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Regulatory guideline for biosimilar products in Korea

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A B S T R A C T

The regulatory framework of biosimilar products in Korea is a 3-tiered system: 1) Pharmaceutical Affairs Act; 2) Notification of the regulation on review and authorization of biological products; 3) Guideline on evaluation of biosimilar products. A biosimilar product is regulated under the same regulation as biological products. The difference from new biological product is that biosimilar product requires full comparability data with reference product. Based on these data, some of the non-clinical and clinical data could be abbreviated. As Korean guideline for biosimilar products was developed along with that of the WHO's, most of the recommendations were based on similar principle except the clinical evaluation to demonstrate similarity. No biosimilar products are licensed yet, however, 4 IND products have been approved for phase I or III clinical trials. The addressed issues during review were as follows: acceptability of reference products manufactured in different sites, determination of acceptable criteria for differences and selection of analytical tests for the comparability exercise to detect potential differences in quality attributes, relevant species for non-clinical study, and duration of toxicity study, etc. These and other future issues will be dealt with scientific advancement, experiences of collaborating work with WHO or other NRAs, which will be reflected in the guidelines on regulations of biosimilar products in Korea.

1. Introduction (legislative basis)

Biotherapeutic products, as opposed to chemical drugs are large, complex molecules produced using complex manufacturing processes. This contributes to the high costs associated with these highly successful medicines. The mean growth of top 8 biotherapeutics such as Humira, Lantus, Herceptin, Neulasta, Avastin, Enbrel, Rituxan, insulin was estimated to be more than 250% during 2004–2007, which is very high compared with 50% growth for the top 8 small molecules [1]. The total global market for protein drugs was $47.4 billion in 2006, which is estimated to reach $55.7 billion by the end of 2011, an average annual growth rate of 3.3% [2]. Because of the high daily treatment costs of biopharmaceuticals, there is an increasing need for reducing the medical insurance and costs by providing access to copy or similar versions of blockbuster biological products such as Erythropoietin, interferon-β, TNF antagonists where patents have expired or are expiring in the near future. Consequently, biopharmaceutical companies are trying to develop copy versions of biological products. Although these products are based on the same gene sequence as originator product, the production system and purification processes are probably different. Because of the complexity associated with biotherapeutic products (e.g., high molecular weight, three-dimensional structure, complex manufacturing process), which results in a product which is dissimilar in characteristics, biological activity, safety, efficacy, and immunogenicity in comparison with the original product [3,4], the generic approach in both development and review of these products is not appropriate. Another approval track (the biosimilar pathway) for them has been prepared in NRAs including Korea where demonstration of similarity in terms of quality, safety and efficacy is essential.

In Korea, the high level regulation to license the drug or biological products is the same. All products are subject to the "Pharmaceutical Affairs Act". As a lower level regulation, there are KFDA notifications. Drugs and biological products including biotherapeutics comply with their own notification. "Notification of the regulation on review and authorization of biological products" are for biological products, and biosimilar products too. In 2009, biosimilar product was defined in Korea as biological products that are proved to be comparable to already marketed reference products in terms of quality, safety, and efficacy in the above regulation. The requirements for biosimilar products were detailed in

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"Guideline on the evaluation of biosimilar products" in 2009, which was developed along with that of WHO's [5,6]. Most of the recommendations are "similar" except the clinical evaluation to demonstrate similarity. Reference product is defined as a biological product already approved by a regulatory authority on the basis of full registration dossier (licensed based on full quality, safety, and efficacy data).

2. Korean biosimilar guideline

2.1. Scope

In the Korean pharmaceutical regulation, the definition of a biosimilar product is a biotechnological product that is proved to be comparable to an already approved reference product in terms of quality, non-clinical and clinical evaluation. The scope of biosimilar products is applied to well-characterized recombinant protein products.

2.2. General consideration

The scientific principle of a biosimilar approach is that the existing generic definition is not appropriate for biosimilars due to the complexicity of biotechnology products. Therefore, approval of a biosimilar product should be based on the demonstration of similarity of quality, efficacy and safety to a reference drug with comprehensive comparative data. The purpose of comparability exercise is to demonstrate that the quality of a biosimilar product is highly similar to a reference drug and to make sure there is no adverse impact on efficacy and safety. In other words, biosimilar products are not merely expected to demonstrate the safety and efficacy of itself, but to demonstrate an absence of clinically meaningful differences to the reference product. Reduction in the non-clinical and clinical data could be possible through comprehensive characterization and comparison at quality level. In the development of a biosimilar product, a stepwise approach of comparability exercise is recommended, beginning with quality studies and followed by non-clinical and clinical studies. An important point to emphasize is that if the biosimilar manufacturer cannot demonstrate the similarity of a biosimilar product and a reference product, the approval process would be required to follow the stand-alone pathway as a new product application, and it cannot be called nor classified as a biosimilar product. The stand-alone pathway for a new product application requires a complete data package. In addition, an 'abbreviated pathway' requiring full quality assessment of the products, a reduced package of non-clinical data, and comparative clinical studies with comparators for each indication is also an option. As mentioned above, the products licensed using this pathway are not biosimilars. Regulatory decision making should be based on science and regulatory principles existing within their jurisdictions.

2.3. Reference drug

A "reference product" is a drug product already approved by a regulatory authority on the basis of full regulatory dossier submission. The reference product is used in demonstrating the comparability of a biosimilar product through quality, non-clinical studies and clinical studies. In addition, the dosage form, strength, and route of administration of the biosimilar products should be the same as that of the reference product. And, a biosimilar product should not be used as a reference drug. However, if a company cannot resource a reference product in the Korean market, the reference product from another country could be acceptable, based on the approval information of the reference product and the demonstration of similarity between the biosimilar product and the reference product.

2.4. Requirements for quality studies

The key issue in quality study is 'how similar is similar' because a protein drug cannot be characterized completely by physiochemical methods, which has the potential to affect the efficacy. Full CMC dossier with comparability exercise data are required, including extensive side by side characterization, physicochemical properties, biological activity, immunochemical properties, impurities and purities, specification, and stability. Analytical techniques should utilize state of the art technologies capable of detecting slight differences in quality attributes. The impact of observed differences in the quality attributes should be assessed and then non-clinical and clinical studies should be designed and conducted on the basis of the results. Acceptance criteria in setting up the specification should be established and justified based on the data obtained from analyses using a number of representative lots of both reference and biosimilar products.

2.5. Requirements for non-clinical studies

The reduction of non-clinical studies depends on the degree of similarity in quality. Non-clinical studies should be designed to be comparative in nature. In vitro studies such as a receptor binding study and cell proliferation assays are required. In vivo studies and biological/pharmacodynamic studies are required as well. For the toxicity studies, at least one repeated dose toxicity study in relevant species, including a toxicokinetic study and antibody measurement is needed. Generally, other routine toxicological studies such as safety pharmacology and reproduction toxicology studies are not required unless indicated by results from repeat dose studies.

2.6. Requirements for clinical studies

Clinical data requirements include pharmacokinetic studies and pharmacodynamic studies, and clinical efficacy & safety trials, or confirmatory PK/PD studies. Clinical studies are required to conduct in a comparative manner, depending on the data in terms of quality and non-clinical studies. In clinical comparability exercises, a stepwise approach is recommended, which means comparative clinical studies should begin with PK and PD studies followed by the pivotal clinical trials. In the design of clinical trials, equivalence trials are preferable, and equivalence margins should be pre-specified and justified. Extrapolation to other indications of the reference drug may be possible if similar efficacy and safety has been demonstrated for a particular clinical indication. Despite the fact the efficacy can be comparable, the biosimilar can show differences in the safety profile in terms of severity or adverse events incidence. Immunogenicity studies are required before approval and even after approval.

3. KFDA activities related to biosimilars

Korea Food and Drug Administration has actively promoted a public dialog on the biosimilar issues, because there are many challenging scientific and policy related questions about biosimilar products. In 2008 and 2009, KFDA held two public meetings and co-sponsored a workshop, in collaboration with stakeholders, to gather input on scientific and technical issues. These meetings resulted in a number of comments and concerns from the interested parties. KFDA established a regulatory and legislative pathway for the approval of biosimilar products in 2009 and

continue to review and approve biosimilar products. There are four IND submissions for biosimilar products, as of November, 2010.

4. Issues on clinical evaluation of biosimilar products

4.1. Reference drug

One of the challenging points in a global development program of biosimilar products is that it is not possible to confirm whether the reference product marketed in one region complies with the requirements in other regions. When NRA requires the reference product to be sourced from within its jurisdiction, it results in duplication of clinical studies in each region. A biosimilar manufacturer should give a clear justification for choice of reference product.

4.2. Clinical trials

The clinical study design depends on several different factors including:

- Treatment practices with reference products may have changed and effect on clinical study design and recruitment
- Clinical endpoints are difficult to choose; choice of appropriate clinically relevant endpoints or surrogate markers is important
- Cross-over studies may not be appropriate for protein therapeutics with a long half-life as they can have carry-over effects, or antibodies against the product
- Patient population may affect sensitivity; adequately sensitive populations to detect a clinically meaningful difference
- Setting a relevant similarity margin; equivalence trials may need to be very large. Usually, narrow equivalence margins require huge clinical trial sizes. So, there is a need to agree on an acceptable equivalence margin based on relevant clinical and statistical consideration.

4.3. Extrapolation of indication

The rationale is that if the biosimilars shows adequate comparability to the reference product for one indication, it may be reasonable to extend the approval of the biosimilar to all the indications of the reference product providing the mechanism of action is the same. A potential concern with the concept of data extrapolation is that the risks for using a biopharmaceutical may differ in various patient populations. So, there is a need to have a more comprehensive and accurate approach to specify which data are based on extrapolation.

4.4. Post-marketing pharmacovigilance

Usually, pre-approval clinical safety data are insufficient to identify all the potential safety profiles, and post-marketing surveillance including an immunogenicity study is required. Therefore, there is an opportunity for international cooperation and exchange of information between regulatory agencies.

5. Further implementation of biosimilar guideline

Regulation and overall guideline for biosimilar products have been prepared in Korea. However, review and approval of biosimilar products will be one of the major challenges, because of little experience of reviewing those, issues that are not solved, rapid advancement of science, lack of resources *etc*. Further efforts should be focused on our capacity building, expertise, collaboration with other NRAs or WHO to promote global consensus on the regulation of biosimilar products. Along with this, product based Korean biosimilar guidelines such as for EPO, G-CSF, and interferon will be prepared as needed. Guidelines on mAbs regarding characterization, manufacturing and control plan to be drafted, as biosimilar products for mAbs are under active development. Registration of biological products such as interferon, G-CSF in the Korean Pharmacopeia is also planned.

6. Conclusions

In conclusion, the rapidly evolving regulatory science in the biosimilar area would benefit from better cooperation, information exchange and collaboration from different NRAs. It is important for all NRAs to work together to have proper regulatory oversight on the clinical use of biosimilar products. KFDA, as a regulatory authority, will keep up with the updates and scientific advances, which will facilitate access to biosimilar products which are authorized as safe and effective for use.

Conflict of interest

Authors have disclosed no potential conflicts of interests.

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