INTERCHANGEABILITY OF BIOSIMILARS IN THE EUROPEAN UNION

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Health Action International

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Addressing the Challenge and Constraints of Insulin Sources and Supply

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Within the European Union (EU), the term interchangeability is defined as the medical practice of changing one medicine for another that is expected to achieve the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by switching or (automatic) substitution. Switching is the decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent (1,2). Another term for switching, which has recently been proposed in literature, is transition (3). (Automatic) substitution is the practice of dispensing one medicine in favour of another equivalent – and interchangeable – medicine at the pharmacy level, without consulting the prescriber (1,2).

It is important to note that interchangeability is not within the remit of the European Medicines Agency (EMA) and should be dealt with at a national level. Furthermore, switching studies are not obligatory part of the EU approval process for biosimilars (4). The ongoing discussion on interchangeability has triggered several national agencies to publish positions on the use of biosimilars. Important aspects that have been taken into account to support these positions include: the rigorous approval pathway for biosimilars in the EU that presents convincing data on similar quality, safety and efficacy at the time of approval; experience with the assessment of production changes that biologicals undergo during their life-cycle; and more than ten years of use of biosimilars in clinical practice without a negative impact on efficacy and safety. Within the rigorous approval pathway, it is important to understand that the biosimilarity exercise and approval of the product as a biosimilar has ruled out significant differences in efficacy and safety. This provides reasonable certainty that switching can safely be done. This has been confirmed by several studies in which patients have been switched from a reference product to a biosimilar (5).

Several national authorities, including Finland, Germany, Ireland, the Netherlands and Scotland, have taken positions on switching from the reference product to the corresponding biosimilar. It is agreed that switching should be done under the supervision of the prescriber, with appropriate monitoring after the switch. Involvement of the patient is also a prerequisite (6-10) and is, specifically, important for insulin since the delivery device (e.g. syringe or insulin pen) might differ between the biosimilar and reference product (4). Involvement and education of the patient is an important aspect of the safe and efficacious use of a biosimilar in clinical practice. A survey including over 3,000 patients with diabetes showed that two-thirds of the respondents were willing to use biosimilars, 17 percent said they did not know if they would use biosimilars, 13 percent said they were unlikely to use biosimilars and only four percent said they would definitely not use biosimilars (11).

Understanding the concept of biosimilars is of crucial importance to their acceptance and use, particularly in relation to switching. Healthcare professionals and patients should be able to obtain unbiased information on biosimilars. The recently published guide for healthcare professionals jointly prepared by the European Commission and the European Medicines Agency is an example(1).

Within the United States (US), companies can choose to have their biosimilar approved as an interchangeable biosimilar. The US Food and Drug Administration (FDA) has recently published draft guidance on demonstrating interchangeability. Demonstration generally needs to be shown based on switching studies, in which patients are being switched between reference product and biosimilar several times. If the biosimilar is approved as an interchangeable biosimilar, it can be substituted automatically by the pharmacist without the intervention of the health care provider who prescribed the reference product (12). Up to this moment, no biosimilars have been approved as interchangeable biosimilars by the FDA.

Studies that look at the process of switching from an insulin reference product to a biosimilar are scarce. Currently, two biosimilars for insulin glargine have been approved by the EMA. The first approved, Abasaglar®, performed two phase III clinical trials as part of the approval process. These trials included 535 patients with type 1 diabetes in one study and 756

patients with type 2 diabetes in the other. Eighty-four percent of the people with type 1 diabetes were treated with the reference product at the moment of randomisation and 40 percent of those with type 2 diabetes were treated with the reference product. Subgroup analyses showed similar efficacy, safety and immunogenicity in the switched group as compared to patients continuously treated with the reference product (13). The second biosimilar insulin glargine, Lusdana®, also performed two phase III clinical trials, one in type 1 and one in type 2 diabetes. In these two studies, patients were treated with the reference product before randomisation. However, the absolute numbers cannot be retrieved from the European Public Assessment Report. The clinical trials did not show a statistically significant difference in efficacy and safety between the treatment arms (14).

In addition, studies that include switching other biologicals from reference products to biosimilars did not show a negative impact on safety and efficacy, supporting the previously described studies for insulin glargine (5). Recently, the landmark NorSwitch study was published. In the NorSwitch study, over 400 patients treated with Remicade® (reference product with the active substance infliximab) were switched to the corresponding biosimilar or continuously treated with Remicade®. No negative impact was seen on efficacy and safety in the patients being switched as compared to the patients who continued treatment with the reference product (15).

In conclusion, based on the experience with biosimilars and the robust regulatory pathway in the EU, several member states have issued statements on the use of biosimilars in clinical practice. Switching is considered safe, so long as the involvement of the patient, prescriber and pharmacist are taken into account. Especially in the case of insulin, involvement of the person using insulin is crucial, especially because the delivery device might differ between biosimilar and reference product. In making a risk-analysis for the decision to switch to a biosimilar, it is important to take the robust regulatory pathway for biosimilars into consideration, to ensure the resulting biosimilar products are of the same quality, and are as safe and efficacious as the reference product. To date, there are only a limited number of switching studies available for insulin, but together with the robust regulatory requirements to obtain approval as a biosimilar, more than ten years of experience with biosimilars in clinical practice in the EU, and emerging clinical experience from switching of other biologicals (from reference product to biosimilar), there is increased confidence that switching is safe.

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