



## IDF EUROPE POSITION ON BIOSIMILARS IN THE TREATMENT OF PEOPLE WITH DIABETES



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## **Rationale and Introduction**

The global prevalence of diabetes in adults aged 20–79 years was estimated to be 8.8% in 2017 and predicted to rise to 9,9% in 2045. 79% of people with diabetes are living in low- and middle-income countries (1). The lack of access to affordable insulin remains a key impediment to successful treatment and results in the development of acute/chronic complications and premature deaths. Moreover, insulin – non-insulin injectable and oral antihyperglycemic agents - are reported as generally available in only a minority of low-income countries (2).

Biosimilars provide an alternative to existing biological medicines that have lost patent protection. Although biosimilars have been used in Europe for close to ten years in different areas (nephrology, oncology, rheumatology or endocrinology), the concept of biosimilars is still not well known to many general practitioners, nurses and other healthcare specialists caring for people with diabetes. In other areas of medicine, this therapy is usually offered for a lower price than the original molecules, and speculation is that price reductions of up to 50% might eventually be expected. However, it is not yet clear whether the potential for lower prices will be realized with biosimilar insulins. High manufacturing and development costs mean that price reductions will be far less than those experienced for generic drugs. On the other hand, the additional rationale of introducing biosimilars is that this therapy may increase the number of treatment options available to patients, prescribers, and payers and may also increase the accessibility of treatments. Based on these rationales, in September 2014 the European Medicines Agency (EMA) granted the first market authorisation (3) valid throughout the European Union for a biosimilar insulin, and the latest at the end of May 2017 (4).

Given the potential opportunities and challenges linked to the introduction of biosimilar insulins, the International Diabetes Federation European Region (IDF Europe) presents a position paper on biosimilars which summarises current regulations and provides recommendations to all diabetes stakeholders: healthcare professionals, people with diabetes, pharmaceutical companies, national authorities and health-related services, as well as IDF member associations.

## **A- Biosimilars vs. generics**

A biosimilar insulin is a biological drug that is similar to an existing insulin (5) but cannot be considered an exact copy of the original branded insulin because of the different manufacturing processes (different cell lines, protein sources, extraction and purification techniques) (6,7), Currently, although the number of studies in this field is increasing, there are not enough data from clinical and experimental studies on whether this lessthan exact copy will translate into clinically significant differences between the reference product and the biosimilar insulin in terms of onset of action, peak effect, duration of action, efficacy, potency and adverse effects. Theoretically, even very small differences between the original branded insulin and the biosimilar insulin could impact the bioavailability, receptor binding and duration of action. These effects could result in different glycemic effects, potency (and therefore dosing), and reduced stability (6,8,9,10). Thus, it is important to first establish a reference standard while assessing biosimilarity between a biosimilar product and the reference product, for example the biosimilarity index approach based on a reference-replicated study, in which the reference product is compared with itself under various scenarios. The reference standard can then be used for assessing the degree of similarity between the test and reference drugs in biosimilar studies (11).

Biosimilars are produced from living cells or organisms using biotechnology, so they show more heterogeneity, which makes them more difficult to be standardized. The majority of biosimilar insulins have high molecular weight and complex heterogeneous structure which can lead to higher immunogenic risk. Biosimilar drugs are therefore different compared to generic drugs, in which the active ingredients that in most cases are not biological products, are identical to the reference small-molecule drug (5).

In addition, very frequently insufficient information is available to the clinicians about the manufacturing process and quality parameters. The process of manufacturing might differ markedly between companies. Also, the procedure which imposes to the manufacturers to demonstrate to the regulators that they will maintain adequate batch-to-batch quality, in many cases is not standardized nor transparent, and is unavailable for independent assessment (10,12).

# **B-** The legal environment of biosimilar medicines in Europe

The high level of complexity in the production of biosimilar insulins also implies that they should face a more stringent regulatory assessment than generics, including the need for clinical trials, which significantly increases costs and timelines to market entry of biosimilars (12). While the approval of a generic drug requires only the demonstration of pharmaceutical and bio-equivalence, regulatory requirements for biosimilars are more complex. The main objective of the approval process is to establish comparability with its reference product in terms of safety, purity and potency. In the European Union (EU), a legal framework for approving biosimilars was established in 2003. In 2005, the European Medicines Agency became the first regulatory body to set out a framework for the approval of biosimilars (13,14,15,16,17,18). Furthermore, this legal environment in Europe is organised around different regulatory documents and guidelines including the EU regulation 1235/2010 (19), the Directive 2010/84/EU (20) on pharmacovigilance and the ones produced by the World Health Organization (WHO) in 2009 and 2014 (21,22).

# **C- Potential impact of biosimilar medicines on patients and healthcare systems**

Biosimilar regulatory requirements in the EU show the complexity of biosimilar approval. In that sense, the biosimilar is being analyzed on whether it has *in vitro* and *in vivo* nonclinical characteristics, as well as pharmacokinetic (PK) and pharmacodynamic (PD) properties similar to the reference product. Also, the analysis includes the search for the presence of clinically meaningful differences in immunogenicity or adverse event profile compared to the reference product.

A biosimilar product may yield a similar efficacy, tolerability and safety to the original, but the switch between these products in patient treatment may require input from a clinician. In this case, there is a clear distinction between biosimilarity and interchangeability (the ability of prescribers to switch between the reference product and a biosimilar). Confirmation of biosimilarity does not imply interchangeability or especially substitution (the automatic substitution of the reference product without the prescribers' consent, for example by a pharmacist) (23). Decisions on interchangeability and/or substitution should rely upon national authorities that have access to the scientific evaluation performed by the EMA, all submitted data, and use other expert opinions.

Thus, for any new biosimilar insulin product, long-term studies with conclusive results are needed, addressing batch-to-batch variability, the use of delivery devices and interchangeability in practice, as well as comprehensive pharmacovigilance and post-marketing surveillance. In fact, the clinical relevance of how these factors can affect the properties of a biological medication is illustrated by one of the biosimilar erythropoietins used to treat anaemia. Increased incidence of life-threatening side-effects were linked to an increased immune response to the drug (24). Moreover, there is a prerequisite of showing the efficacy, safety and cost benefit ratio vs. the reference products, which should include the major therapeutic aspects already evaluated for the reference products.

### **D- Recommendations**

#### a) Healthcare professionals (HCPs)

 HCPs should ensure that people with diabetes (PWD) well managed on an existing insulin are not changed to another insulin formulation, including biosimilars, without good clinical reason and evidence of interchangeability.

 HCPs should present the reasons and agree jointly with the PWD on the appropriate use of biosimilar insulins, providing clear and sufficient information.

HCP should take into consideration the person's preference in the choice of biosimilar insulins through individual features such as pen injectors for delivery.

• HCPs should report any adverse reaction to a biosimilar insulin (as they would for other insulin formulations) so that appropriate monitoring can take place.

Pharmacists should be well-informed about insulin formulations, including biosimilars.

• Pharmacists should be in contact with the prescribing physician in case of substituting the product, in order to track the assessment of the clinical outcomes.

#### b) **People** with diabetes (PWD)

• PWD treated with insulin should be acquainted with all relevant aspects of the use of a biosimiliar insulin to ensure they are able to have informed discussions with their HCPs if a suggestion to change is made.

• PWD should report any adverse reaction to a biosimilar insulin (as they would for other insulin formulations), so that appropriate monitoring can take place.

#### c) Pharmaceutical industry

Pharmaceutical industry is expected to provide conclusive and reproducible data on pharmacokinetics and pharmacodynamics in comparison to the reference product, as well as comprehensive data showing acceptable batch-to-batch variability and efficient use in delivery devices.

 Pharmaceutical industry should also report the results of the comparison in safety and efficacy to the reference product in all major aspects of the therapeutic use, apart from the cost-benefit ratio. This refers especially to immunogenicity data.

 Pharmaceutical industry should provide comprehensive data on interchangeability in practice, pharmacovigilance and post-marketing surveillance.

• Pharmaceutical industry should work closely with national health authorities, other relevant health administrations, clinicians and PWD to ensure adequate understanding of the properties of their biosimilar insulins.

#### d) National authorities and health-related services

• National authorities should refer to the "Guidelines on evaluation of similar biotherapeutic products (SBP)" of the World Health Organisation (21).

• National authorities should also refer to the EU overarching guidelines and specific insulin guidelines (19,20).

• National guidance should include recommendations on insulins as an approach in insulin therapy (whether originator or biosimilar insulin), regarding all aspects of their use.

• Both HCPs and PWD should be more involved in the process of introducing biosimilars. A suitable model would be to create and follow the documents equal to EU regulation 1235/2010 (19) and DIRECTIVE 2010/84/EU (20) which emphasize patient involvement in pharmacological vigilance.

• Routine diabetes education should include biosimilars.

#### e) IDF Europe Member Associations

• National Associations should ensure that appropriate guidelines, especially those of the WHO, are implemented nationwide.

 National Associations should support the education of all relevant HCPs including nurses and pharmacists.

• National Associations should support diabetes education including the information about biosimilars among PWD.

 National Associations should contribute to the coordinated approach among national health services, HCPs, PWD and the pharmaceutical industry to develop and implement an adequate positioning of biosimilars in diabetes treatment.

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## E- Glossary of key terms

**Biosimilar:** A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (25).

**Biosimilarity**: Absence of a relevant difference in the parameter of interest within biological product.

**European Medical Agency (EMA):** The European agency responsible for the scientific evaluation, supervision and safety monitoring of medicines in the European Union.

**Generic medicine:** A generic medicine contains the same active pharmaceutical ingredient as and is bioequivalent to an originator (comparator) medicine. Since generic medicines are identical in the active pharmaceutical substance, dose, strength, route of administration, safety, efficacy, and intended use, they can be substituted for the originator product.

**Interchangeability**: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber (26).

**Originator pharmaceutical product/originator brand:** Generally the product that was first authorised worldwide for marketing, normally as a patented product, on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorisation The originator product always has a brand name; this name may, however, vary between countries.

**Pharmacodynamics:** Pharmacodynamics (PD) is an area of pharmacology concerned with the relationship between a drug's concentration at the site of action and the resulting effect, and with measurement of that relationship within an individual or group. Factors influencing a drug's pharmacodynamics include the concentration of drug target and the signalling pathways downstream (27).

**Pharmacokinetic:** Pharmacokinetics (PK) is an area of pharmacology concerned with the time course of absorption, distribution, metabolism and excretion (collectively ADME) of drugs from biological systems in order to understand the effect of the drug, or of the organism, on the drug's impact. Pharmacokinetic parameters can also include toxicology and a drug's liberation from its medicinal formulation (28).

**Pharmacovigilance**: Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (29).

**Type 1 diabetes:** Type 1 diabetes used to be called juvenile-onset diabetes. It is usually caused by an auto-immune reaction where the body's defence system attacks the cells that produce insulin. The reason this occurs is not fully understood. People with type 1 diabetes produce very little or no insulin. The disease may affect people of any age, but usually develops in children or young adults. People with this form of diabetes need injections of insulin every day in order to control the levels of glucose in their blood. If people with type 1 diabetes do not have access to insulin, they will die (30).

**Type 2 diabetes:** Type 2 diabetes used to be called non-insulin dependent diabetes or adultonset diabetes, and accounts for at least 90% of all cases of diabetes. It is characterised by insulin resistance and relative insulin deficiency, either or both of which may be present at the time diabetes is diagnosed. The diagnosis of type 2 diabetes can occur at any age. Type 2 diabetes may remain undetected for many years and the diagnosis is often made when a complication appears or a routine blood or urine glucose test is done. It is often, but not always, associated with overweight or obesity, which itself can cause insulin resistance and lead to high blood glucose levels. People with type 2 diabetes can often initially manage their condition through exercise and diet. However, over time most people will require oral drugs and or insulin (31).

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