



# The Importance of Countering Biosimilar Disparagement and Misinformation

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Published online: 20 July 2020  
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## Abstract

Biosimilar use is limited in some healthcare systems because biosimilars are not well understood by many healthcare professionals and patients. The knowledge gap is exacerbated by disparagement of biosimilars and dissemination of misinformation, whether intentional or otherwise. There are several different types of disparagement and misinformation directed towards biosimilars as a class, including statements about biosimilar science or policy that are factually incorrect; misleading information, where the information is correct, but is provided out of context; incomplete information, where only partial or a limited set of facts are provided; creation of a false narrative, especially in scientific and medical literature, that provides a set of references to support incorrect conclusions; and negative message framing of factual statements to create a negative perception. Disparagement and misinformation about biosimilars can be countered by educational efforts, appropriate oversight, and regulatory activities with the option of enforcement action by governmental agencies, if warranted. Balanced educational materials about biosimilars should be made easily accessible. Physicians, nurses, pharmacists, and patient advocacy groups should work together to provide patients with consistent, positive messages about the value of biosimilars.

## Key Points

Biosimilars will contribute to multiple-source biologics markets when they are allowed to compete fairly with their reference products.

There are several different types of disparagement and misinformation directed against biosimilars, individually and collectively, that are impeding their ability to contribute to a sustainable multiple-source biologics market.

Disparagement and misinformation about biosimilars can be countered by balanced educational outreach across stakeholders, appropriate regulatory oversight, and use of enforcement powers already granted to government agencies.

## 1 Introduction

Biosimilar drugs developed to the standards of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), or the World Health Organization (WHO) offer multiple benefits at patient and societal levels [1]. Biosimilars are viable treatment options because they provide the same safety and efficacy as their reference biologic products [2–4]. In some healthcare systems, availability of biosimilars has expanded patient access to optimal treatment and increased the sheer number of patients receiving care [5]. In addition, competition from biosimilars has led to lower overall costs for both reference biologics and biosimilars. In some locales, biosimilar savings have enabled health plans to cover additional drugs or hire more healthcare professionals (HCPs) [6, 7].

Despite these benefits, biosimilar use is still limited in some healthcare systems because they are not well understood by many HCPs and patients [8]. This mistrust is exacerbated by negatively biased information disseminated by some parties [9, 10], some of which was observed as early as 2013 [11]. In this Current Opinion article, we examine the challenges that biosimilars face due to disparagement and dissemination of misinformation, whether intentional or otherwise. To our knowledge, this is the first detailed

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analysis of this topic as it pertains to biosimilars. Examples are provided for each category, but they are not intended to be an exhaustive list.

## 2 Conceptual Challenges

There are conceptual differences between reference biologics and biosimilars that may not be well understood. Surveys of physicians and patients have revealed knowledge shortcomings and highlight the need for further education on biosimilar drug development and approval [12, 13].

### 2.1 Product Variability

HCPs are generally unaware that all biologics, especially those with post-translational modifications, are complex mixtures of related molecular variants that share the same amino acid sequence and that there is inherent batch-to-batch variability among both reference biologic products and biosimilars because they are produced in genetically engineered living cells [12]. This heterogeneity is controlled during manufacturing, and the extent of heterogeneity is quantified via process and product testing [14]. With a lack of understanding of this fact, the term “biosimilar” can be problematic because “similar” can be misunderstood as implying a difference of some sort. It may be conceptually difficult to appreciate that a copy product can provide the same clinical outcome even if it is not absolutely identical in structure to its reference product, which as noted above can have batch-to-batch variability and can even vary within a batch.

### 2.2 Abbreviated Licensure Pathway

Biosimilar approvals in the USA are developed using “an abbreviated licensure pathway,” a term used by the FDA in their implementation guidances and in their educational documents that describe the US *Biologics Price Competition and Innovation Act* of 2009 (BPCIA) [15, 16]. The term “abbreviated” could be perceived as being less rigorous or “more relaxed” [17]; however, this does not mean that a lower standard of approval is applied to biosimilar or interchangeable products than to reference biological products. As explained by the FDA, abbreviated licensure refers to “the ability to rely on FDA’s previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly (clinical) drug development program” [18].

### 2.3 Totality of Evidence

Biosimilars are approved based on “the totality of evidence,” with analytical analysis as the foundation and clinical safety and efficacy studies conducted as needed only to confirm the similarity already established through direct structural, functional, and pharmacokinetic/pharmacodynamic (PK/PD) comparisons of the reference biologic and biosimilar. This differs from originator biologic approvals, which are typically developed and approved based on phase 3 safety and efficacy studies conducted individually for each indication [18, 19]. Approval based on totality of evidence is a new concept for HCPs.

### 2.4 Clinical Data

HCPs routinely review data from clinical studies to understand the outcomes that they can expect for their patients. The data expectations for biosimilars are novel and different from what HCPs have been trained to accept for the reference biologics that biosimilars are designed to match. Clinical safety and efficacy studies conducted with biosimilars are designed to confirm the biosimilarity that was established by use of structural, functional, and PK/PD methods. As a result, the endpoints in clinical studies used to establish biosimilarity may be different from those used in the studies used to approve the reference product. And in general, there are fewer clinical studies conducted with a biosimilar compared to its reference product. While the clinical data package supporting biosimilar approval is more streamlined compared to the reference product, the overall data package is equally rigorous [18, 19]. Furthermore, it is misleading to compare data packages across biosimilars, as different developers of biosimilars to the same reference product may elect to use different study designs or even study different indications.

### 2.5 Extrapolation

The concept of extrapolation may be difficult to understand in the context of biosimilars. Extrapolation of indications is based on structural and functional similarity and PK/PD data, and not between the indications of the reference product [18]. It is understandable that patients and their health-care providers might prefer a drug explicitly studied in each indication when they lack an understanding and appreciation of how extrapolation is applied towards biosimilars. However, extrapolation is a scientific principle that has been used widely for decades in other regulatory settings, most notably in the development of chemical and biological drugs when manufacturers seek to modernize one or more steps used in synthesis, fermentation, purification, or formulation [20].

## 2.6 Wording of Legislation

The wording of legislation can be confusing. The BPCIA specifies that biosimilars must have “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” [15]. This is slightly different wording when compared to one of the criteria for interchangeability, a US regulatory designation that is different from biosimilarity. Interchangeability is a designation that is specific for the US and means a biosimilar may be substituted by a pharmacist for the reference product without the intervention of the HCP who wrote the prescription, consistent with state law [21]. The BPCIA specifies that interchangeable biologics are (1) biosimilars that “can be expected to produce the same clinical result as the reference product in any given patient” [15], and that (2) there is no clinical impact if patients switch back and forth multiple times between reference biologic and interchangeable biologic. In their guidance on the topic, the FDA has stated that unless explicitly agreed upon otherwise, a distinct clinical PK or PD switching study will be required to demonstrate interchangeability [21]. In our opinion, the use of similar wording that is functionally identical for biosimilarity and for the first of the two criteria for interchangeability has led to confusion in the USA in understanding the difference between biosimilarity and interchangeability.

## 3 Types of Biosimilar Disparagement and Misinformation

An analysis of negative and inaccurate information disseminated about biosimilars reveals several different types of disparagement and misinformation directed towards biosimilars as a class of products (Table 1).

### 3.1 Statements About Biosimilar Science or Policy that are Factually Incorrect

Factually incorrect information is often directed at one aspect of the biosimilar pathway or data supporting biosimilars. For example, one of the strongest sets of data supporting biosimilars is the extensive safety monitoring of biosimilars in the EU since the region’s first biosimilar approval in

2006. With over 700 million patient days of exposure as of 2019 [22], the EMA concluded that “over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines” [23]. Nonetheless, claims have been made that the EU pharmacovigilance monitoring of biosimilars is inadequate and patients cannot be confident about the reliability of these data [24, 25]. If believed, this could cause some to dismiss the extensive EU safety experience with biosimilars and could lead to unwarranted concerns about their safety. The fact is that these assertions are far from the truth [26]. There are many EU countries with sizable populations that have advanced pharmacovigilance systems that are as excellent as any pharmacovigilance system in the world [27]. The EMA and the FDA have been emphatic that HCPs and patients can be reassured that biosimilars approved in the EU and the USA are as safe and effective for their intended use as their respective reference medicines [18, 23].

Another common but incorrect assertion is that in the USA, interchangeability is a higher quality standard than biosimilarity [28]. The FDA has been clear that there is only a single set of quality standards for drugs of biological origin [18]. A designation of interchangeability is intended by statute to meet a regulatory standard that would enable substitution by the pharmacist in either a retail or specialty pharmacy setting without the intervention of the HCP who prescribed the reference product [21]. It is a different regulatory category compared to biosimilarity and requires additional and different clinical data. But the quality standards for biosimilars and interchangeable biologics are absolutely identical.

### 3.2 Misleading Information, Where the Information is Correct but is Provided Out of Context

At times, biosimilar information is provided that is correct but presented out of context, causing a misleading impression. Claims have been made that while biosimilar infliximabs are available, there are no “interchangeable” biosimilar infliximabs available in the USA [29]. While this is factually correct because the FDA has not yet approved

**Table 1** Types of biosimilar disparagement and misinformation

1. Statements about biosimilar science or policy that are factually incorrect
2. Misleading information, where the information is correct but is provided out of context
3. Incomplete information, where only partial or a limited set of facts are provided
4. Creation of a false narrative, especially in scientific and medical literature, that provides a set of references to support incorrect conclusions
5. Negative framing of factual statements to create a negative perception

an interchangeable biologic, it is misleading as a scientific and clinical matter. Such claims do not provide the full context that in the USA an interchangeability designation is only relevant for drugs administered in a retail or specialty pharmacy setting [21]. Infliximabs are administered by a provider in out-patient clinics or in doctors' offices. In these non-retail settings, US pharmacists do not have the ability to substitute reference biologics and biosimilars. As a result, there is no practical application for pharmacist-mediated interchangeability of infliximabs in US hospitals, out-patient clinics, or physician offices, so there is no reason for a manufacturer of biosimilar infliximab to seek a US interchangeability designation. It is interesting to note that the FDA and the EMA agree that for purposes of physician prescribing, all approved biosimilars may be freely substituted by prescribing physicians without the need for additional clinical switching studies [29].

### 3.3 Incomplete Information, Where Only Partial or a Limited Set of Facts are Provided

Misleading perceptions can be created when only a limited portion of facts are shared without providing full details. For example, statements noting that biosimilars are not identical to their reference products are common [30, 31]. But these often omit the important fact that there is inherent batch-to-batch variability for all biologics, including reference biologics currently on the market. When making manufacturing changes to currently approved biologics, reference companies are required to complete a comparability exercise that is similar to the analytical comparisons done for the development of a biosimilar [14]. It should be reassuring to HCPs to know that health authorities require pre-defined limits for batch-to-batch variability of all biologics, including both originator biologics and biosimilars [32].

### 3.4 Creation of a False Narrative that Provides a Set of References to Support Incorrect Conclusions

Incorrect or misleading conclusions about biosimilars have been published in scientific literature, enabling others to quote the misleading conclusions as fact and creating a false narrative. An article on the ethics of biosimilars [33] cited three literature reviews [34–36] to conclude that the safety and efficacy of switching once from a reference product to a biosimilar is still controversial, and therefore physicians are ethically obligated to inform prospective biosimilar recipients of this “fact.” However, a close examination of the three reviews found that none of them identified any specific safety or lack of efficacy concern related to switching once from a reference biologic to a biosimilar. Another recent review of 178 switching studies also concluded that for the products studied, a single switch is not intrinsically

linked to an increase in immunogenicity, safety, or efficacy issues [37]. Nonetheless, the “fact” that there is a supposed controversy about the practice of switching from a reference biologic to a biosimilar was cited by another publication as part of a set of arguments against a Canadian provincial policy of switching from reference infliximab to biosimilar infliximab [38]. There is no scientific controversy about the practice of switching [39], but the false narrative persists.

### 3.5 Negative Framing of Factual Statements to Create a Negative Perception

Negative message framing of factual statements can also create a negative perception. As cited previously, one example is that biosimilars are highly similar but not identical to their reference products, which can be understood as implying a difference of some sort. The impact of message framing on biosimilar use was evaluated in a recent study that compared patient responses to a hypothetical switch from a reference biologic to a biosimilar that was accompanied with either positive or negative framing [40]. The authors found a greater patient willingness to switch to a biosimilar if the switch was explained to them by physicians (1) who emphasized the similarities between reference product and biosimilar and (2) who used positive body language and verbal cues to promote a positive interaction. In a real-world assessment of patient outcomes after switching to biosimilar infliximab or biosimilar etanercept, a study found higher acceptance and persistence rates after switching to a biosimilar when patients received an enhanced and coordinated communications strategy across the entire patient healthcare team that included positive messaging [41]. It has been demonstrated that negative perceptions may lead to negative outcomes, a phenomenon known as the nocebo effect [42–44].

Another example of negative framing is the pervasive use of the term “non-medical switching” or “non-medical substitution” when describing the transition from reference product to a biosimilar. This phrase has been used by both publications that support this practice as well as by those that warn against it [38, 45]. However, the terms non-medical switching and non-medical substitution actually refer to formulary-driven changes between drug options that are thought to be therapeutically equivalent, but that are very different in structure [46]. In contrast, biosimilars are proven to be highly similar in both structure and function to their reference products. Because a transition from a reference product to a biosimilar is between two highly similar products that health authorities have explicitly found to have no meaningful clinical differences, the concept and terms of non-medical switching and non-medical substitution do not apply to biosimilars [47]. The common but inappropriate use of these terms in respect to biosimilars conveys a negative connotation regarding switches to patients and their

HCPs when in fact such switches may be very beneficial in increasing access and possibly lowering costs to individual patients [47]. This was quantified in a survey that reported that 60% of EU physicians were either very comfortable or comfortable in switching of stable patients to biosimilars, but when the very same question was posed with the phrase "non-medical switching" inserted, the percentage declined to 42% [48].

#### 4 Potential Impact of Biosimilar Disparagement and Misinformation

Biosimilar disparagement and misinformation has a very real potential to slow adoption of biosimilars, diminishing opportunities to increase patient access and help generate healthcare system savings on pharmaceutical expenditures [9, 49].

Continued dissemination of disparaging, misleading, or incorrect information may lead to unwarranted concerns that patients will not attain maximal efficacy on a biosimilar or may have an adverse event that they would not have had with the reference biologic [43, 44, 50].

An HCP's lack of trust about the safety and effectiveness of biosimilars may be reflected in the manner and tone of conversations that they have with their patients [50].

Biosimilar disparagement and misinformation may cause patients to fear that they will receive an ineffective, inferior, or unsafe product. Patients could specifically request not to be treated with a biosimilar, or if they do receive a biosimilar, a negative preconceived opinion of the biosimilar may lead to poor clinical outcomes [43, 44, 50].

#### 5 Steps to Overcome Biosimilar Disparagement and Misinformation

Biosimilar disparagement and misinformation will continue unless it is challenged; we cannot ignore these activities. It is the responsibility of all stakeholders to challenge biosimilar disparagement and misinformation when encountered. Clear and unbiased scientific messaging will help biosimilars become widely accepted by patients and their HCPs as valid therapeutic options. Fortunately, authorities at the FDA and the US Federal Trade Commission have acknowledged that biosimilar disparagement and misinformation may exist and are considering steps to counter any such activity and to support the nascent biosimilar industry [51, 52]. This is not a US-specific concern, as biosimilar disparagement and misinformation may also be encountered in Europe and other developed or developing economic markets [53]. The public should be encouraged to report examples of

potential biosimilar disparagement and misinformation that are observed or encountered to health authorities and other governmental bodies with oversight. These bodies would then evaluate the report and take actions if appropriate [54].

Reviewers and editors of scientific journals and trade publications have a responsibility to rigorously review biosimilar articles submitted for publication to ensure that they are truthful and balanced.

Education with a focus on clarity is critical to dispelling these activities. There are a multitude of educational materials already developed by health authorities, professional societies, patient advocacy groups, and industry [23, 55–63]. A cascade of verified information from these groups to patients will help allay patient concerns and support biosimilar acceptance. These efforts are already ongoing, but must be accelerated and amplified.

Biosimilar education should be incorporated into curricula of all medical, nursing, and pharmacy schools [64].

Key sources of information about biosimilars should be provided in graphical format and in locations that are easily accessible and understandable to the public [65–67]. Patients frequently use internet search engines as their first stop in seeking information [68, 69].

Positive framing of key concepts will help address disparagement by highlighting the quality and benefits of biosimilars. Positive framing will also lead to supportive overall narratives that could encourage biosimilar use [40–44, 50].

#### 6 Conclusion

The negative impact of slower than initially anticipated uptake of biosimilars should not be underestimated. Patient health and the fiscal sustainability of healthcare systems are at stake. Furthermore, the importance of countering biosimilar disparagement and misinformation should not be dismissed based on an increase in uptake of some biosimilars, although it varies by both country and product [70, 71], because that would give license for the disparagement and misinformation to continue and ignores the long-term impact on HCP and patient trust.

Although there are multiple contributing factors [49], the slow uptake of biosimilars is likely due in part to the fact that patients and HCPs have at times been subjected to misleading, incomplete, out-of-context, and at times incorrect information about biosimilars. These activities can be countered by educational activities from respected sources and by regulatory actions. National authorities and governmental agencies with appropriate oversight should monitor to prevent dissemination of misinformation with the option of taking enforcement action if warranted. Balanced, educational materials about biosimilars should be

made easily accessible, and physicians, nurses, pharmacists, and patient advocacy groups should work together to provide patients with consistent, positive messages about the value of biosimilars.

**Acknowledgements** The authors thank Saiza Elayda and Julie Zawisza of Merck, Kim Campbell and Jeffrey Robinson of Sandoz, and Robert Popovian of Pfizer for their helpful comments.

**Author Contributions** Hillel P. Cohen wrote the initial draft and Dorothy McCabe edited the manuscript. Both authors finalized the manuscript together and take responsibility for the content.

## Compliance with Ethical Standards

**Funding** No funding was received by the authors for preparation of this article. The Biosimilars Forum, a US-based biosimilars trade association, provided funding to make this publication available to the public via Open Access.

**Conflict of interest** Hillel P. Cohen is an employee of Sandoz Inc., a division of Novartis and may own stock in Novartis. Dorothy McCabe is an employee of Boehringer Ingelheim. Hillel P. Cohen and Dorothy McCabe are co-chairs of the Education Committee of the Biosimilars Forum. The views expressed here are those of the authors in their roles with the Biosimilars Forum and not of their respective companies.

**Availability of data and material** Not applicable.

**Code availability** Not applicable.

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