Policy Position

Pharmacy-mediated substitution for Similar Biotherapeutic Products (SBPs)

Geneva, April 2016

Appropriate use of biotherapeutics including SBPs - SBPs, also known as biosimilars, are developed to be similar to their respective Reference Biotherapeutic Products (RBPs) in terms of quality, safety, and efficacy.[1] As a consequence, SBPs may be considered as treatment options to their RBPs for the approved indications of the SBP. A physician may prescribe different treatment options at initiation or during the course of therapy.

As individual patient responses to a biotherapeutic may vary between similar versions thereof, any decision, regarding the choice of therapy at the time of initiation or to switch between an RBP and an SBP, should be taken with the involvement of the physician.

Adverse events (AEs) or "..any undesirable experience associated with the use of a medical product in a patient",[2] at initiation of therapy or emerging during the course of therapy could be related to a number of patient-specific or product-specific factors, and the appropriate management of the AEs may require clinical judgment. Accordingly, and following the principle of physician's autonomy, they should always have access to details of the specific biotherapeutic dispensed or administered to the patient and this should be recorded in the patient's health record in order to support optimal clinical management and to promote pharmacovigilance.

This is where clarifying the approach of **pharmacy-mediated substitution for SBPs** is crucial. Pharmacy-mediated substitution is defined as a framework permitting substitution of biotherapeutics at the pharmacy level without the consent of the prescribing physician.[3] The practical consequences of pharmacy-mediated substitution are that patients may not get the specific product prescribed for them. They may also undergo multiple switches between versions of a biotherapeutic during the course of their therapy without the involvement of any physician. When multiple SBPs are available, this practice would include switches between SBPs that have never been directly compared.

There is currently no scientific consensus about evidentiary standards sufficient to justify unsupervised switches between biotherapeutics. There is also no robust evidence as to whether switching may be harmful or not to patients based on the historical experience with medically supervised switching for certain classes of biotherapeutics. It should be noted that neither the originator product nor the SBP development program is typically intended to inform such practices.

Based on the preceding considerations, there should be a distinction in public health policy between medically-supervised switching and pharmacy-mediated substitution. While there may not yet be a consensus about the degree of the risk or the specific evidentiary standards to support a risk assessment it

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[1] *SBPs are here defined as biotherapeutics licensed according to standards that are generally consistent with the WHO Guidelines on evaluation of SBPs of October 2009.*

[2] *US FDA. http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm, Accessed April 2016.*

[3] *See notes on **Setting of care and the role of the pharmacist***

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is worthwhile to consider the more general requirements of a policy framework for pharmacy-mediated substitution. The following recommendations are intended to inform risk assessments by a competent authority and the relevant pharmacy practice considerations for pharmacy-mediated substitution. Some of these considerations may also be relevant in other health delivery frameworks where procurement or formulary policies have the *effect* of promoting medically-unsupervised switches between biotherapeutics.

IFPMA Policy Recommendations for Pharmacy-Mediated Substitution

Pharmacy-mediated substitution of biotherapeutics is not appropriate *except* where all of the following criteria are met:

1. The *specific* SBP has received a formal *substitution designation,* contingent upon a competent authority[4] performing a risk assessment establishing that the SBP is interchangeable with its RBP (see items 2 and 3). The basis of the substitution assessment should be transparent to payors, patients, and health care providers;

2. The SBP meets the *regulatory* requirements to be able to be approved for all indications of the RBP and has been *approved for all accessible indications* of the RBP. Exclusions should thus only exist for administrative or legal reasons (for example, intellectual property);[5]

3. For biotherapeutics that typically are administered multiple times in the course of treatment, the substitution designation should be justified including clinically relevant evidence that switching or alternating between the SBP and RBP would not impact safety or efficacy;[6]

4. Legal frameworks have been established to permit the substitution of *designated interchangeable* SBPs while allowing the prescribing physician the '*right-to-refuse'*;[7] and

5. The jurisdiction has established a robust pharmacovigilance system, including adequate reporting of adverse events. Furthermore, the patient, pharmacist and the prescribing physician can readily access (for example, via patient health records) *unique identifiers* for the dispensed biotherapeutic, including *a unique product identification and batch information*, so as to support pharmacovigilance.[7]

[4] *See notes on* ***Competent authority(ies)***
[5] *See notes on* ***Extrapolation of indications***
[6] *See notes on* ***Assessment of substitution***
[7] *See notes on* ***Criteria for ensuring patient care and pharmacovigilance***

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Additional notes explaining the policy recommendations:

1. **Competent authority(ies)**

Due to legal, regulatory, and jurisdictional considerations the competent authority(ies) responsible for a substitution assessment may or may not be the same as the drug regulatory agency (DRA). For example, substitution may be assessed by an authority at the national or sub-national level where the competent health authority is distinct from the DRA that recommended the licensure of the SBP. A key consideration is that a substitution assessment requires a multidisciplinary input including the DRA expertise gathered during the review of SBP development data and the physician (prescriber) expertise on medical practice and experience. Also the expertise from pharmacists and other experts who could inform about the use of the product and potential risks encountered with switching may contribute to a proper assessment.

IFPMA notes that, at present, World Health Organization (WHO) does not have a formal standard on substitution for biotherapeutic medicines; instead WHO recognizes that issues related to the use of SBPs should be defined and regulated by national authorities.

2. **Setting of care and role of the pharmacist**

In many settings an institutional pharmacist is given authority to implement formulary decisions, including therapeutic substitution among therapeutically equivalent members of a drug class. The formulary decision is made by a team often comprising physicians, pharmacists, nurses, administrators, quality improvement managers, and other health care professionals and staff who participate in the medication-use process. This situation is not within the scope of pharmacy substitution, as described in this policy recommendation. However, in some cases the prescribing physician may not be included in the formulary decision making process, so information from a substitution designation should be used to inform formulary practices or other settings, where the decision to switch therapies is taken on a population basis, and not at the direction of the treating clinician.

Generally, the term “pharmacy-mediated substitution” in this policy recommendation refers to decisions taken by a 3rd party pharmacist. Typically, this would be a retail pharmacist, although other situations may also apply. The important concept is that the prescribing physician is not represented in the 3rd party pharmacy formulary decisions and would have no prior knowledge of the product to be dispensed for a given prescription.

3. **Extrapolation of indications**

Competent authorities should designate substitution only if the SBP meets the regulatory requirements for all indications and conditions of use (for example, patient populations and routes of administration) for the RBP and is licensed for all accessible indications for the RBP. In other words, the regulatory authority should have no scientific concerns about safety or efficacy of the SBP in a given indication due to evidence, or the absence of evidence, regarding mechanism of action, immunogenicity, sensitivity to dose, or other relevant considerations for indication extrapolation.[8] Accessible indications are those indications that are listed on the

[8] *WHO (2009) Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) at Section 10.7.*

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RBP label at the time the SBP sponsor provides justification for the intended SBP label indications and that are not otherwise excluded due to intellectual property or other exclusivity protections (for example, pediatric or orphan drug). In practice, competent authorities might designate substitution when certain indications are not accessible to the SBP sponsor for procedural or exclusivity reasons, but not when there are specific unknowns or affirmative concerns relating to safety or efficacy in the excluded indication(s).

4. Assessment of substitution

In addition to the regulatory considerations for extrapolation discussed in item 3, a substitution assessment should consider the risks that switching or alternation from the RBP to the SBP might provoke an immune response that differs from that expected with uninterrupted therapy with the RBP. The assessment should be done on a product-by-product and case-by-case basis, and the requirements for additional clinical studies for a given SBP may depend on several factors:

First, the substitution assessment should focus on immunogenicity associated with switching or alternation from the RBP to the SBP, and include a detailed characterization and comparison of the immune response to the SBP and RBP. For example, a demonstration of similar incidence, immunoglobulin class, titers, binding epitopes, and neutralizing capacity of anti-drug antibodies (ADAs) would be relevant to the assessment. The assessment should also consider how switching or alternation between RBP and SBP impact on clinical safety and efficacy outcomes.

Second, the assessment should consider historical association of ADAs with safety or efficacy issues for either the RBP or the SBP or other members of the product class. If there are known risks of clinically relevant immunogenicity for the product class the burden of proof may be higher. Risk assessments based on switching studies involving one class of biotherapeutics should not be generalized to other classes.[9] Some SBPs may be developed with clinical studies that include a patient cohort experiencing a single, medically-monitored transition from RBP to SBP, or may consider evidence from patient histories with other biotherapeutics prior to the beginning of the study. Evidence from such one-time transitions of therapy may help partially address concerns about short term efficacy, tolerability, or acute reactions to the SBP after the transition from the RBP, but will have limitations addressing immunogenicity risks associated with switches or alternations.

Evidence that switches or alternations do not impact safety or efficacy would likely require broader clinical evidence, typically including clinical switching studies. Such switching studies might focus on surrogates for potential impact of switching to safety and efficacy such as drug bioavailability and anti-drug antibody characteristics, being sensitive endpoints. Other clinical endpoints may compliment the information gathered by assessing clinical surrogates such as efficacy & safety endpoints, if they exist. These clinical surrogates may account for potential differential immunogenicity of switches or alternation of therapies versus that of continuous administration of both products being studied.

[9] *For example see Ebbers HC et al. Expert Opin Biol Ther. 2012 Nov;12(11):1473-85.*

Some biotherapeutics are administered to patients using a limited number of doses, such that patients are unlikely to experience more than one switch between medicines during a course of therapy. The risk assessment and the scope of potential clinical switching studies should be based on use of the medicine in its various indications (for example, duration of therapy, number of doses, etc.).

In addition to an adequately designed switching study the competent authority may assess evidence from the SBP's post-marketing experience to inform the substitution determination. Relevant supportive evidence may accrue from post-marketing studies (for example, registries or other observational data) collected in conjunction with medically-supervised switches or alternations between the RBP and its SBP. The authorities may also evaluate the available pharmacovigilance data to assess the SBP's benefit-risk profile with respect to certain rare adverse events (for example, rare immunogenicity-related events).[10]

In some cases clinical switching studies may be considered unethical or unfeasible for a given product, patient population and indication. In such cases, especially when the product class is associated with clinically relevant immune reactions, it may be appropriate to withhold an substitution designation for the SBP. Such an approach would encourage ongoing prescriber involvement and approval for any switches.

5. Criteria for ensuring patient care and pharmacovigilance

Medical and pharmacy practice are typically outside of the authority of a drug regulatory authority but are typically subject to laws or regulations. For example, many jurisdictions currently include provisions permitting prescribers to preempt a generic drug substitution. While IFPMA encourages the inclusion of such protections for any framework permitting pharmacy-mediated substitution of biotherapeutics, we note that prescriber "opt out" provisions are not the same concept as ensuring prescriber involvement in the decision to switch a patient. Therefore, these provisions should not be used to justify substitution of SBPs that have not been designated as interchangeable.

Good pharmacovigilance practice for biotherapeutics requires that the specific product and batch information should be documented in patient records and included in adverse event reports. Substitution could potentially undermine these practices if prescribers are not aware of the setting, timing and nature of a substitution, and therefore cannot easily access pharmacy records for a given patient. Therefore, IFPMA supports measures to encourage capture of biotherapeutic product identifiers for the patient's health record in a way that is accessible to the treating physician.

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[10] *WHO (2009) Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) at Section 11.*

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