

Evaluation Guidelines for Biosimilars

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This guideline was prepared to present the state-of-the-art general principles and methods for development and evaluation of biosimilar products, reflecting the results of research projects conducted by KFDA, and the suggestions from interested parties in related business area and experts in industry, academy and research domains. This guideline contains up-to-date view of KFDA based on the experience in reviewing biological products and the experts opinion, and may be revised with the advance in science in the future.

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Evaluation Guideline for Biosimilars

1. Introduction

Since DNA recombinant insulin was approved as antidiabetics, DNA recombinant products have been expanding their realm to antiarthritics and antitumor agents. While biological products have lower risk in research and development compared with chemically-derived products owing to less adverse drug reactions and higher therapeutic effect from target therapy, they require higher expenditure. However, when patents for new biologics expire, “biosimilar products” may be developed for which comparability to originator products would be demonstrated in quality, safety, and efficacy, and it is expected to reduce the payment burden.

Meanwhile, in case of chemically-derived products, “generic products” have been used which have the same chemical structures as originator products with expired patent or data protection. However, biological products are usually proteins of high molecular weight and very complex structure, and therefore structure and activity are very sensitive to type of cell strain and change in manufacturing method. Even when the same manufacturer manufactures the same product, the same product cannot be guaranteed if manufacturing method is changed, and equivalence is evaluated for quality, safety, and efficacy. Consequently, it is not appropriate that existing established approval procedures or evaluation methods for generic chemically-derived products are directly applied to biological products. With this background, European Medicines Agency (EMA) has been arranging and implementing separate regulations and guidelines for biosimilar products, and national regulatory bodies worldwide are also preparing for the provision.

This guideline is prepared to provide a guide for the considerations in evaluating the biosimilar products as well as a regulation for item approval-review of biosimilar products in Korea, collecting suggestions from internal and external experts through operating the councils and referring to the foreign cases and the ongoing preparation for a guideline by World Health Organization (WHO).

2. Scope

This guideline could apply, in principle, to all biologicals. However, in practice, it will mostly be applicable to the products that can be showed the similarity thorough characterization, and non-clinical/clinical studies and contain well-characterized therapeutic proteins as an active substance.

3. General Considerations

Biosimilar products are developed through sequential process, which demonstrates the

equivalence by conducting parts of test items of non-clinical and clinical studies, supposing the equivalence in quality characteristics with a product which is already approved for item manufacturing-selling-importing.

Although the extent of testing of the similar biological product is likely to be less than is normally required for an innovator product (new biological entity), it is essential that the testing of the similar biological product be sufficient to ensure that the product meets acceptable levels of quality, safety and efficacy to ensure public health. Generally, a reduction in data requirements is possible for non-clinical and/or clinical parts of the development program by guaranteeing quality of product, which may vary depending on the characteristics of the already approved reference product.

Major difference for biosimilar products is that they can be recognized for indications of reference products without performing clinical studies for all the clinical indications that reference products are approved for, supposing the equivalence with reference products by extrapolation of indications of reference products.

This guideline describes the method for evaluating the comparability between reference products and biosimilar products in conducting quality evaluation and non-clinical and clinical studies, and does not cover the biological products which are intended to be approved based on only clinical equivalence.

4. Glossary

The definition of terms used in this guideline is as follows. The definitions which are not defined in this guideline will be abided by relevant regulations such as the regulation on approval review of biologics (posted by KFDA).

1) Biosimilar products

Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy

2) Reference product

A medicinal product that was approved on the basis of a full data package (registration dossier). In this guideline, reference products are used as the comparators in head-to-head studies to show similarity in terms of quality, non-clinical and clinical studies of biosimilar products.

3) Originator product

A medicine which is the first to be approved and which has been approved by the national regulatory authorities on the basis of a full registration dossier. The originator product is usually used as a reference product as it tends to be the product with publicly available safety

information and long market experience

4) Comparability

The scientific evaluation of a comparison of biosimilar product and reference product to determine absence of any detectable differences at the level of quality, non-clinical and clinical studies.

5) Clinical equivalence

Clinical equivalence is being equivalent when evaluated based on major clinical parameters, and any observed differences are clinically non-relevant.

6) Impurity

Any components present in the drug substance or drug product which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process-related or product-related.

7) Immunogenicity

The ability of a substance to trigger an immune response or reaction (e.g., development of specific antibodies, T cell response, allergic or anaphylactic reaction)

5. The choice of Reference Products

The chosen reference product that will be used to develop biosimilar products should already be licensed in Korea. Product which is the same (including manufacturing site and manufacturing method) as a biological product already approved domestically may be purchased abroad and used as reference product, only if validity is confirmed, e.g., in case of no feasibility to purchase reference products despite the domestic approval for the product.

The same reference product should be used throughout the comparability exercise for quality, non-clinical and clinical studies. The reference product also provides the basis for dose selection, dosage form and route of administration, and is utilized in the comparability studies required to support the licensing application.

Reference products should have accumulated data on safety and efficacy through enough experience in use, and medicinal products approved as biosimilar products may not be used as reference products.

6. Quality

6.1. Manufacturing Process

Manufacturing process should be described in detail from drug substance to drug product, since biosimilar products are produced by their own manufacturing process different from those of reference products. It should be demonstrated that manufacturing method is proper and valid on a modern technological level with regard to the particulars of the item, and that quality is ensured through consistent production in accordance with Good Manufacturing Practice (GMP). Data for submission should include quality control/assurance system, manufacturing process control, and process validation.

In addition, if any change is made in manufacturing process of biosimilar products, comparability study should be performed according to "Evaluation Guideline for Changes in Manufacturing Method of Biological Products" or ICH Q5E, and comparabilities before and after the change should be evaluated.

6.2. Comparability

The quality comparison between the biosimilar and the reference product is essential and it should be tested and evaluated adequately taking the effect on safety and efficacy into consideration. The applicant should submit a full quality dossier including the results of comparability exercise between the biosimilar and the reference product. A standardized batch which proved its consistency in manufacturing processing should be used.

Because the aim of the comparability exercise is to demonstrate of all characteristics of the biosimilar product to a chosen reference product in terms of quality, safety and efficacy, tests always should be conducted for both level of drug substance (active ingredient) and drug product. When determining the final comparability, non-clinical/clinical data are required to consider together. Differences between biosimilar products and reference products in each quality component can be existed. Appropriate data should be submitted to verify that the difference do not impact on the safety and efficacy.

The quality comparison between the biosimilar and the reference product should be employed state-of-the-art analytical techniques, including the analytic methods that are sensitive enough to detect the possibilities of changes to the product, which are validated.

Due to the unavailability of direct comparison at the level of drug substance, if the active ingredient is need to isolate from reference product,, the documents which demonstrate appropriateness pertaining to isolation process and characteristics of the active ingredient isolated must be submitted.

Major items on processing that may impact on product's characteristics, adequacy of in-process control, and necessity on supplementary documents which derives from non-clinical, clinical studies should be considered.

6.2.1.Characteristic analysis

In order to show the similarity between biosimilar product and reference product in terms of quality, broad and state-of-the-art analytical tests should be conducted. Characterization studies include basically physicochemical properties, biological activity, immunochemical properties, purity(process- and product-related impurities etc), contamination, strength, and content. (The studies can be conducted by the ICH guideline (ICH Q6B) 'Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products'). When conducting a comparability study using the biosimilar approach, head-to-head characterization studies are required to compare the biosimilar and the reference product at both levels of drug substance and drug product. Differences between the biosimilar and the reference product should be evaluated for their potential impact on safety and efficacy of the biosimilar, and additional characterization studies may be necessary.

– *Structural* □ *Physicochemical Properties*

The physicochemical characteristic analysis should include composition of active ingredient, physical and chemical properties, and the determination of primary and higher order structure. If information on higher order structure is unavailable, the biological assay also complements the physicochemical analyses by inferring the correct higher order structure of the molecule. Thus, the method of biological assay used should provide appropriate precision and accuracy. Also, if process and product-related impurities are made, or, degradation products are found in accelerated and stressed stability studies, it should be clarified.

An inherent degree of structural heterogeneity may occur in proteins due to the biosynthesis process such that the reference product and the biosimilar are likely to contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate, identify and quantify these forms.

– *Biological Activity*

Since the proteins in biological products have variant biologically characteristics, various bioassay should be considered to measure the biological activity. For a product with multiple biological activities, manufacturers should perform, as part of product characterization, a set of relevant functional assays designed to evaluate the range of activities of the product because the biological activity test is associated with the related protein's action mechanism and clinical effects.

Biological assay is a quality measure for protein function, and is used for determine whether

a change in product quality originates from active components or inactive impurities. In addition, biological assay may help supplement the results on the physicochemical properties owing to the potential as a method for confirming higher order structure of protein. Therefore, it may be possible to demonstrate that biosimilar products have no major functional difference from reference products by biological assay with appropriate accuracy and precision. However, because biological assay(s), in nature, can have high changeability, the possibility that the assay(s) does not distinguish the differences between the two products should be also considered.

The results of the biological assay(s) should be provided and expressed in units of activity. Assays should be calibrated against an international or national reference standard, when available and appropriate. If the methods of bioassay(s) are documented in the specification, test(s) can be conducted by the specification.

- Immunological Properties

It is important to identify immunological properties of biosimilar products, since product- or manufacturing process-related impurities or post-translational protein modification can cause immunogenicity. If immunological properties are to be included in characteristic analysis (antibody or antibody-derived product), biosimilar products should be compared with reference products for specificity, affinity, binding strength and Fc function, and results from immunogenicity evaluation in animal studies should be considered.

- *Degree of purity or Impurities*

Drug substance or product should be evaluated by various analytical methods for quantitative and qualitative analysis. It is required to confirm accelerated and degraded conditions, the possibility of post-translationally modification.

Product-related impurities should be identified, quantified and compared between the biosimilar and reference product by using cutting-edge technologies. If possible, more than one technology, being able to applied to each item, should be considered.

Some differences may be expected in quantitative and qualitative analysis because process-related impurity is different depending on each manufacturing processes. Consequently, quantitative comparison may not be related to comparability studies. However, if differences are observed in the impurity profile of the biosimilar relative to the reference product, the differences should be evaluated to assess the potential impact on safety and efficacy of the product by using cutting-edge technologies.

Impurities should be controlled by in-process acceptance criteria or action limit on active ingredients or products. New impurities should be evaluated regarding its impact on quality, safety, and efficacy.

6.3. Specifications

Standard specification for the product is for routine quality control. Analytical methods in the specification should be appropriate and specified to ensure product quality, and follow relevant regulations and guidelines.

Reference to Acceptance limits for each test parameter should be provided and justified based on the data from sufficient lots of biosimilar (e.g. non-clinical/clinical studies, lot tests to show the consistency of manufacturing process, stability tests, and comparability exercise to show the similarity in terms of quality, safety, and efficacy).

6.4. Analytical Methods

In order to show the comparability between biosimilar product and reference product, broad and state-of-the-art analytical tests should be conducted at both levels of drug substance(s) (active ingredient) and drug product(s).

Due to the complicated and heterogeneous composition that protein may have, it is recommendable more than one analytical methods apply to each item of quality in order to demonstrate physiochemical and biological nature sufficiently.

The measurement of quality attributes in characterization studies does not necessarily require the use of validated assays, but the assays should be scientifically sound and well-characterized. They should provide results that are meaningful and reliable. The methods used to measure quality attributes for lot release should be validated in accordance with relevant guidelines (e.g. KFDA guidelines), as appropriate

6.5. Stability

To set a shelf-life and storage condition of drug product, its real time stability test should be conducted. Side-by-side accelerated and stressed studies comparing the biosimilar product to the reference product will be of value in determining the similarity of the products by showing comparable degradation profiles though those tests are not mandatory. Stability studies on drug substance should be carried out using containers and conditions that are representative of the actual storage containers and conditions, according to relevant guidelines(e.g. The KFDA stability guideline for biologics, ICH Q5C).

7. Non-clinical evaluation

The establishment of safety and efficacy of a biosimilar product usually requires the generation of additional non-clinical and/or clinical data besides a thorough quality characterization.

Non-clinical studies in nature should be conducted with the final formulation of the biosimilar product intended for clinical use. When the formulation study is impossible (i.e. toxicological test which requires high-dosage administration, etc.), appropriate minimal modification could be allowed in order to enable to study. The dosage form, strength and route of administration of the biosimilars should be the same as that of the reference product. In case of differences in these parameters, justifications for the differences should be provided.

Because the non-clinical studies constitute a part of the overall comparability exercise, non-clinical study program should be designed to prove the comparability with the chosen reference product and conducted abiding by existing guideline(e.g. ICH S6 etc). It is important to note that the design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Result from characterizations should be reviewed from the point-of-view of potential impact on efficacy and safety.

One reference product has to be used throughout the entire non-clinical development program and must be the same as that used in the quality and clinical part of the comparability exercise.

The approach described below may be considered and should be tailored to the specific biosimilar product concerned on a case-by-case basis. The approach taken will need to be fully justified.

In vitro studies:

Assays like receptor-binding studies or cell-based assays (e.g. cell-proliferation assays) should normally be undertaken in order to establish comparability in biological/pharmacodynamic activity of the biosimilar and reference product. Such data are usually already available from biological assays described in the quality part of the dossier and reference to these studies can be made in the non-clinical part of the dossier.

In vivo studies:

Animal studies should be designed to maximize the information obtained. Such studies

should be performed in (a) species known to be relevant (i.e. species in which the reference product has been shown to possess pharmacodynamic and/or toxicological activity) and employ state of the art technology. Generally, consideration should be given to monitoring a number of endpoints such as:

- Biological/pharmacodynamic activity relevant to the clinical application

: Such data are usually already available from biological assays described in the quality part of the dossier and reference to these studies can be made in the non-clinical part of the dossier.

- Non-clinical toxicity as determined in at least one repeat dose toxicity study with a relevant species including toxicokinetic measurements.

: If applicable, toxicokinetic measurements should include determination and characterization of antibody responses. The duration of the studies should be sufficiently long to allow detection of toxicity and antibody responses between biosimilar and reference product. Although the predictive value of animal models for immunogenicity in humans is considered low, antibody measurements in the repeat dose toxicity study help to interpret the toxicokinetic data to help assess, as part of the overall comparability exercise, whether differences in structure or impurity profile exist between the biosimilar and reference product. Also, the comparative repeat dose toxicity study is considered to provide reassurance that no 'unexpected' toxicity will occur during clinical use of the biosimilar product. If performed with the final formulation intended for clinical use, the repeat dose toxicity study will in principle allow for expectation of potential toxicity associated with both the active substance and product- and process-related impurities.

- Local tolerance test

: Depending on the route of administration, local tolerance should be evaluated. If feasible, this evaluation may be performed as part of the described repeat dose toxicity study.

- Other toxicity test

: On the basis of the reassurance provided for comparability of the biosimilar and reference product by the additional comparability exercise performed as part of the quality evaluation, normally other routine toxicological studies such as safety pharmacology, reproduction toxicology, genotoxicity and carcinogenicity studies are not required when using the biosimilar approach unless indicated by results of repeat dose toxicity studies and/or triggered by known toxicological properties of the reference product (e.g. known adverse effects of the reference product on reproductive function) which requires additional toxicological studies.

8. Clinical Evaluation

The major clinical data should be generated with the product derived from the final manufacturing process and therefore reflecting the product for which marketing authorization is being sought. Any deviation from this recommendation needs to be justified and additional bridging data is necessary.

Clinical trials for the demonstration of comparability with the chosen reference product could include PK, PD and efficacy clinical studies. In certain cases the comparability could be proved with comparative PK/PD studies, the efficacy studies could be exempt

8.1. Pharmacokinetic (PK) studies

Generally, the PK profile is part of the basic description of a medicinal product and should always be investigated. PK studies should be performed for the routes of administration applied for and using the dose(s) within the therapeutic dosing range recommended for the reference product.

In order to prove comparability of biosimilar product, PK studies must be comparative and should be designed to enable detection of potential differences between the biosimilar and the chosen reference product. This is usually best achieved by performing single-dose PK studies in a sensitive homogenous study population and by using a dose where the sensitivity to detect differences is largest. For example, for a medicinal product with saturable absorption (saturation kinetics), the lowest therapeutic dose would be most appropriate, provided the employed assay can measure the resulting drug plasma levels with sufficient accuracy and precision. If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homogenous model for such comparative PK studies.

The choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population should be justified by the applicant. The cross-over design is not appropriate for biological medicinal products with a long half-life or if formation of anti-product antibodies is likely. In parallel designs, care should be taken to avoid relevant imbalances between treatment groups. In cross-over designs, the fact that the results of PK studies are not affected by half-life, antibody formation, and etc. needs to be justified.

PK comparison of the biosimilar and the reference product should not only include absorption/bioavailability but also elimination characteristics, i.e. clearance and/or elimination half-life, since differences in elimination rate of the biosimilar and the reference product may occur.

Acceptance criteria for the demonstration of similar PK between the biosimilar and the reference product should be pre-defined and appropriately justified. It is emphasized that the criteria used in standard clinical comparability studies (bioequivalence studies), initially developed for chemically-derived, orally administered products may not necessarily be appropriate.

Other PK studies such as interaction studies (with drugs likely to be used concomitantly) or studies in special populations (e.g. children, elderly, and patients with renal or hepatic insufficiency) are usually not required for the biosimilar approach, supposing the comparability on quality and non-clinical aspects.

Historically, the PK evaluation of peptide or protein products has suffered from limitations in the assay methodology thus limiting the usefulness of such studies. Special emphasis should therefore be given to the analytical method employed and its capability to detect and follow the time course of a given analytical object (the parent compound and/or metabolites) in a complex biological matrix that contains many other proteins with satisfactory specificity, sensitivity and a range of quantification with adequate accuracy and precision.

In case the active substance of biosimilar is an endogenous protein and the concentration of endogenous protein is measurable, it may substantially affect the concentration-time profile of the administered exogenous protein. In such cases, the applicant should describe the approach to minimize the influence of the endogenous protein.

8.2. Pharmacodynamic (PD) studies

In general, PD parameters could be investigated in the context of combined PK/PD studies and be selected based on their clinical relevance. Since for biological products not only pharmacokinetics but also the concentration-response relationship may differ between products, PK/PD data may be useful to support clinical data. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different dose levels.

In the obligatory comparative PD studies, PD effects should be investigated in a suitable patient population using a dose within the steep part of the dose-response curve in order to best detect potential differences between the biosimilar and the reference product. But if PD effects are able to be evaluated comparably based on PD markers established by healthy population, it could be investigated by healthy population.

In most cases, similar efficacy of the biosimilar and the reference product will have to be

demonstrated in comparative efficacy clinical trials. However, similar PD profiles will further support the biosimilarity.

8.3. Efficacy studies

Dose finding studies are not required for the biosimilar approach because the biosimilar will adopt the posology of the reference product.

Equivalent rather than non-inferior efficacy should be shown in order for the biosimilar to adopt the posology of the reference product and to open the possibility of extrapolation of efficacy data to other indications of the reference product, which may also include different dosages. Equivalence margins need to be pre-defined and justified and should be established within the range which is judged not to be clinically different from reference products in clinical regards.

Clinical equivalence between the biosimilar and the chosen reference product will usually have to be demonstrated in adequately powered, randomized, parallel group clinical trial(s), so-called “equivalence trials”. Clinical studies should preferably be double-blind or at minimum observer-blind. In the absence of any blinding, careful justification will be required to prove the trial results are free from significant bias.

Potential differences between the biosimilar and the reference product should be investigated in a sensitive and preferably well-established model, e.g. in the case of hormones, patients with hormone deficiency disorders usually represent the most appropriate study population.

8.4. Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

Usually, clinical trials are required to demonstrate efficacy of a biosimilar product. In certain cases, however, comparative PK/PD studies may suffice, provided that

- the PK and PD properties of the reference product are well characterized,
- at least one PD marker is an accepted surrogate marker for efficacy, and
- the relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the reference product(s) is established.

The study population and dosage should be selected considering a test system that is known to be sensitive to detect potential differences between the biosimilar and the reference product. Otherwise, it will be necessary to investigate a relevant dose range to demonstrate

that the test system is discriminatory. In addition, the acceptance ranges for demonstration of equivalences in the main PK and PD parameters should be pre-defined and appropriately justified.

8.5. Safety

Pre-approval safety data should be obtained in a sufficient number of patients to characterize the safety profile of the biosimilar products.

Safety data obtained from the clinical trials can be expected to mainly detect frequent and short-term adverse events/reactions. Comparison with the reference product should include type, frequency and severity of adverse events/reactions. Such data are usually satisfied with safety data obtained before the approval, but further close monitoring of clinical safety of the biosimilar may be necessary in the post-marketing phase.

8.6. Immunogenicity

Even if efficacy and safety of a biosimilar and the reference product have been shown to be similar, immunogenicity may still be different. The immune response against a biological product is influenced by many factors such as the nature of the active ingredient, product- and process-related impurities, excipients and stability of the product, route of administration, dosing regimen, and patient-, disease- and/or therapy-related factors. The consequences of unwanted immunogenicity may vary considerably, ranging from clinically irrelevant to serious and life-threatening. For example, neutralizing antibodies directly alter the pharmacodynamic effect, binding antibodies may affect pharmacokinetics. Thus, an altered effect of the product due to anti-product antibody formation might be a critical composite of safety effects.

Thus, the frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared for the biosimilar and the reference product before the approval of the biosimilar.

Immunogenicity of a biological medicinal product should always be investigated in humans since animal data are usually not predictive. Antibody testing should be investigated with humans, and should be performed in all patients participating in clinical trials.

The applicant will need to justify their antibody testing strategy including selection, assessment, and characterization of assays, identification of appropriate sampling time points including sample volumes and sample processing/storage as well as selection of statistical methods for analysis of data. Antibody assays need to be validated for their intended purpose. A screening assay of sufficient sensitivity should be used for antibody detection and a

neutralization assay should be available for further characterization of antibodies, if present. Possible interference of the circulating antigen with the antibody assay(s) should be taken into account.

If the antibody incidence is increased with the use of the biosimilar compared to the reference product, their potential clinical implications regarding safety, efficacy and pharmacokinetics need to be investigated. Also, special attention should be paid to the possibility that the immune response seriously affects the endogenous homeostasis related to the endogenous protein and its unique biological function.

The required observation period for immunogenicity testing should be sufficient to detect clinically relevant antibodies and depend on the intended duration of therapy and the expected time of antibody development. In the case of chronic administration, sufficient data (i.e. the duration of the studies should be sufficiently long to allow to collect necessary data) will usually be required pre-licensing to assess antibody incidence and persistence, development of antibody titers over time, a potential change in the character of the antibody response and possible clinical implications.

The results of immunogenicity assessment that obtained throughout efficacy clinical studies should be provided in application for the approval, and additional follow-up data may be necessary. Since submission data related to evaluation of immunogenicity are limited, further characterization of the immunogenicity profile may be necessary post-marketing, particularly, if rare antibody-related serious adverse events may occur, which are usually not detected in the pre-marketing phase.

8.7. Extrapolation of efficacy and safety data to other indications

If equivalence on efficacy and safety of the biosimilar and the reference product have been demonstrated in a particular indication, extrapolation of these data to other indications of the reference product of which PMS period is expired may be possible if:

- A sensitive test model has been used, which is able to detect potential differences between the biosimilar and the reference product and
- The mechanism of action and/or involved receptor(s) are the same
- Safety and immunogenicity have been sufficiently characterized

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