

## Biosimilar Insulin and Insulin Antibodies

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The introduction of biosimilar insulins in regulated markets is anticipated to happen in the next few years.<sup>1,2</sup> However, biosimilar insulins are already on the market in a number of countries with little or no guidelines for approval of biosimilars and where approval is relatively easy to obtain. In such countries, insulin is bought in tenders, which means that large quantities of different insulin formulations are bought at varying intervals following a bidding process. In other words, the cheapest price usually determines which offer is accepted. This is already a reality in many countries, for example, Mexico and other South American countries. The consequence of such attempts to reduce the financial burden for the health care systems is that it might lead to insulin-treated persons with diabetes and their treating physicians having to switch, for example, from one basal insulin formulation to another every 6 months or so. In view of substantial differences in the time-action profiles of the different intermediate- and long-acting insulin formulations, it remains to be systematically evaluated what impact this type of situation will have on the individual's overall quality of metabolic control (glycated hemoglobin), frequency of hypoglycemic events, and quality of life. It would be of enormous value to undertake such a study, for example, in Mexico, where insulin is bought by tendering by means of a large registry.

However, the question that we would like to highlight here is as follows: What is the level of risk that such switches in insulin formulations will induce an increase in insulin-neutralizing antibodies? If this were the case, this would have the potential to increase the dose of insulin, and thereby the savings are lost. In addition, it might also be that the insulin bound and released by the antibodies induces changes in the pharmacokinetic and pharmacodynamic properties of the applied insulin, resulting in a worsening of metabolic control. The background for these concerns are based on rather old data that suggest that those with type 1 diabetes require a higher dose of insulin in the presence of an increase in neutralizing antibodies. This knowledge about insulin antibodies became available during the 1960s and 1970s when impure insulin formulations were still available. A resurgence of interest was seen when an increase in circulating insulin antibodies in response to treatment with pulmonary insulin was detected.<sup>3</sup> In 2003, good analytical methods for measurement of insulin antibodies were established. However, when Exubera and other inhaled insulins failed, the interest in this topic also diminished. It is worth mentioning that the observed increase in insulin antibodies was mainly driven by non-neutralizing antibodies, the observed increase was not accompanied by any change in insulin requirements, insulin kinetics, or any other clinical parameter. Thus, this response of the immune system (i.e., exposure of insulin to immune competent cells in the lung) had no prominent adverse metabolic impact. Consequently, interesting questions from this observation are whether an increase in non-neutralizing antibodies or neutralizing antibodies would be induced by switching insulin formulations (with conventional subcutaneous administration) and whether this will have a clinically relevant impact. If the titres of antibodies increase from switching from one insulin to another, then how do we track this? Also, what happens if, for some reason, only a subgroup of patients reacts in such a manner?

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**Abbreviations:** (BI) Biosimilar insulin, (EPO) Erythropoietin

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Therefore it is of considerable importance to establish methodologies to measure and evaluate such potential side effects of changes in insulin therapy. It goes beyond the aim of this editorial to discuss the ability of pharmacovigilance systems/approaches to detect clinically relevant effects. It is clear, however, that there is underreporting of side effects, and therefore the situation requires well-established health care systems to ensure patient safety. Another interesting question is, if such a “side effect” shows up, who is ultimately responsible?

To be clear, our comments are purely speculative when it comes to insulin therapy, although we firmly believe that it is better to discuss these important issues right now and to address this potential risk in a systematic manner. In this context, it is worth mentioning that the risk of stimulating the immune system or inducing other side effects is not theoretical; in patients treated with different brands (i.e., biosimilars) of erythropoietin, a number of studies reported a need to increase dosage and other severe side effects.<sup>4</sup>

It is fully understandable if the health care systems wish to reduce their expenses on insulin therapy, especially in view of the rapid increase in persons with diabetes who require relatively expensive therapy such as insulin. However, biosimilars are not generics. In contrast to low-molecular-weight drugs, which can be replaced safely by other drugs that are similarly chemically synthesized, this does not hold true for the complex world of biosimilars.<sup>3</sup> It might very well be that there is a need to explain to the responsible people inside the governmental authorities the differences between generics and biosimilars based on a sound scientific approach (in principle these are not biosimilar insulins but should be called “insulin copies” as they are not approved according to appropriate regulations). Nevertheless, the option to save 20% to 30% (at maximum) by buying biosimilar insulins might be more relevant for them. The hope of such health authorities might also be that the price of insulin will go down much more in the years to come, as experienced with the introduction of many generics. In view of the high costs for the production of proteins, for example, this wish will most probably not come true in the foreseeable future. It also remains to be seen how seamlessly the insulin supply can be handled in daily practice, i.e., will there always be enough insulin of the appropriate formulations available at the right time and place to fulfill the requirements of the patients/physicians?

Shortly, we will start to witness the results of this huge “experiment,” which has already started in a number of countries where the study participants were apparently not asked if they were willing to participate in this study. It appears that nobody has informed them about the potential side effects of their unwitting participation in this study. It can very well be that the outcome of the experiment is negative, i.e., that we see no side effects as discussed before; however, we should be aware of the potential risk and have the measures in place to detect them and redress the situation where and when necessary.

There is now a window of opportunity to monitor the logistics of insulin availability in the various countries and also the consequences for the patients. The details of the prescriptions, i.e., the brand name (ideally the batch number), should be documented, as this would allow tracking of the insulin formulations. At least a representative group of patients should fill out a questionnaire to indicate their awareness and understanding and the impact of such changes.

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**Disclosures:**

Lutz Heinemann advises various companies in the development of new diagnostic and therapeutic approaches to diabetes therapy. He is a shareholder and consultant at Profil Institute for Metabolic Research, Neuss and Profil Institute for Clinical Research, San Diego, USA. He is consultant for Sanofi Aventis for biosimilar insulins. David Owen has received honoraria from Sanofi, Roche Diagnostics, Eli Lilly, and Boehringer Ingelheim for providing advice and lecturing.

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