IFPMA Position Paper on:

PHARMACY-MEDIATED SUBSTITUTION FOR BIOSIMILARS

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 health care practitioner, typically the prescribing physician.

For many years, the practice has been in place in many countries for generics referencing small-molecule originator products and has proven effective at reducing healthcare costs for patients and society.

For biosimilars and their biological reference products, automatic substitution is only emerging and is not implemented in many countries. As in the case of generics, the practice is usually based on cost considerations only.

Requirements vary, but in general, pharmacy-mediated substitution is allowed only when the patient can expect the same efficacy and side effects following the switch. Furthermore, there should not be any need for additional instruction or supervision of the patient by health care providers or any increased risk to the patient.

Terminology

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.

The US has adopted a regulatory “interchangeability” designation in reference to biosimilars meeting certain additional criteria to mean that the product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. Depending on laws and regulations in each individual state, some states in the US may then permit pharmacy-mediated substitution. It should be noted that the designation is specific to the US and that the term “interchangeability” sometimes has a different meaning outside the country.

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, switches that are driven by the prescribing physician or the hospital where the patient is treated, or switches resulting from formularies or from tendering and other procurement practices, even if some of the same considerations outlined in this position paper may also apply in those cases.

REGULATORY AND SCIENTIFIC ASPECTS

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

Due to legal, regulatory and jurisdictional factors, the authority responsible for evaluating pharmacy-mediated substitution for a given medicine may not be the same as the authority responsible for licensing the medicine. For example, in the EU, all biosimilars are evaluated by the European Medicines Agency, whereas decisions about pharmacy-mediated substitution designations are made by each member state.

In addition to quality, non-clinical and clinical as well as regulatory skills, decisions about substitution designations also require expertise on prescriber practices, IT prescription infrastructure and how pharmacies work at a national or local level.

Evaluation of immunogenicity risk

Biological products are complex molecules. Their safety and efficacy can be affected by the manufacturing process, for example through impurities, glycosylation, tertiary structure changes and aggregations. This may result in adverse clinical consequences. Immunogenicity is a particular concern with all biological products[1]. All these aspects should be considered in the regulatory evaluation before licensing a biosimilar.

However, the documentation considered adequate for licensing a biosimilar may not be sufficient to establish that substitution at the pharmacy level can be implemented without posing an increased risk to patients.

Switching between the reference product and the biosimilar could prompt an immune response different from the one encountered with uninterrupted use of the reference product or the biosimilar. The potential risk of increased immunogenicity associated with switching depends on several factors, which all must be considered, for example:

- The complexity of the protein (small peptide, larger protein, monoclonal antibody...)
- The immunogenic properties of the reference product and its class (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 reference products within the class
- Will pharmacy-mediated substitution apply to first-time users of the active substance only?

The evaluation of pharmacy-mediated substitution should be done on a product-by-product basis. The need for clinical data in addition to that required for licensing should be considered. This may include a switching study evaluating immunogenicity in subjects exposed to repeated switching between the reference product and the biosimilar vs. subjects treated continuously with the reference product[2].

Other aspects to be considered

Usually, the biosimilar will be licensed for all indications of the reference product. However, scientific concerns relating to extrapolation of indications or intellectual property rights may in some cases result in fewer indications being 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.

Since the delivery system (typically an injection device) may differ significantly between the reference product and the biosimilar, and as this may result in a need for additional instruction to the patient when switching between the two products, aspects related to the handling of the delivery system following an unsupervised switch should also be assessed before allowing pharmacy-mediated substitution.

Good pharmacovigilance practice for biological medicines requires that the specific product and batch information should be documented in patient records and included in adverse event reports. Pharmacy-mediated substitution could undermine these practices if prescribers are not aware of the setting, timing, and nature of a substitution, for example in the absence of electronic health records for a given patient. Therefore, measures to ensure traceability and the unique identification of the biological medicine handed out to the patient at the pharmacy are particularly important when implementing pharmacy-mediated substitution of biosimilars.

IFPMA POSITION

A structured **science-based framework** should be in place for the regulatory evaluation of pharmacy-mediated substitution.

Pharmacy-mediated substitution for biosimilars should only be granted after an **evaluation of the immunogenicity risk** concluding that unsupervised switches do not pose an increased risk to patients.

A switching study demonstrating that **repeated switching** between the reference product and the biosimilar is not associated with a higher risk than continuous treatment with the reference product should be considered. Such a study may be waived in certain situations, for example if:

- the product is not for chronic use;
- the product is a less complex and well characterised protein where clinical experience with the reference product and its class shows that the immunogenic potential is low; or
- pharmacy-mediated substitution only applies to first-time users of the active substance.

Pharmacy-mediated substitution should only occur for the indications for which the biosimilar **is licensed**.

The **delivery system** and differences in handling following an unsupervised switch should also be evaluated.

The prescribing physician should have the **right to refuse** substitution.

Unless the requirements outlined above have been met, transition of a patient from a reference product to a biosimilar product should be **supervised by the treating healthcare provider**.

1 EMA Guideline on Immunogenicity assessment of therapeutic proteins. May 2017

2 US FDA Guidance for Industry. Considerations in Demonstrating Interchangeability With a Reference Product. May 2019