Medsafe Position on Biosimilar Medicines

Introduction

The expiration of the patents for many biological medicines has prompted the development of similar biological products termed biosimilar medicinal products or biosimilar medicines. A biosimilar medicine is thus a new version of an existing product that has already been authorised for marketing in New Zealand.

The active substance is considered similar but not identical to the biological reference (innovator) medicine. The manufacture of biological medicines is highly complex and small process changes can result in the production of a glycosylated protein that has clinically different effects.

The approach to biosimilar medicines

Biological medicines are usually more difficult to characterise than those that are chemically derived. In addition there is a range of molecular complexity among the various products e.g. recombinant DNA, blood or plasma derived, immunological products. Parameters such as the structure, the amount of acid-base variants or the glycosylation profile can be significantly altered by seemingly minor changes to the manufacturing process. As a consequence the safety and efficacy of such products is highly dependent on the robustness and the monitoring of the "quality" aspects. The standard "bioequivalence" approach to generic medicines applied to chemical products is therefore not appropriate for biological medicines and Medsafe will apply an approach based on the comparability of the products i.e. a demonstration of similarity.

The amino acid sequence is the most basic characteristic of a protein and current technologies enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein, analysis of other aspects of a protein's structure requires much more sophisticated technologies and is fraught with uncertainties that increase with the size and complexity of the protein itself.

The ability to predict the clinical comparability of two products depends on the understanding of the relationship between the structural characteristics of the protein and its function, as well as on the ability to demonstrate structural similarity between the biosimilar product and the reference product. Although this may currently be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products. Similarity will therefore need to be confirmed via non-clinical and clinical studies.

Documentation requirements

In its approach to the evaluation of applications for biosimilar medicines, Medsafe will apply the CHMP guidelines on Similar Biological Medicinal Products Containing Biotechnology Derived Proteins as Active Substance: Quality issues (CHMP/48348/05)* as amended, Non-clinical and clinical issues (CHMP/42832/05) and annexes*.

In addition to the standard full evaluation pathway Medsafe operates an abridged evaluation procedure, should an application be made using this route for a biosimilar medicine the documentary requirements will be the same as those for a chemical new medicines application made through this route.

Choice of reference product

Regardless of the choice of application pathway since an application for a biosimilar medicine is essentially "bridging" to an already approved product, the chosen reference product must be an innovator biological medicine that has consent for distribution in New Zealand.

Immunogenicity

The immunogenicity of a biosimilar medicine must always be investigated; the extent of testing needed is determined by a variety of factors such as the indication, duration of administration, overall potential for immune reactions and/or the possibility of generating cross-reactivity with an important endogenous molecule. When assessing immunogenicity Medsafe will apply the principles described in the CHMP Guideline on Immunogenicity Assessment of Biotechnology Derived Therapeutic Proteins (CHMP/BMWP/14327/06)*.

Interchangeablity and Substitutability

In general a product is considered interchangeable with another if both products are approved for the same indication and can be used for said indication. Two products are substitutable if they can be used in lieu of one another during the same treatment period.

Interchangeable products cannot be substituted with one another during a treatment period. Interchangeability does not imply substitutability.

Unlike generic chemical medicines where the chemical structure is identical to that of the innovator product a biosimilar medicine does not usually have an identical structure to the innovator. As a consequence even though a biosimilar medicine may be assessed to be similar in terms of the quality, safety and efficacy to the reference product the immunogenicity profile *may* preclude switching between products.

Medsafe considers that the choice to interchange a medicine is one best made by the clinician treating the patient, in terms of biological medicines clinicians should be warned of the risks associated with switching the product during treatment and substitution should not occur.

Post-market safety monitoring (Pharmacovigilance)

When a medicine receives consent for distribution information on the product is relatively limited, there may be some potential risk that have not been identified due to the factors such as the relatively small study population, specific inclusion and exclusion criteria and short duration of exposure. When a medicine is used more widely new risks associated with use may emerge, for biosimilar medicines an unwanted immune response will be the primary concern.

A potential immunological response is, in part, a reflection of the complexities of manufacturing a biosimilar medicine. As manufacturing protocols are proprietary information owned by the innovator company, it is impossible for a manufacturer of biosimilar products to duplicate the process. This invariably leads to structural differences in the final products, resulting in differences in efficacy and adverse events such as the potential to trigger an unwanted immune response, which has the potential for serious consequences.

In principle the current pharmacovigilance systems relating to medicines in New Zealand are applicable to biosimilar medicines. In view of the inherent potential of biological products to provoke immunological reactions special care should be taken with regard to the reporting and assessment of adverse reactions. Medsafe anticipates that an applicant will submit a risk management plan that will mitigate the potential risks associated with the biosimilar medicine. Measures included in a plan may include additional monitoring activities utilising a patient registry, prospective cohort studies or other post-market observational studies.

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* CHMP Guidelines available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c