IFPMA

Pharmacy-mediated substitution for biosimilars

Position paper

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Introduction

What is pharmacy-mediated substitution?

Pharmacy-mediated substitution is a framework permitting substitution of medicines at the retail pharmacy without the consent of the prescribing physician. The terminology for pharmacy-mediated substitution is not consistent across countries and regions. Often terms like “automatic substitution”, “pharmacy-level substitution” and “generic substitution” are used.

What products does this position paper refer to?

This position paper only addresses substitution relating to biosimilars and their reference products at the retail pharmacy level. It does not address non-biological medicines, nor does it relate to medical switches that are done by the prescribing physician or the hospital where the patient is treated.

Who is the target audience?

In this paper, we outline a set of principles that can guide pharmacy-mediated substitution. While the principles are intended for the awareness of pharmacists, they can also relate to other healthcare providers, regulators, payers, and those involved in formulary and procurement decision-making.

Who evaluates whether a pharmacy-mediated substitution should be granted?

For recombinant biological products, which include biosimilars and their reference products, pharmacy-mediated substitution is not routinely implemented. In the limited number of countries where it occurs, it is generally based on cost considerations. The decision within a country to allow a pharmacist to substitute one biological product for another is not always made by the authority who approves (licenses) the medicine for use. For example, in the European Union (EU), all biosimilars are approved by a centralized process facilitated via the European Medicines Agency that allows them to be marketed in all EU Member States and associated countries. The EU approval process does not opine on pharmacy-mediated substitution, it is up to individual EU Member States to decide[1,2]. Currently, most of the EU Member States and the three European Economic Area States do not allow pharmacy-mediated substitution of biological products, neither does the United Kingdom (UK).

In the U.S, the Food and Drug Administration (FDA) approves biological products and may designate certain approved biosimilars as interchangeable.[3] However, individual states, based on their own laws and regulations, ultimately decide if pharmacy-mediated substitution is allowed for U.S FDA-approved interchangeable biosimilars. For Latin American, Asia-Pacific, African and the Middle Eastern countries, regulations are still evolving. However, the responsibility of implementation can be with the reimbursement agency (Australia) and physicians respectively (Brazil and Japan)[4].

[1] Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU
[2] Q&A on the Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU
[3] Considerations in Demonstrating Interchangeability with a Reference Product: Update Guidance for Industry
[4] Biosimilar regulation and guidelines in Japan

Regulatory and scientific aspects

Considerations for pharmacy-mediated substitution of biological reference products and their biosimilars

In general, pharmacy-mediated substitution should only be possible if the active substance has an identical international non-proprietary name (INN) and the patient can expect the safety and efficacy outcomes to be the same. Furthermore, for any medical devices needed to administer the product, such as pens, autoinjectors, or others, the patient should be able to use the product without additional instruction from the health care provider or supervision from the pharmacist. Exemptions should be considered if significant differences exist in the device to avoid medication errors and/or interruption of the treatment.

Usually, the biosimilar will be licensed for all indications of the reference product, however, there may be some instances where fewer indications are granted to the biosimilar. To avoid the use of a biosimilar in an indication for which it has not been licensed, pharmacy-mediated substitution should only occur for the indications for which the biosimilar is licensed.

Good pharmacovigilance practices for biological medicines require that specific product and batch information be documented and included in adverse event reports. Pharmacy-mediated substitutions could undermine these practices if prescribers are not aware of when, where, or how a substitution occurs, especially in the absence of any electronic health records for a given patient. Therefore, measures to ensure traceability and the unique identification of the biological medicine dispensed at the pharmacy to the patient are important.

Evaluation of immunogenicity risk

Biological products are complex molecules whose quality, safety and efficacy can be impacted by the manufacturing process, for example through different impurities, variations in glycosylation, or tertiary structure changes. Such changes may potentially lead to adverse clinical reactions. Immunogenicity is a particular concern with all biological products[5].

Therefore, a biosimilar product should be developed according to the WHO guidelines on evaluation of biosimilars and relevant guidelines published by stringent regulatory authorities (e.g., EMA, US FDA, Health Canada, Swissmedic). The guidelines describe the relevant quality, non-clinical and clinical data that is needed to address immunogenicity concerns.

[5] EMA Guideline on Immunogenicity assessment of therapeutic proteins. May 2017

Switching between the reference product and a biosimilar, or between various biosimilars to the reference product, could prompt an immune response different from the one encountered with uninterrupted use of one product e.g. the reference product or the biosimilar.

Ultimately, each product should be assessed on a case-by-case basis. The potential risk of increased immunogenicity associated with switching depends on several factors, for example:

- The complexity of the protein (e.g., small peptide, larger protein, monoclonal antibody)
- The immunogenic properties of the reference product and its class (e.g., antibody titers, neutralising capacity and cross-reactivity with endogenous substances, clinical experience)
- Potential clinical consequences of increased immunogenicity
- Route of administration
- Chronic/intermittent use vs. one-time use
- Evidence from switching between biosimilars and/or reference products.

Consequently, the risk of increased immunogenicity when switching should be carefully evaluated.

IFPMA recommendations on pharmacy-mediated substitution

Patient safety and access to medicines are critical in the context of pharmacy-mediated substitution, especially when it comes to biologic products including biosimilars.

- A structured science-based framework should be in place for the regulatory evaluation of pharmacy-mediated substitution.
- The prescribing physician should have the right to state on a prescription, “do not substitute” or “dispense as written” or some other statement that recognises no substitution must occur.
- Pharmacy-mediated substitution for biosimilars should only be granted if data is available to demonstrate that repeated switching between the reference product and the biosimilar is not associated with a higher risk than continuous treatment with the reference product. This data may come from a switching study but in some cases, it may not be necessary such as:
    - the product is not for chronic use
    - the product is a less complex protein where clinical experience with the reference product and its class shows that the immunogenic potential is low.
- Pharmacy-mediated substitution should only occur for the indications for which the biosimilar can be marketed (e.g., not excluded by intellectual property rights).
- The patient should be able to use the medical device associated with the biosimilar without supervision from the prescribing physician or nurse.
- Measures to ensure traceability (the unique identification) of the biological/biosimilar medicine including batch number handed out to the patient at the pharmacy are particularly important for pharmacovigilance when implementing pharmacy-mediated substitution with biosimilars.

If the above principles cannot be met, changing a patient from a reference product to a biosimilar or vice versa should only be done under supervision of the prescribing physician.