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COMMENTARY





# Global policies on pharmacy-mediated substitution of biosimilars: a summary

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An extensive overview of policies related to pharmacy-mediated substitution of biosimilars across the world was carried out by Larkin et al. in 2017. The details of this are discussed in this commentary.

**Keywords:** Biosimilar, policy, regulation, substitution, switching

## Introduction

An extensive overview of policies related to pharmacy-mediated substitution of biosimilars has been carried out by Larkin et al. in their paper 'Pharmacy-mediated substitution of biosimilars – a global survey benchmarking country substitution policies' [1]. The paper includes information on 82 countries, which has enabled the authors to provide a global perspective and compare different regions of the world.

The authors find that, in 72% of the countries surveyed, substitution at the pharmacy level does not occur, either because it is not permitted or for other reasons. This was based on data collected by Pfizer company representatives working in the specific countries/areas.

## Clarifying the difference: substitution and switching

The paper by Larkin et al. focuses on the policies related to substitution of biosimilars in 82 countries across the globe [1]. Substitution is generally defined as the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [2]. Within the European Union (EU) most regulatory agencies and organizations representing healthcare professionals and/or patients have taken a position on the use of biosimilars. In general, the positions focus on switching instead of substitution [3]. Switching is defined as a decision made by the prescriber to exchange one medicine for another medicine with the same therapeutic intent. Switching generally involves all the stakeholders: the patient, prescriber, pharmacist and a specialized nurse [2]. It is known that any change to the medication can be met with negative expectations towards the new treatment (nocebo effect) and/or certain adverse events can be falsely related to the change in medication [4]. This stresses the importance of the involvement of the patient in insuring that they are given adequate information on switching and their treatment regimen. Involvement of the patient is specifically important when biological treatment is being administered by the patient himself or herself, e.g. subcutaneous administration in the home setting. This is because the device by which the biosimilar is administered might differ from the device of the reference product and the patient should be instructed how to use the new device.

## Recommendations for globally successful biosimilar substitution

In their discussion, Larkin et al. suggest six measures that should be considered by countries that are looking to develop guidance on pharmacy-mediated substitution of biosimilars. The authors believe these are essential if pharmacy-mediated substitution is to occur to safeguard patients and the first measure is to establish a legal framework for substitution. Most of the measures are not specific to substitution but are also applicable to switching and are applicable to all biologicals. This assumption is supported by measure 6, which states that a mechanism should be in place to ensure that patient and physician are informed when a product is substituted. With this measure, substitution is moving towards the definition of switching and this is in line with current practice in the EU [3].

The authors also describe measure 2, which proposes that an additional level of scientific evidence, in addition to the biosimilarity exercise, is required to enable designation as a biosimilar that can be substituted. In this context it is important to stress that a biosimilar approved in a country with stringent regulatory requirements, such as in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) countries, has shown to be similar to the reference product in terms of quality, biological activity, clinical efficacy and safety. Switching or substitution is therefore considered to be safe. The experience with changes in the production process that all biologicals undergo is also supportive for switching [3]. Additional switching studies face specific challenges related, among others, to the design (single-arm studies versus double-arm studies, one switch versus multiple switches), the endpoint, e.g. immunogenicity, pharmacokinetics, clinical efficacy, and the number of patients to be included [5]. The importance of a stringent regulatory system for biosimilars is supported by measure 5, as proposed by the authors. Measure 5 states that the country in question should actively apply stringent regulatory authority approval requirements for biosimilarity and therefore so-called non-comparable biotherapeutic products cannot be approved.

A robust pharmacovigilance system, as proposed by measure 3, is important for all medicinal products, as is traceability, due to the inherent batch-to-batch variability of biologicals. Several studies have shown that identification of the administered brand can be traced with a certain amount of certainty [6, 7]. These studies showed that identification of the product was possible without the availability of different International Non-proprietary Names (INNs), as has been proposed by the authors. At present it is not clear if different INNs will have a positive influence on traceability and this needs to be investigated further. In addition, several EU states have expressed concern as they think that different INNs could have a negative impact on the trust in biosimilars [8]. Identification of the

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batch numbers remains a challenge and needs improvement. Vermeer et al. have provided an overview of the challenges related to traceability and conclude that long-term solutions lie in expanding the accessibility to and increasing the electronic exchange of exposure data. This is specifically important to reduce the burden on clinical practice as in the current situation; there is a need to record batch numbers manually in patient dossiers [9].

Measure 4 states that the biosimilar should be approved for all indications of the reference product not protected by exclusivity. However, regulations in the EU state that biosimilar companies are not obliged to apply for all indications, for which the reference product is approved [10]. A reason not to apply for a specific indication can, for example, be that a specific formulation is not produced by the biosimilar company. There is a risk of off-label use, especially in the case of substitution. Switching is expected to reduce this risk of off-label use, as is the implementation of electronic patient files, which can be accessed by the pharmacist during patient care.

## Limitations

The authors highlight a number of limitations in their study. For example, country regulations can be different to what happens in actual clinical practice [1]. This is specifically relevant when a prescribed brand is not available and so, in such circumstances, clinical practice can go against country regulations in place as a different medication may be dispensed. In addition, the study does not clarify how different country viewpoints are taken into consideration. It is assumed that legislations are the primary basis for biosimilar substitution but, if there is no specific legislation in place related to the use of biosimilars, information is based on guidelines and viewpoints. This is complicated due to the different roles played by the stakeholders involved in the biosimilar discussion. For example, it is possible that physicians and pharmacists will have different guidelines to payers regarding substitution. This is important when considering the discussions on switching and substitution from reference product to biosimilar and that these are mostly driven by financial concerns and the increasing costs of medical care.

## Conclusion

Overall, Larkin et al. have provided valuable data on the substitution policies regarding biosimilars around the globe. In most countries, substitution is not permitted. This is in line with the current thinking in the EU, that involvement of all stakeholders is important during the implementation of biosimilars. This 'so-called' practice of switching will help patients, physicians, pharmacists and nurses build trust in biosimilars.

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