besides education, that also affect uptake (i.e., payer and reimbursement issues, formulary management, interchangeability, non-medical switching, step therapy, etc.). Early education intervention should definitely leverage resources available at the FDA, and other organizations, for content (especially content that informs the students about the regulatory pathways behind biosimilars approval). Additionally, early educational initiatives need not wait until students enter professional programs; undergraduate textbooks could (and should) include introductory discussions on biologics/biosimilars, for example, when describing monoclonal antibodies and their development as therapeutics.

5.5 Develop a Patient Messaging Strategy

Since this article introduced the importance of educating the patient, this is the first action item related to this goal. As discussed above, the impact of the nocebo effect on patient outcomes during biosimilar therapy can no longer be ignored. The importance of education in combating the nocebo effect has been recognized across many specialties, from inflammatory disease [41] to ophthalmology [42] and will not be reviewed here. The key question is how this educational need can be effectively met? A recent study suggests the importance of a unified messaging strategy from all providers interacting with the patient [31]. However, a messaging strategy without actual messaging tools is unlikely to be successful. To this end, it is instructive to highlight a couple of examples of recent efforts aimed at providing such tools. First, a laudable effort by ESNO has resulted in a practical guide for communicating with patients about biosimilars [43]. This document provides concrete examples of dialogue to use with patients when addressing common questions that arise during treatment with biosimilars. Second, the Biosimilar Toolbox from the International Association of Patient Organizations (IAPO) offers relevant information for patients’ organizations and advocacy groups [44]. Because these entities play an important role in patient education, it is crucial that they can disseminate the most up-to-date information in a clear and approachable fashion. It is precisely these types of messaging tools that will be indispensable in helping to bridge the information gap for patients and enable them to gain confidence in the treatment being prescribed. It will also be increasingly important to ensure that the development of similar messaging tools occurs across different media channels (print, mobile, video, audio/podcast), which
can be accessed by providers across different platforms. An excellent example of what a multi-channel tool (or platform) may look like is The Biosimilar Hub of the Generic and Biosimilar Medicines Association of Australia [45]. Aimed at providers and patients, this web-based clearing house of information goes beyond articles and news stories, incorporating videos, podcasts, and interactive experiences in a multi-pronged approach to disseminate useful information.

Finally, it bears mentioning that in addition to the contents of the message delivered to the patient, the way in which the message is delivered is also vital. Patients can be influenced by the same types of behavioral economics biases that have been described to influence physician attitudes towards biosimilars [38]. For instance, the framing of differences between originator and biologic can influence patient desire to switch, with positive framing (e.g., focusing on the similarities between originator and biosimilar) being more effective than negative framing (e.g., focusing on the minor differences between originator and biosimilar). In one recent study proposing a hypothetical switch, willingness to switch to a biosimilar was 2.36-fold higher ($p = 0.041$) in a study group exposed to positive framing versus one exposed to negative framing [46].

### 5.6 Recognize and Leverage the Key Role Played by Nurses

Nurses are the first point of contact for many patients visiting a physician’s office, and the main point of contact for patients in hospitals. Since many biosimilars require injection or infusion, these tasks are also most frequently carried out by nurses. So, while it is entirely reasonable to discuss the importance of the education of clinicians, and other healthcare providers, for biosimilars uptake, when the issue of educating patients comes into play, the importance of nurses cannot be overstated. There are many strong online resources, from regulatory agencies [47] to industry associations [48, 49], that can provide educational information for patients about biosimilars; they are important to the overall goal of improving knowledge. However, disparities in access to information (lack of broadband access in rural areas, affordability issues of broadband service and/or computer hardware, etc.), physical accessibility issues (such as vision problems), differences in comfort with internet use (especially among elderly), and language barriers, mean that even the best online resources will be out of reach for a segment of the population and thus of little use. These individuals will continue to get their healthcare information primarily from their healthcare providers and, for all the reasons outlined above, those providers will most frequently be nurses. Therefore, any education strategy aimed at improving patient knowledge must include, and leverage, that critical nurse-patient relationship.

### 5.7 Educate the Public Before They Become Patients (or Caregivers)

One of the previous action-items called for starting provider education on biosimilars early, during their professional school years. Similarly, individuals would ultimately benefit from an awareness of biosimilars even before they may eventually need them as patients or caregivers. Public service advertising campaigns have successfully educated society about topics as diverse as seat-belt use, impaired driving, and tobacco use. While advocating for national biosimilars education campaigns is definitely not the aim of this action-item (nor would it be necessary), the ability of concerted communication efforts aimed at the public to shape attitudes and opinions is not insignificant. While the number of individuals receiving biologic (or biosimilar) therapy at any one time may not be a large percentage of the population, one should consider that patients themselves are not the only members of the public that would benefit from rudimentary knowledge of biologics, including biosimilars. Family members and caretakers are often important components of the treatment process, especially when patients may not be in a position to fully grasp the details of the therapies (for example, individuals who take on the task of researching treatment options because their spouse is still processing their recent cancer diagnosis or children taking care of elderly parents with dementia). Education at the appropriate literacy levels can equip the broader population with exposure to these treatment options in order to minimize the potential for familiarity bias, whereby preference is given to what individuals know based on previous experience or simply, exposure. Patients will be better served if they, or their caregiver, are not starting from an absolute zero-level of knowledge. Therefore, any educational efforts by stakeholders in healthcare about biosimilars that are aimed at the general public are welcome; especially helpful will be targeted informational or education campaigns through patient advocacy organizations, or foundations supporting relevant disease states, which can provide meaningful, tailored support to those who would benefit most directly.

### 6 Conclusion

A period of familiarization precedes the widespread adoption of any new technology. This is a time of becoming acquainted with the benefits of the new advance and of evaluating potential drawbacks or concerns. In can be argued that biosimilars have undergone a period of familiarization over the past decade and a half, since the first-in-world approval of somatropin biosimilar. And while their adoption has steadily risen over that period of time, it is also clear that certain challenges to more widespread uptake remain. One of these is provider...
education. This article has highlighted some of the educational gaps often raised in surveys of various healthcare professionals regarding biosimilars and offered a number of action-items whose implementation will ensure continued improvements in the understanding of this important class of therapeutics. However, it is necessary to point out that education is not the only (and perhaps not even the most important) barrier to biosimilars adoption. The FDA’s Biosimilars Action Plan, referenced in the introduction of this article, is an example of governmental and/or regulatory authority acknowledgment of the importance of education to uptake [1]. But the very same Plan also listed improving efficiency of approvals process, maximizing regulatory clarity, and maximizing competition by minimizing gaming of the regulatory system as equally important. If increased biosimilars adoption is a worthy goal, then educational efforts will not succeed in isolation. Improvements in education must be part of a broader uptake strategy, including effective healthcare delivery models and stakeholder incentives, if the promise of increased access and affordability offered by biosimilars is to be realized.

Declarations

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References

1. Biosimilars action plan: balancing innovation and competition. 2018. https://www.fda.gov/media/114574/download. Accessed 30 Mar 2021.
2. Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn’s and Colitis Organization. J Crohns Colitis. 2014;8(11):1548–50. https://doi.org/10.1016/j.crohns.2014.06.007 (Epub 2014/07/11).
3. Grabowski D, Henderson B, Lam D, Keystone EC, Thorne C, Jamal S, et al. Attitudes towards subsequent entry biologics/biosimilars: a survey of Canadian rheumatologists. Clin Rheumatol. 2015;34(8):1427–33. https://doi.org/10.1007/s10067-014-2835-4 (Epub 2015/01/15).
4. Cohen HP, McCabe D. The importance of countering biosimilar disparagement and misinformation. BioDrugs. 2020;34(4):407–14. https://doi.org/10.1007/s40259-020-00433-y (Epub 2020/07/20).
5. Leonard E, Wascovich M, Oskouei S, Gurz P, Carpenter D. Factors affecting health care provider knowledge and acceptance of biosimilar medicines: a systematic review. J Manag Care Spec Pharm. 2019;25(1):102–12. https://doi.org/10.18553/jmcp.2019.25.1.102 (Epub 2018/12/28).
6. Vanderlaan M, Maniatis A, Olney R, Rahmaoui A, Yau L, Quarmby V, et al. Changes in manufacturing processes of biologic therapies can alter the immunogenicity profile of the product. Clin Pharmacol Ther. 2020;107(4):988–93. https://doi.org/10.1002/cpt.1694 (Epub 2019/10/20).
7. Mehr SR, Zimmerman MP. Is a biologic produced 15 years ago a biosimilar of itself today? Am Health Drug Benef. 2016;9(9):515–8 (Epub 2017/05/04).
8. Changes to an approved application: biological products. 1997. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-application-biological-produ cts. Accessed 11 July 2021.
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. https://doi.org/10.1016/j.drudis.2019.06.016 (Epub 2019/06/30).
10. Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, 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. https://doi.org/10.1002/cpt.1836 (Epub 2020/04/30).
11. FDA’s overview of the regulatory guidance for the development and approval of biosimilar products in the US. https://www.fda.gov/files/drugs/published/FDA%20%28%20%29s-Overview-of-the-Regulatory-Guidance-for-the-Development-and-Approval-of-Biosimilar-Products-in-the-US.pdf. Accessed 30 Mar 2021.
12. Guidance on the licensing of biosimilar products. 2021. https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products. Accessed 11 July 2021.
13. Gibofsky AB, Badawi S. Biosimilar knowledge among US rheumatologists—a survey [abstract]. Arthritis Rheumatol. 2017;69. https://acrabstracts.org/abstract/biosimilar-knowledge-among-us-rheumatologists-a-survey/. Accessed 30 Mar 2021.
14. Yeh TJ-SY, Phillips E, Gajra A, Feinberg B. US community rheum atologists’ knowledge and perceptions of biosimilar expanded indication approval by extrapolation [abstract]. Arthritis Rheumatol. 2019;71. https://acrabstracts.org/abstract/us-community-rheumatologists-knowledge-and-perceptions-of-biosimilar-expande d-indication-approval-by-extrapolation/. Accessed 30 Mar 2021.
Biosimilar Uptake: The Importance of Healthcare Provider Education

15. Cohen H, Beydoun D, Chien D, Lessor T, McCabe D, Muenzberg
16. Aladul MI, Fitzpatrick RW, Chapman SR. Healthcare profession-

18. Biosimilar and interchangeable products: The U.S. FDA perspec-

23. Gibofsky A, McCabe D. US rheumatologists' beliefs and knowl-

25. Peyrin-Biroulet L, Lonnfors S, Avedano L, Danese S. Changes in

28. Scherlinger M, Langlois E, Germain V, Schaeferbeke T. Accept-

32. Scherlinger M, Langlois E, Germain V, Schaeverbeke T. Accept-

33. Biosimilars in the EU. Information guide for healthcare profes-

sionals. 2019. https://www.ema.europa.eu/en/documents/leaflet/
biosimilars-eu-information-guide-healthcare-professionals_en.
pdf. Accessed 11 July 2021.

34. Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with origin-

ator infliximab (NOR-SWITCH): a 52-week, randomised, double-
blind, non-inferiority trial. Lancet. 2017;389(10086):2304–16. 
https://doi.org/10.1016/S0140-6736(17)30068-5 (Epub 2017/05/16).

35. Keating NL, O'Malley AJ, Onnella JP, Gray SW, Landon BE. Association of physician peer influence with subsequent physi-

ician adoption and use of bevacizumab. JAMA Netw Open. 2020;3(1):e1918586. https://doi.org/10.1001/jamanetworkopen. 
2019.18586 (Epub 2020/01/04).

36. Reinsch W, Geese K, Halfvarson J, Irving PM, Jahnson J, Pey-

rin-Biroulet L, et al. Clinical practice of adalimumab and inflixi-

mab biosimilar treatment in adult patients with Crohn's disease. 
Inflamm Bowel Dis. 2021;27(1):106–22. https://doi.org/10.1093/ 
ibd/izaa078 (Epub 2020/07/08).

37. Armuzzi A, Bouhnik Y, Cummings F, Bettey M, Pieper B, Kang 
T. Enhancing treatment success in inflammatory bowel disease:
optimising the use of anti-TNF agents and utilising their biosimil-
ars in clinical practice. Dig Liver Dis. 2020;52(1):1259–65. 
https://doi.org/10.1016/j.dld.2020.06.008 (Epub 2020/07/01).

38. Nahban C, Feinberg BA. Behavioral economics and the future of 
biosimilars. J Natl Compr Canc Netw. 2017;15(12):1449–51. 
https://doi.org/10.6010/jnccn.Jnccn.2017.7023 (Epub 2017/12/11).

39. Al Tabaa O, Etcheto A, Dumas S, Bateau F, Goulvestre C, Molto 
A, et al. Doctor’s aptitude for switching from innovator etan-

ercept to biosimilar etanercept in inflammatory rheumatic diseases: experience from a single French rheumatology tertiary care center. Eur J Clin Pharmacol. 2021;77(1):25–33. 
https://doi.org/10.1007/ 
s00228-020-02957-2 (Epub 2020/09/06).

40. Li E, Liu J, Ramchandani M. A framework for integrating biosimil-

ars into the didactic core requirements of a doctor of pharmacy 
curriculum. Am J Pharm Educ. 2017;81(3):57. https://doi.org/10. 
5688/ajpe81357 (Epub 2017/05/13).

41. Kim H, Alten R, Avedano L, Dignass A, Gomollon F, Greveson 
K, et al. The future of biosimilars: maximizing benefits across 
immune-mediated inflammatory diseases. Drugs. 2020;80(2):99– 
113. https://doi.org/10.1007/s40265-020-01256-5 (Epub 2020/02/01).

42. Sharma A, Kumar N, Bandello F, Loevenstein A, Kuppermann 
BD. Need of education on biosimilars amongst ophthalmologists: 
combating the nocebo effect. Eye (London). 2020;34(6):1006–7. 
https://doi.org/10.1038/s41433-019-0722-6 (Epub 2019/12/01).

43. Switch management between similar biological medicines—a 
communication and information guide for nurses. 2019. 
https://
www.esno.org/assets/files/biosimilar-nurses-guideline-final_EN-lo.pdf. Accessed 30 Mar 2021.
44. Biosimilars Toolkit. an information and advocacy toolkit for patients’ organizations. https://www.iapo.org.uk/biosimilars-toolkit. Accessed 11 July 2021.
45. Welcome to the biosimilars hub. https://biosimilarhub.com.au/home-page-hcp/. Accessed 11 July 2021.
46. Gasteiger C, Jones ASK, Kleinstauber M, Lobo M, Horne R, Dalbeth N, et al. Effects of message framing on patients’ perceptions and willingness to change to a biosimilar in a hypothetical drug switch. Arthritis Care Res (Hoboken). 2020;72(9):1323–30. https://doi.org/10.1002/acr.24012 ((Epub 2020/07/23)).
47. Biosimilars. 2020. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars. Accessed 30 Mar 2021.
48. Patient learning track. https://www.biosimilarshandbook.org/patient-learning-track/. Accessed 30 Mar 2021.
49. Medical professional learning track. https://www.biosimilarshandbook.org/medical-professional-learning-track/. Accessed 30 Mar 2021.