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REVIEW ARTICLE

Interchangeability among reference insulin analogues and their biosimilars: regulatory framework, study design and clinical implications

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Biosimilars are regulated differently from small-molecule generic, chemically derived medicines. The complexity of biological products means that small changes in manufacturing or formulation may result in changes in efficacy and safety of the final product. In the face of this complexity, the regulatory landscape for biosimilars continues to evolve, and global harmonization regarding requirements is currently lacking. It is essential that clinicians and patients are reassured that biosimilars are equally safe and effective as their reference product, and this is particularly important when interchangeability, defined as 'changing one medicine for another one which is expected to achieve the same clinical effect in a given clinical setting in any one patient', is considered. Although the automatic substitution (i.e. substitution without input from the prescribing healthcare provider) of biosimilars for reference products is currently not permitted by the majority of countries, this may change in the future. In order to demonstrate interchangeability between reference products and a biosimilar, more stringent and specific studies of the safety and efficacy of biosimilars are likely to be needed; however, guidance on the design of and the need for any such studies is currently limited. The present article provides an overview of the current regulatory framework around the demonstration of interchangeability with biosimilars, with a specific focus on biosimilar insulin analogues, and details experiences with other biosimilar products. In addition, designs for studies to evaluate interchangeability with a biosimilar insulin analogue product are proposed and a discussion about the implications of interchangeability in clinical practice is included.

Keywords: biosimilar, insulin

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Introduction

As several biologically derived therapeutic proteins (biologicals) are no longer protected by patents, or as exclusivities expire, biosimilars (a biological product that contains a version of the active substance of an already authorized original biological) offer an opportunity to curtail the high costs of biological treatments as well as fulfil an unmet need. Given the large and growing markets for biologicals such as insulin, biosimilars have become increasingly attractive targets for development by pharmaceutical companies worldwide.

Relative to generic medications, biosimilars have substantial regulatory barriers to overcome before approval. The regulatory pathways for approval of biosimilars require more data than for small-molecule generic medicines because of the complexity of biological/biotechnology-derived products, and considerations such as immunogenicity or the impact of manufacturing and pharmaceutical form changes [1,2] (between, for example, concentrated solution for dilution in a vial, ready-to-use solution in a cartridge or prefilled pen, and powder to reconstitute in a vial). Each biosimilar development programme is assessed on a case-by-case basis, beginning with the cell-line source, upstream (fermentation) and downstream (purification) manufacturing, and quality controls, even if the protein entity is 'similar', and proceeding through a range of preclinical (with emphasis on *in vitro*) and clinical studies (phase I and phase III only).

Although the approval of a biosimilar may demonstrate efficacy and safety to the standards set by regulatory agencies, there remains a question as to whether the same level of evidence is sufficient to demonstrate interchangeability between a biosimilar and its reference product. Interchangeability, defined as 'changing one medicine for another one which is expected to achieve the same clinical effect in a given clinical setting in any one patient' [3], is an important consideration for clinicians in the context of biosimilars, especially as interchangeability represents a regulatory designation that might facilitate automatic substitution (i.e. exchange of a prescribed biological with an 'equivalent' biosimilar) without input from the prescribing healthcare provider.

Biosimilar insulin analogues present particular challenges because of the complexity of their manufacturing process, and

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