FACT SHEET 8

KEY RECOMMENDATIONS OF THE WHO BIOSIMILARS EVALUATION GUIDELINES[1]

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SOURCES

1. World Health Organization. WHO Technical Report Series, 60th Report (No. 977) - Annex 2. Guidelines on evaluation of similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization, ed. WHO Technical Report Series. Geneva, Switzerland, 2009: http://who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf

KEY RECOMMENDATIONS

OF THE WHO BIOSIMILARS EVALUATION GUIDELINES

1 The reference biologic, or reference biotherapeutic product (RBP), must be a well-established biologic medicine with a full dossier of quality, safety, and efficacy data to allow for a comprehensive comparison with the biosimilar candidate.

This criterion automatically disqualifies any biosimilars as a choice for a RBP, because they are approved through a reduced amount of quality, safety, and efficacy data built on the established profile of the reference product.

At the end of the development, a RBP and its biosimilar product must share the same dosage form (physical characteristics) and route of administration (e.g. subcutaneous injection).

- Latitude for national adaptation: If an appropriate RBP is not available in a given country, it can select a RBP from another country with robust regulatory frameworks, considerable experience in using biologics and post-marketing surveillance activities.

2 Quality assessment aims to establish the first layer of molecular similarity between a biosimilar and its RBP. Ensuring similarity from the manufacturing process and characterisation to stability profile builds the foundation of establishing therapeutic equivalence.

The manufacturing process must be designed to resemble that of the RBP as closely as possible, within the knowledge available in the public domain and past experience with the RBP. Because a manufacturer developing a biosimilar will not have the detailed knowledge of the original manufacturing process, some differences between the biosimilar and RBP are expected despite the efforts to minimise them. Such differences are acceptable if non-clinical and clinical evaluations show no meaningful differences in terms of safety and efficacy throughout the development process.

A biosimilar candidate must also be comprehensively characterised in terms of physicochemical properties, biologic activity, immunochemical properties, and impurities using the appropriate state-of-art analytic technology. The primary structure of the biosimilar and its RBP must be identical. If any other differences are found, additional head-to-head comparisons must be undertaken to evaluate their potential impact on safety and efficacy.

Stability studies are also required to capture any hidden differences between a biosimilar candidate and its RBP. Even though a head-to-head study is not required in this case, stability studies are required to record the full details of how a biosimilar medicine breaks down over time under different conditions. The results are used to establish the guideline for storage and expiry dates which may or may not be the same as that of the RBP.

- Latitude for national adaptation: A high degree of similarity found at this stage forms the scientific basis for reducing the non-clinical and clinical evaluation requirements. Differences are expected to be found during quality assessment, but they must be shown to have no significant clinical impact through non-clinical and clinical evaluations.

Non-clinical evaluation

Non-clinical evaluation is the first step toward establishing the safety and efficacy profile of a biosimilar, and it assesses the pharmacodynamics and repeat-dose toxicity of a biosimilar candidate using animals. Because biosimilars mainly consist of protein molecules, they may elicit unpredictable metabolic or immune responses difficult to interpret during animal studies, especially if the RBP also carries limited knowledge of mechanism and clinical experience. Animal studies do not provide high value data for predicting immune responses in humans, but it adds to the comprehensive body of knowledge for assessing the degree of similarity.

Clinical evaluation

Clinical evaluation is the most important part of the biosimilars development to assess safety, immunogenicity, and efficacy in humans. Even the minor differences in protein molecular structures can often elicit unpredictable clinical consequences, but animal studies do not usually provide predictive results for a biosimilar candidate's immune response in humans. Unlike generics, clinical evaluation of biosimilars is absolutely necessary to capture potential ADRs or low efficacy in comparison to the RBP. If any clinically meaningful differences are found during this stage, the biosimilar candidate in question should instead be considered for a full licensing application as a stand-alone product, rather than a biosimilar medicine.

Clinical studies to evaluate biosimilars are abbreviated; they require less data submission requirements than those intended to register a new biologic product. There are no set rules for the minimum requirements (e.g. minimum sample sizes) as it is intended to be a case-by-case evaluation. However, they must be designed as a stepwise investigation with sufficient statistical power to show a head-to-head comparability, or therapeutic equivalence, to the RBP in a large population.

Based on the clinical trial results, the extrapolation of a biosimilar medicine to other clinical indicators of the RBP can also be considered if and only if a high degree of similarity has been sufficiently demonstrated in the highest standards possible in quality, safety, and efficacy.

- Pharmacovigilance - All ADRs should be documented and reported up to the national regulatory agency in order to capture a full picture of the quality, safety, and efficacy of biosimilars.

Although the clinical evaluation during development would identify the majority of ADRs, others – adverse immunogenic reactions in particular – may arise during real-world use when the drug is used outside of an experimental setting. Manufacturers of a biosimilar medicine should submit to the national regulatory agency a plan for monitoring the real-world performance of their product. The NRA, in response, must ensure the manufacturer complies with the submitted plan once the medicine is in clinical use.

Traceability of the biosimilar is also a key issue. In order to trace the source of problems to specific biosimilars, in addition to the International Nonproprietary Name (INN), ADR reporting should include proprietary (brand) name, manufacturer's name, lot number and country of origin.

Prescribing information and label

Biosimilars must be clearly identifiable by a unique brand name as well as an INN and the lot number in order to ensure traceability for improved pharmacovigilance. Prescribing information should be a close match to that of the RBP except for the product-specific aspects in order to provide clear information on contraindications, warnings, and potential adverse events.
In case where a biosimilar medicine has fewer clinical indicators than the RBP, some omission of information is permitted. However, it should not be permitted if the information is considered important to inform doctors and patients about certain risks in case of off-label use.