Korean regulations for biosimilars

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Regulations for biosimilars in the Republic of Korea have been in place since 2009. Since then, the country has also put in place specific guidelines and approved four biosimilars.

Keywords: Biosimilar, guidelines, regulations, Republic of Korea

The legislative basis for the regulation of biosimilars and its guideline for evaluation of biosimilars in the Republic of Korea (South Korea) was established in 2009 [1-2]. The Ministry of Food and Drug Safety (MFDS), through its National Institute of Food and Drug Safety Evaluation, is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in South Korea.

The MFDS guideline is a general guideline covering considerations for the authorization of biosimilars, selection of reference products and quality, non-clinical and clinical evaluation of biosimilars. The guideline covers 'well-characterized recombinant protein products'. The guideline was revised in 2014 to reflect the current thinking of MFDS.

Product-specific guidelines are also being published annually, with guidelines for erythropoietin and somatropin (2011), granulocyte colony-stimulating factor (2012) and monoclonal antibody biosimilars (2013) already issued.

The Korean guideline for biosimilars was co-developed with the World Health Organization guidelines and is thus harmonized with the European Union guidelines in its scope, data requirements for authorization. The guideline therefore requires a demonstration of similarity and a comprehensive characterization and comparison at the quality level to enable a reduction in the non-clinical and clinical data required for authorization. The regulatory decision is then based on a comprehensive evaluation of quality, safety and efficacy data.

MFDS defines a biosimilar as 'a biotechnological product that is comparable to already marketed reference products in terms of quality, safety and efficacy'.

Reference products should be authorized on the basis of a complete dossier package in South Korea. However, the guideline does allow for the use of out-sourced reference products provided that sufficient information to justify the comparability to reference products sourced in the South Korean market would be demonstrated. MFDS provides a list of the available reference products on its website. Current biological reference products in South Korea include Remicade (infliximab), Enbrel (etanercept), MabThera (rituximab), Humira (adalimumab), Herceptin (trastuzumab), Nesp (darbepoetin alfa), Lantus (insulin glargine) and Eprex (epoetin alfa).

Dossier requirements

Quality

A full quality dossier, along with comparability exercise data (including extensive side-by-side characterization) between the biosimilar and the reference product is required.

Justification of the acceptance criteria used in the comparability exercise, taking into account the sufficient number of reference product lots tested, is important. While the impact of observed differences in quality attributes should also be assessed.

A comprehensive characterization and quality comparison provides the basis for a reduction in the amount of non-clinical and clinical data required for biosimilars, see Figure 1.

Non-clinical

Comparative non-clinical studies should be designed to detect significant differences between biosimilars and reference products:

- *In vitro* study – Receptor binding study, cell-based bioassay
- *In vivo* study – Biological/pharmacodynamic studies relevant to the clinical application
- Toxicity – At least one comparative repeated-dose toxicity study in relevant species, including toxicokinetic study, anti-drug antibody measurement

Clinical

Comparative clinical trials are required:

- Pharmacokinetic (PK) studies/Pharmacodynamic (PD) studies
- Clinical efficacy and safety trials
- If applicable, confirmatory PK/PD studies can be used
- Equivalence design is recommended and equivalence margins should be prespecified and justified. Non-inferiority design may be used with strong justification
- Safety data from a sufficient number of patients and study duration should be provided to compare the nature, severity and frequency of adverse reactions (including immunogenicity study) before approval

Extrapolation of indications

In South Korea, if similar efficacy and safety of the biosimilar and the reference product have been demonstrated for a particular clinical indication, then the biosimilar product may receive authorization for other indications of the reference product. The extrapolation of clinical indications of a biosimilar product is allowed

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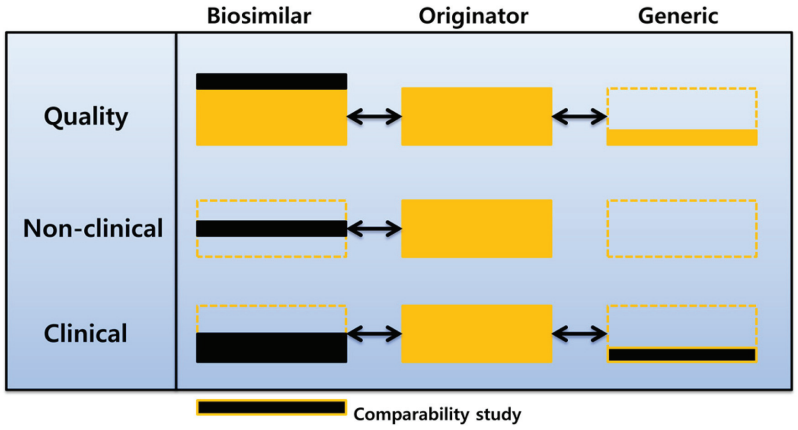
Figure 1: MFDS data requirements for drug approval in the Republic of Korea



Source: Ministry of Food and Drug Safety (MFDS)

for indications where the post-marketing surveillance period of the reference product has expired and if all of the following conditions are fulfilled:

- A sensitive clinical test model to detect potential differences (between the biosimilar and the reference product) is used
- The clinically relevant mechanisms of action and the involved receptors are the same for the different indications
- The safety and immunogenicity have been sufficiently characterized

Interchangeability

Unlike small-molecule chemical generics, automatic substitution of biosimilars at the pharmacy level is not allowed in South Korea.

Pharmacovigilance

Four years of post-marketing surveillance covering both the safety and efficacy profile, is required for biosimilars. The post-marketing surveillance study plan should be submitted to MFDS before the biosimilar is marketed in South Korea. The findings obtained from the post-marketing surveillance study should be reported to MFDS periodically.

Biosimilars in South Korea

To date, MFDS has approved four biosimilars [3]. The first biosimilar to receive approval in South Korea was Celltrion's arthritis treatment Remsima (infliximab) in July 2012. This was followed by Celltrion's breast cancer treatment Herzuma (trastuzumab) and Sandoz's growth hormone Omnitrope (somatropin) in January 2014. The fourth biosimilar product approved by MFDS was Hanhwa Chemical's arthritis treatment Davictrel (etanercept) in November 2014.

There are currently 11 local manufacturers and four global companies active in the biosimilars arena, with 21 biosimilar candidates in the pipeline. There are 10 phase I trials and 19 phase III trials underway with these candidate biosimilars.

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