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Considerations for physicians on switching decisions regarding biosimilars

Introduction

Switching describes the medical practice of a physician deciding to exchange the product that a patient receives for another product. The practice of a physician electing to switch between different biological molecules is not new. Usually, this type of switching is motivated by a clinical imperative to find another suitable therapy for the patient because of efficacy and/or tolerability issues with the previous product.

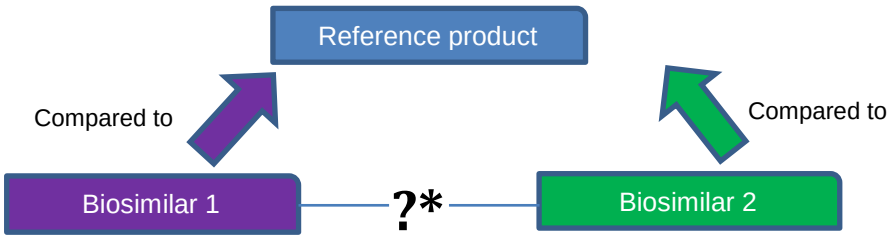
Biologics, including biosimilars are medicinal products that are often derived from proteins that have been produced using living organisms. Biologic medicines are usually larger and more complex than small molecule medicines therefore the clinical response depends on many patient, disease and product related factors (see below) and is best judged by the physician.

This means that:

- the prescribing physician must always retain the option to designate which biological product should be dispensed to a patient and treatment decisions must be made first on the basis of clinical judgment and then on the overall value proposition offered by individual medicines; and
- the treating physician, in consultation with the patient, should make any decision to switch patients from one biological product to another. Where switching occurs, it must be accompanied by adequate clinical monitoring and the patient must be informed appropriately at all times.

All biologics approved by regulatory authorities in compliance with relevant WHO guidelines are safe, effective and of high quality. With the introduction of biosimilars, i.e. biological products that are highly similar but not identical to their respective reference product, physicians may be encouraged within the healthcare system to switch patients from a reference product to any of its biosimilars (or vice versa) to reduce costs.

Group of Similar Products



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This position paper outlines some considerations that are relevant when making a decision to switch. As the diagram above highlights, to gain regulatory authority approval a biosimilar must be compared in terms of quality, safety and efficacy with its reference product before it qualifies for approval. However, there is no regulatory authority requirement for individually approved biosimilars to the same reference product to be compared with each other. *****Consequently, this type of data may not be available for any stakeholder to refer to when evaluating a switch between two biosimilars to the same reference product.

The complex nature of biological molecules, which are often used to treat patients who have multifaceted, chronic diseases, means that any decision to switch should be made on a case-by-case basis and must be patient, disease and product specific. A 'one size fits all' approach is not appropriate. Rather, it is important for the physician to balance the level of evidence against the level of risk or uncertainty in each particular case.

Key considerations when considering a switch

The following table outlines key factors and considerations. All these factors and sources of evidence need to be evaluated in the light of the patient, disease and product related factors for the case in question. For example, knowledge of the patient history, e.g. number of previous switches, patient's co-medications and co-morbidities and the therapeutic options available all need to be taken into account.

Potential Risk Factor	Considerations	Sources of evidence
Product not approved according to principles in global guidelines supporting biosimilar development	Has the biosimilar been approved according to the principles outlined in the WHO Similar Biotherapeutic Product (SBP) guidance? In some parts of the world so-called "non-comparable biotherapeutic products", are available those that have not been directly compared with the reference product and therefore may not meet global standards. Switching scenarios between these types of products and their reference product represent the highest level of uncertainty and risk to patient safety.	Approved by Regulatory Authorities in compliance with WHO guidelines on SBP's
Switching between the reference product and its biosimilar	Regulatory submissions for a biosimilar may sometimes include some data on switching from the reference product to the biosimilar and/or vice versa. The amount and type of data will vary with each submission.	For example public assessment reports from Regulatory Authorities & scientific literature

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Switching between biosimilars	There are unlikely to be any clinical data directly comparing different biosimilars to the same reference biologic in the similar group of related products. This is not required in regulatory filings. Switching between biosimilars represents an unknown, and one that harbours considerable uncertainty.	There may be anecdotal or real world data available
Nature of the product	All biologics are immunogenic, however, the nature and consequences of immunogenicity vary depending on the product. Information on the reference product and the biosimilar products may be helpful in this regard. For biological products that are substitutes for a naturally-occurring hormone/cytokine/receptor, there is an increased risk of serious consequences, (e.g. if antibodies directed towards native proteins are produced).	For example public assessment reports from Regulatory Authorities & scientific literature
Route of administration and dosing device	Subcutaneous administration is inherently more immunogenic than intravenous administration. Use of a different dosing device for the biosimilar may potentially increase the uncertainty as end users may be not be sufficiently familiar, when administering the product.	Label for biosimilar and reference product for dosing instructions
Extent and scope of post approval safety data	Where robust mechanisms for post approval safety monitoring of biologics including biosimilars exist, i.e. in jurisdictions compliant with WHO guidelines, such data may provide reassurance that the real-world use of the product does not result in any unexpected risks.	Assess risk management plan or post marketing safety reports via Regulatory Authorities. Publications on review of safety data

When is switching not recommended?

There are two scenarios in which switching from a reference product to a biosimilar (or between any products within a similar group of related products) is **NOT** recommended:

1. **When the initial treatment choice, e.g. reference product or biosimilar, loses efficacy or when there are tolerability issues, switching to a similar product within the same group of related products is not recommended.** This is because all of these products are expected to have similar clinical efficacy and safety to each other such that there is no incremental clinical benefit to the patient.

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2. **If the physician feels that on balance a switch is likely to compromise future treatment options for the patient, (e.g. with an alternate biological therapy), then a switch is not advisable**, although little is known about the consequences of multiple exposures to the same group of related products and the consequences on immunogenicity of future treatments with biologics.

Conclusions

The physician is best placed to assess the patient, disease and product, when deciding if and how to switch the biological product that a patient is receiving for another one. Therefore, the physician should retain decision-making autonomy and have unrestricted choice of products to prescribe. The physician should balance the level of risk and related uncertainties against the availability of evidence on a case-by-case basis. When physicians are considering to switch treatment it is important that the patient history is taken into account and switches are recorded appropriately in the patient's file, as well as the brand name and batch number of the products prescribed and dispensed.

Effective pharmacovigilance (PV) for biologics is always important, especially when there are multiple treatment options available. Product level traceability is critical, for biologics even more so than other medicines due their potential immunogenic effects, throughout the cycle of prescribing, dispensing, recording and reporting of these medicines. To achieve this, measures to identify the product by brand name and batch number are needed in policy and in practice. However, much of this effort relies upon the effectiveness of the PV system, as well as on safety reporting practices amongst not only Regulatory Authorities and manufacturers, but also healthcare providers, patients and the wider public.

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