Biosimilar Product Evaluation Guideline

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Ministry of Food and Drug Safety
National Institute of Food and Drug Safety Evaluation

Biopharmaceuticals and Herbal Medicine Evaluation Department

Recombinant Protein Products Division

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Document History

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1. Introduction

In 1982, the first recombinant DNA product (hereafter referred to as biotherapeutic product interconvertably), human insulin was approved by the U.S. FDA. Since then, recombinant DNA products continued to expand its therapeutic scope to many types of treatments such as immunomodulators and anticancer agents. A biotherapeutic product has relatively less adverse drug reactions with a wider therapeutic effect, including targeted therapy, compared to synthetic chemical drugs. But the high cost of these products discourage the accessibility to patients. Expiration of the patent of original biotherapeutic product has allowed the development of 'biosimilar products' by the demonstration of comparability in terms of the quality, safety, and efficacy. It is expected that more patients would secure treatment opportunities with more affordable prices.

For a synthetic chemical drugs, the term 'generic drug' is used to describe small-molecules that are structurally and therapeutically equivalent to an original product whose patent or data protection period has expired. On the other hand, biotherapeutic product is a protein with high molecular weight and complex structures; therefore, its structure and functional activities are very sensitive to the type of production cell lines and changes in the manufacturing process. For this reason, it cannot be guaranteed that the same structured product is reproduced when the manufacturing process has changed by the same manufacturer. This is why comparability evaluation is required for the quality, safety and efficacy. Thus, it is not appropriate to apply the same regulatory process established for existing generic drugs directly to biotherapeutic product. With such a background, regulations for 'biosimilar products' needed to be newly established. Following the establishment of regulations and guidelines on biosimilar products by

the European Medicines Agency (EMA) in 2005, the World Health Organization (WHO) also established an international guideline on biosimilar product evaluation in 2009 and regulatory agencies in many countries have their own regulations in place that are aligned with the WHO guidelines.

In Korea, biosimilar evaluation guideline was published in 2009 in line with the WHO similar biotherapeutics guideline. We also referred to the regulations from stringent national regulatory authorities as well as comments from many internal and external experts. Thereafter, the guideline has evolved based on the experiences of local and global experiences from biosimilar product development, clinical trials, marketing authorization and international regulatory harmonization. Additionally, in alignment with the intention of the recent WHO international guideline revision, this guideline is also revised as below.

2. Scope

This guideline describes the principles and recommendations on comparability exercise of biosimilar products, which falls under the Regulations on Product Authorization and Review of Biological Products (Ministry of Food and Drug Safety Public Notice) [Attached table 1] Part 2. Type and Scope of Submission for DNA Recombinant protein products and Cell Culture Products, II. Drugs Subject to Document Submission 3. Biologics.

In principle, scope of biosimilar product may apply to any biological products, however in fact, it only applies to the products of which the active substance is well-characterized and demonstrate equivalence based on comparability evaluation of quality and non-clinical and clinical study results (recombinant DNA protein products). Biotherapeutic products requesting authorization solely based on clinical equivalence are not applicable.

3. General Considerations

A biosimilar product defines as a biotherapeutic product that demonstrates quality, non-clinical and clinical comparability to reference product which was granted market authorization in Korea. Authorization of all or some indications of reference product can be obtained based on highly comparable data of biosimilar product without conducting clinical studies to support those indications.

The posology and route of administration of biosimilar product should be same as for reference product. The strength, composition, container-closure system and pharmaceutical form do not necessarily be the same as the reference product if it is properly justified.

Development of a biosimilar product is based on sufficient prior knowledge of the quality, safety, and efficacy of the reference product. Recombinant protein product generally has large and complex structure that has inherent diversity in its quality attributes. Manufacturing process can greatly affect in quality as well as pharmacokinetics and pharmacodynamics, efficacy, and safety. Therefore, demonstrating comparability solely based on quality aspects has limitations and that's why extensive comparability exercise in terms of quality, safety and efficacy should be demonstrated.

The first step in development of a biosimilar product is to deeply understand known information about the reference product and to identify extensive quality attributes of the reference product and to define quality target product profile (QTPP) through characterization of quality attributes of multiple batches of reference products. Subsequent comparability exercise should demonstrate in terms of quality, non-clinical and clinical studies between biosimilar and reference product

Demonstration of high similarity of a biosimilar and a reference product in terms of structural and functional aspects and non-clinical

in vitro data is pre-requisite for establishing comparability. An extensive quality comparability evaluation should be conducted from the beginning of the development and the evaluation results should be considered to establish a development plan, including non-clinical and clinical studies.

At any stage, if relevant differences between the biosimilar and the reference product are found, underlying reasons for differences should be investigated and fully understood. The relevant difference should be justified based on the consideration of effects on safety and efficacy and additional studies may be required if necessary. A difference that is not considered significant in terms of clinical (functional) equivalence, e.g., improvement in purity or immunogenicity profile may be accepted.

Determination of comparability with the reference product is not just to meet a pre-specified comparability margin for some analytical attributes but also based on the totality-of-evidence with respect to quality and non-clinical and clinical data.

In case that clinical efficacy of a product is intentionally improved, the development of such a product is not considered as biosimilar product.

4. Selection of a Reference Product

A reference product used as the comparator for biosimilar product development should be nationally licensed as a new drug or a new product (a biotherapeutic product licensed on the basis of a full registration dossier) with accumulated data in place on safety and efficacy based on sufficient marketing experiences. Therefore, a biosimilar product should not be chosen as a reference product.

During development of a biosimilar product, the same reference product must be used throughout the comparability exercise of quality, non-clinical clinical studies.

When it is difficult to secure a sufficient quantity of a reference product in the national market, the same reference product can be source from

foreign country during development, if justified. The reference product purchased from a foreign country should be licensed in well-established regulatory authorities (e.g., ICH member state) of which regulatory frameworks are equivalent to those in South Korea. To justify the use of a foreign reference product in comparability exercise, proper analytical bridging data should be provided between foreign- and nationally-sourced reference product. The result of analytical comparability data that directly compares the biosimilar product, nationally-sourced reference product, and foreign reference product used for development should be submitted and such a result should meet the pre-specified comparability margin. In some case three-way comparative PK and/or PD study may be required if for example, difference exists in the composition of foreign and nationally-source reference products.

If marketing authorization of a reference product has been canceled or withdrawn, use of the product as a reference product is considered canceled upon acknowledgment of such cancellation and withdrawal as a rule. The exception is where the development is already on-going at the time of such product cancellation or withdrawal (e.g., a clinical study protocol has been approved or has been submitted for approval with the existing reference product) and comparability can be demonstrated (e.g., sufficient analytical bridging data using a domestic reference product are already secured).

5. Quality Evaluation

Requirements for marketing authorization on biosimilar products are defined in the 「Regulations on Authorization and Review of Biological Products」(Ministry of Food and Drug Safety Public Notice). As with other biological products, complete quality dossier demonstrating consistent and robust manufacturing capability and quality control capability should be submitted. Comparability data on quality between the biosimilar product and a reference product should be included as part of quality dossier in addition.

5.1. Evaluation of Quality Comparability with a Reference Product

Quality comparability study should be conducted extensively by using state-of-the-art analytical methods with appropriate sensitivity and specificity as to adequately identify known quality attributes of a reference product including the identity, purity, potency and quantity and to detect any differences that may exist.

Generally, comparability exercise means to compare biosimilar drug product with reference drug product on a direct head-to-head manner. The evaluation result is determined based on the comparability range that are scientifically and reasonably established from the analytical results of multiple batches of reference products.

There may be an expected difference in quality attributes due to pharmaceutical form, composition and container-closure system of the reference product and the biosimilar product. Also an unexpected difference may be observed during an extensive quality comparability exercise. Such a difference should be identified and compared. Additionally, a potential effect of such a difference on the safety and efficacy should also be understood and justified that there should be no significant clinical effect(s). To justify a differences, additional analytical studies or non-clinical or clinical studies may be required

(1) Analytical consideration

All possible known quality attributes and performance attributes, including molecular structure, physicochemical properties, immunochemical properties, biological properties, purity/ impurity, and degradation profiles, should be evaluated (refer to Sections 5.1.1 to 5.1.6 of the same guideline).

Protein products may not be feasible to characterize all structural and functional diversities that may potentially exist because of its structural complexity and inherent heterogeneity. Therefore, it is important to

thoroughly understand the limitations of each analytical method, and it is recommended to employ state-of-the-art technology and to use orthogonal methods that complement multiple analytical technologies for a single quality attribute.

(2) Product Batches to be Analyzed

When obtaining a reference product, multiple batches with different ages within the shelf-life for different manufacturing campaigns should be included so that the variability of the reference product itself can be checked.

As a rule, biosimilar product batches to be analyzed are drug products manufactured with a final commercial process, composition and container-closure system, and it is desirable that these are manufactured from different drug substance batches. Small-scale or pilot batches may be included provided their representativeness is recognized with appropriate demonstration of comparability. Also batches used for major clinical settings should be included.

If there is little difference in composition between the drug substance and the drug product or the quality attributes are not altered by the drug product's manufacturing process, drug substance batches may be used for analysis, for which justification must be provided.

(3) Number of Batches of Reference Product and Biosimilar Product

Generally, the more batches there are for evaluation, the better the understanding that is obtained on the quality variability of a product that may be incurred by process performance and analytical method performance. The number of batches required to understand batch-to-batch variability of reference products and biosimilar products for each evaluation item and to detect a difference that may be present depends on the characteristics of the product and the analysis item(s).

Particularly the number of batches needed for the comparability

exercise will mainly depend on the criticality of the quality attributes and the approach chosen for demonstrating similarity (e.g., statistical approach). For instance, in a test for quantity or potency test which has a high risk ranking due to its high clinical relevance, a statistical approach such as an equivalence testing of mean values based on the analysis result of multiple reference product batches may be used. In this case sufficient number of batches are required to be analyzed to secure the reliability of statistical approach used.

The applicant should provide scientific justification for the number of reference product and biosimilar product batches used for comparability assessment

(4) Comparability ranges

A risk ranking of quality attributes can be evaluated with consideration of the effects or uncertainty on the safety, efficacy, pharmacokinetics, and immunogenicity. For a risk ranking tool, refer to relevant guidelines.

The equivalence evaluation method and margin per test item are determined based on the risk ranking. For quantitative items, a statistical approach is recommended. For qualitative items, a direct profile comparison such as chromatogram or analytical method limitations are considered.

For the statistical approach, generally min-max range, an equivalence evaluation in the mean difference, mean ±x·standard deviation (SD), tolerance interval and prediction interval can be used. The used approach should be scientifically justified, including the criticality of quality attributes. Comparability ranges are normally not wider than the batch-to-batch variability present in the reference product.

Performance of the analytical method should also be considered. For example, cell-based bioassay with higher variability may lead to failure in detecting differences that are present between the reference product and the biosimilar product. Thus, it is encouraged to employ a relevant

biological assay with appropriate precision, accuracy, and sensitivity to confirm no significant functional difference between the reference product and the biosimilar product.

The applicant should provide scientific justification for the comparability ranges per test item used for evaluation.

(5) Analytical techniques

The methods for characterization studies should be scientifically sound and reliable with proper sensitivity and specificity to detect a difference from a reference product and biosimilar product. The measurement of quality attribute in characterization studies does not necessarily require the use of validated assays, but the assays should demonstrate to be suitable for their intended use with appropriate precision, accuracy, specificity and sensitivity. If necessary, assay qualification data may be required.

For some products or quality attribute items, direct comparison at the level of a drug product may not be feasible and drug substance may need to be purified from the reference drug product. In this case, studies should be carried out to demonstrate that relevant attributes of the active moiety are not affected by the isolation process. The Alteration or loss of related substances and impurities should also be considered in addition to the effect of active substance due to isolation process.

(6) In case where there is uncertainties or differences between the reference product and biosimilar product

There may be a clear difference or tendancy to be different although the difference is within the range of comparability. Such a difference may be expected results due to difference in pharmaceutical form, composition and container-closure system between the reference product and biosimilar product, or may also be an unexpected difference observed in the extensive quality comparability study.

If differences between biosimilar and reference product are found, the

underlying reasons for the difference should be explained and the impact on safety and efficacy should be investigated. For example, a difference identified from low clinical relevant attribute can be justified using the available public references. For an attributes with high clinical relevance, an additional analytical study or clinical study on biological activity may be required to determine the clinical effects. If justified, for case of difference in impurities, the measured difference between reference and biosimilar product can be accepted (e.g., a lower level of impurity is generally accepted). In the end, the decision is made based on the totality of all available data.

Unless differences are explained and justified in the quality comparability studies, the proposed product cannot be considered as a biosimilar product.

(7) Quality Comparability Evaluation Data

The summary for the quality comparability evaluation plan and the results should be provided.

The summary should include information on batches of the reference product and biosimilar product used for analysis for each item, analytical technology and comparability range. For the analyzed reference product and biosimilar product batches, the product name, volume, batch number, date of manufacture or shelf-life, expiry date and the intended use (e.g., for phase III clinical study) should be clearly identified. If necessary, information on the pharmaceutical form and composition should be also included. For evaluation results, details such as a representative chromatogram should be included in addition to a summary, and discussion of the results needs to be described.

5.1.1. Structural and Physicochemical Properties

Structural and physicochemical attributes requiring analysis include but not limited to the following:

1) Structure

- Primary structure and terminal sequence variant (N/C-terminal variant), amino acid sequence variant, etc.
- Molecular weight
- Post-translational modification [deamidation, isomerization, oxidation, glycosylation, glycation, etc.]
- Disulfide bond structure, free sulfhydryl groups
- Higher-order structure [secondary, tertiary, and in some cases, quaternary structures]

2) Physicochemical attributes

- Molecular size, charge, hydrophobic profile, etc.
- Purity, related substances, product-derived impurities

3) Major quality profile of the final product (drug product)

- Quantity, pH, insoluble particulate matter, etc.

The amino acid sequence of a biosimilar product should be the same as that of a reference product. Minor structural heterogeneity such as N- or C-terminal truncation (e.g., C-terminal lysine of a monoclonal antibody) that may occur as a result of biosynthesis process may be accepted provided that it is not expected to affect the biological activity. An unintended sequence variant may also develop at a low level, and if it is present, it should be identified. Such a variant may be accepted provided that its presence is well explained and controlled to a reasonable level. Evaluation of potential clinical effects of such a variant should be considered.

An inherent degree of structural heterogeneity occurs in proteins as a result of the biosynthesis process. These include; C-terminal processing, N-terminal pyroglutamation, deamidation, oxidation, isomerization, fragmentation, disulfide bond mismatch, and free sulfhydryl groups, N-linked and O-linked oligosaccharide, glycation, and aggregation.

Particularly for a monoclonal antibody, the experimentally measured disulfide bond pattern should be compared with a predicted structure.

For a complex molecule, it may not be feasible to completely identify its higher-order structure even with orthogonal tests. In this case, biological activity may play a role to complement the higher-order structure integrity evaluation. Therefore, a difference found from a higher-order structure measurement between the reference product and the biosimilar product should be evaluated in terms of the potential effect(s) on the biological properties and stability.

5.1.2. Biological Properties

The biological assay will reflect the understood mechanism of action of the active substance of the reference product and will thus serve as a link to clinical activity. A biological assay is a quality measure of the activity of the drug substance and can be used to determine whether a product variant is active (i.e. a product-related substance) or inactive (and is therefore defined as an impurity). It also complements the protein higher-order structure integrity evaluation.

For a product with multiple biological (functional) activities, all relevant activities should be evaluated and compared. For example, a monoclonal antibody requires evaluation of binding activity to a target antigen and additional relevant activities, such as affinity to Fc receptors (e.g., FcRn, C1q and FcγR) and relevant biological activity (e.g., CDC, ADCC, ACDP, etc.).

The used biological activity measurement method should provide a scientifically reasonable, consistent, and reliable results. Suitability of the developed analytical method, including sensitivity, specificity, range, accuracy, precision and robustness, should be confirmed first before use. Some biological activity methods may have a high variability, such that it leads to a failure in the detection of a small but significant

difference between a reference product and biosimilar product. So it is desirable to develop an analytical method that is sensitive to changes in activity and has a low variability.

5.1.3. Immunological Properties

When there are product- or process-related impurities or structural variants such as post-translational modification, these may cause immunogenicity. Thus, it is important to determine the immunochemical properties of a biosimilar product, which is also related to the evaluation of identity, structural microheterogeneity, or purity attributes.

Particularly for a product that has an immunochemical attribute as part of activity (e.g., antibody or antibody-based product), affinity should be analyzed, compared, and evaluated to determine the affinity to purified antigen, epitope and the immunoreactivity, including cross-reaction.

5.1.4 Purity and Impurity

Process- and product-related impurities of a biosimilar product and reference product should be identified and quantified using state-of-the art and orthogonal analytical techniques.

For related substances and product-derived impurities such as those derived from post-translational modification or protein degradation (e.g., oxidation, deamidation, aggregation), the reference product and biosimilar product should be appropriately characterized and quantified to compare and evaluate the potential effects on safety, purity, and potency.

To obtain sufficient information on related substances and product-derived impurities, it is useful to conduct a comparative study under accelerated conditions and/or conditions enabling degradation (stress conditions). When product-related impurities of two products are found

in a similar level, an additional pharmacological/toxicological study to characterize potential biological effects of specific impurities may not be required. If a difference is identified from analysis result, effects of such a difference on clinical relevance of the product should be evaluated, including biological activity evaluation.

Process-related impurities (host cell-derived peptide, host cell DNA, culture medium residue, etc.) may show a quantitative and/or qualitative difference between a biosimilar product and reference product because the two products are produced using different manufacturing processes. Therefore, a comparative evaluation of the biosimilar product and the reference product may not be necessary. However, new impurities that are only identified from a biosimilar product should be subject to a risk-based evaluation and an additional study may be required to evaluate the effect(s) on safety. Process-related impurities should be maintained at a minimal level by using state-of-the-art manufacturing technology if possible.

5.1.5 Quantity

Generally, comparability of the concentration or the strength of the active substance between a biosimilar product and reference product is evaluated with consideration of the pharmaceutical form, administration regimen, and dosage of the two products. Comparison should be conducted using the same analytical method and be expressed as same unit. A description with appropriate justification should also be included to describe how quantity was calculated (e.g. the selection of extinction coefficient for UV absorption).

5.1.6 Stability and Degradation Profile

Equivalence of the stability profile, degradation profile and degradation rate are evaluated using an accelerated and/or stress stability study and forced degradation study (e.g., oxidation, light exposure, Freezing-thaw,

etc. depending on the attributes of the product). It should be considered that stability and degradation profiles can be affected by the pharmaceutical form, composition, volume, concentration and container-closure system. If a difference is found from the evaluation result, the cause should be investigated. Additional control conditions for manufacturing and storage to ensure the same quality and performance should be identified and applied.

A comparative study to evaluate equivalence for a long-term storage study is not required.

5.2. Manufacturing Process

The manufacturing process of a biosimilar product should be developed to enable production of the product with similar quality attributes as compared to a reference product based on the understanding of the quality profile of the reference product. A biosimilar product doesn't have to use the same host cell as a reference product but it is favorable to use a similar host cell type if feasible in order to reduce the possibility of a major difference in critical quality attributes (CQA) that may affect immunogenicity and clinical attributes such as impurity profile, oligosaccharide profile and biological activity. An appropriate pharmaceutical form, composition and container-closure system should be selected in consideration of the effects on the degradation and stability profiles.

An established manufacturing process must comply with the GMP regulations and demonstrate consistency and robustness.

If a change occurs to the manufacturing process during development, a comparability study must be conducted in accordance with the 'Guidelines on the Comparability Evaluation Following Changes to the Biotherapeutic Products Manufacturing Process' or 'ICH Q5E' and a comparability evaluation must be conducted using a sufficient number

of batches of before and after such a change. This is conducted in addition to the comparability evaluation with a reference product.

5.3. Specifications

Specifications are intended for quality control and are established independently for a biosimilar product and reference product because the two products have different manufacturing process and quality control settings. Nonetheless, the specifications should capture and control important known product quality attributes for the reference product. Further, effects of a potential interaction on the product safety, purity and activity, as well as the measurement range for a reference product should be considered (e.g., if oligosaccharide profile affects the biological activity).

Specifications should be established based on the data obtained from representative batches (e.g., non-clinical study; clinical study; study data on batches used to demonstrate consistency of the manufacturing process; stability study data; data generated during product development; comparability study data on quality, safety, and efficacy as compared to a reference product), and justifications for the analytical method and acceptance criteria should be provided. Generally, an acceptance criteria should not be significantly wider than the range of variability throughout the shelf-life of a reference product, unless justified

5.4. Stability Study

A long-term stability study, accelerated condition study, and various stress condition studies should be conducted on the drug substance and drug product of a biosimilar product according to ‘Public Notice of Stability Study Standards,’ ‘Stability Study Guideline on Biological Products’ and ICH Q1/Q5C.

The shelf-life and storage condition of a biosimilar product may be different from those of a reference product as these are determined by their own long term stability study data.

6. Non-clinical Evaluation

It is important to note that to design an appropriate nonclinical study program, a clear understanding of the reference product characteristics is required. Characteristics and complexity of a reference product affect the scope of a non-clinical study required to assess the comparability between the reference product and the biosimilar product. Thus, differences between biosimilar product and the reference product observed in physicochemical and biological assessment and mechanism of action in approved indications of the reference product should be considered when planning a non-clinical study.

For a non-clinical assessment, a stepwise approach is applied to evaluate the comparability of the biosimilar product and reference product. *In vitro* studies should be conducted first and a decision then made whether additional *in vivo* animal studies will be required.

In vitro and *in vivo* studies mentioned below should be considered case by case depending on the attributes of each product and the study should be adequately justified.

6.1 *In Vitro* Study

In vitro study is considered to be more specific and sensitive to detect differences between biosimilar product and reference product than *in vivo* studies in animals. In general, in order to evaluate the difference in pharmaco-toxicological activity between a biosimilar product and the reference product, (receptor) binding assay or cell-based assay (e.g. cell proliferation study) or other *in vitro* studies should be conducted. Data from such studies are generally related to the biological characteristics from quality assessment and are partially derived from quality evaluation data.

For an *in vitro* study, the following general principles apply:

- Series of binding and cell-based functional studies should be conducted to detect a difference and identify the cause of clinically relevant difference between a biosimilar product and reference product.
- Such studies should evaluate the overall range of clinically relevant pharmaco-toxicity of the reference product and its product family. The scope of an *in vitro* study that is considered to represent or predict the clinical environment based on the current scientific knowledge should be discussed.
- The studies should be comparative and designed to be sufficiently sensitive, specific and discriminatory to allow to detect clinically relevant differences in pharmaco-toxicological activity between biosimilar and reference product.
- The Studies should compare the concentration-activity/binding relationship of the biosimilar product and the reference product in a pharmacological target covering the concentration range where differences are accurately detectable.

6.2 Considerations for Determining Conduct of an *in Vivo* Study

Additional *in vivo* study can be considered based on the comprehensive evaluation of quality and non-clinical *in vitro* study and the extent to which there is residual uncertainty about the comparability between a biosimilar product and reference product. When a non-clinical *in vivo* study is to be waived, the following should be considered:

- If the quality biosimilar comparability exercise and the non-clinical *in vitro* studies are considered satisfactory and no issues are identified which would block a direct start of clinical evaluations, an additional *in vivo* animal study is not considered necessary.
- Before a clinical study, if any of the following between a biosimilar

product and reference product remains uncertain, an additional *in vivo* animal study (if there is a relevant animal model) can be considered, provided that such animal study is expected to present meaningful information

· Quantitative and/or qualitative differences between a biosimilar product and reference product that may be clinically relevant (e.g., quantitative and/or qualitative differences in post-translational glycosylation)

· Differences in composition/formulation that may be clinically relevant (e.g., use of an excipient that is not widely used for medicinal product)

6.3 In Vivo Study

Animal study should be designed to present sufficient information and to use a relevant species for the study drugs (e.g., animal model where reference product shows pharmacological and toxicological activity), and to employ the state-of-the art/orthogonal technology. If an animal model does not have the sensitivity to assess the difference between a reference product and the study drug or there is no appropriate *in vivo* animal model, *in vivo* study may be omitted. Generally, the followings are needed to be considered:

· Pharmacokinetic and/or pharmacodynamic study

If necessary, pharmacokinetics and/or pharmacodynamics of a biosimilar product and reference product should be quantitatively compared using a model enabling dose-response assessment, including estimated level of human exposure.

· At least one repeated-dose toxicity study with toxicokinetics in an appropriate animal model

When an *in vivo* study is required, the 3R principle should be applied.

A repeated-dose toxicity study can be conducted under a refined design provided that it is justified.

If applicable, the toxicokinetic study should include antibody reaction measurement and characterization analysis. Study period should be sufficient enough to allow the observation of toxic reactions and antibody reactions between a biosimilar product and reference product. Though there may be limitations in predicting immunogenicity in a human from animal model, it helps the interpretation of toxicokinetic data and evaluation of overall comparability study results.

Comparative repeated-dose toxicity study can assist in predicting the 'unexpected' toxicity in clinical studies for biosimilars. If such a study is conducted using the final pharmaceutical form for clinical use, potential toxicities of active substance, product- and process-related impurities can all be predicted.

· Local tolerance study

Local tolerance study is generally not required. However, if an excipient with no clinical experience is applied to given route of administration, local tolerance study may be required. If applicable, this evaluation can be conducted as a part of a repeat-dose toxicity study.

· Other toxicity studies

Once comparability between a biosimilar product and reference product is confirmed from quality assessment, no additional toxicity study such as pharmacological safety, reproductive toxicity, genetic toxicity or carcinogenicity study is required.

7. Clinical Evaluation

Pivotal clinical study should be conducted using a drug product with the final manufacturing process. If there is a difference in the manufacturing process between the drug used for the clinical study and the drug that sought for marketing authorization, it should be justified and additional data may be required.

Clinical studies to evaluate comparability with a reference product include pharmacokinetic study, pharmacodynamic study and efficacy study. If the comparability can be demonstrated based on a confirmatory pharmacokinetic-pharmacodynamic study, an efficacy study may be omitted.

7.1. Pharmacokinetic study

To develop a biosimilar product, a comparative pharmacokinetic study designed to confirm the similarity of pharmacokinetics, including primary pharmacokinetic endpoints between biosimilar product and the reference product must be conducted. Every intended route of administration of reference and biosimilar product should be included in pharmacokinetic study in principle and such study should be conducted within the recommended dosing regimen of the reference product.

Pharmacokinetic study should be comparative manner to detect the potential difference between selected reference product and to demonstrate the comparability of the biosimilar product. Single-dose pharmacokinetic study using a dose with maximal sensitivity is generally considered to be most effective in terms of detecting difference in sensitive and homogenous study group. For example, when an analytical method with sufficient accuracy and precision is available for serum drug concentration, the lowest of therapeutic dose range is appropriate for a drug showing absorption saturation.

Methodology of a clinical study for pharmacokinetics, e.g., single-dose study, steady state study, and repeated measurement of pharmacokinetic endpoints should be justified. The sample size of a study group should be appropriate so as to explain the pharmacokinetic variability in subjects. If an appropriate population pharmacokinetics or a pharmacokinetic-pharmacodynamic model is available from literature, modeling and simulation may be considered as an appropriate to design the study. Generally, the most effective one is a single-dose pharmacokinetic study using the most sensitive dose level in a study group that is sensitive and homogeneous to detect the difference. Additionally, a randomized, 2-period, 2-sequence, single-dose, cross-over, pharmacokinetic study can be conducted on a single dose level.

When using a cross-over study design, it needs to be demonstrated that attributes such as half-life or antibody formation do not affect the pharmacokinetic study result, because a long half-life or the high possibility of antibody formation against a drug may not be suitable for a cross-over study design. In a parallel study design, it is important to avoid imbalance between the study groups. If ethically reasonable, healthy volunteers can be considered as a sufficiently sensitive and homogeneous study group in a pharmacokinetic study to demonstrate comparability. If a pharmacokinetic study is not available in healthy volunteers, it can be conducted in patients. In this case, the most sensitive patient group should be selected to minimize inter-subject variability or time-dependent variability. If a single-dose study cannot be conducted in healthy volunteers due to safety or tolerability reasons, a pivotal pharmacokinetic study using multiple doses in patients can be conducted. A multi-dose pharmacokinetic study is less sensitive than a single-dose pharmacokinetic study to detect a difference in the peak plasma concentrations (Cmax), this will be acceptable with sound justification.

Conducting an additional pharmacokinetic study in an efficacy clinical study enables evaluation of the clinical effects of pharmacokinetic characteristics, including major target-mediated clearance, high immunogenicity, and high variability of pharmacokinetic endpoints which can be confirmed with pharmacokinetic profile evaluation in some patient groups or population PK evaluation. An anti-drug antibody should be measured in parallel with pharmacokinetic evaluation at appropriate sampling time points.

If the approved route of administration of a reference product is intravenous or subcutaneous, absorption and excretion can all be observed with subcutaneous administration. Therefore, if comparability in absorption and excretion has been demonstrated with the subcutaneous administration route, pharmacokinetic comparison of the intravenous administration may not be required.

The margin applied to demonstrate pharmacokinetic comparability between a biosimilar product and reference product should be predefined and reasonably established. The margin (80 to 125%) for a standard bioequivalence study can be used unless otherwise indicated. If the equivalence margin needs to be expanded, the proposed margin should be justified, including the impact on clinical efficacy and safety.

Endpoints of a pharmacokinetic study can be considered depending on the study design. For example, in a single-dose pharmacokinetic study, primary endpoints can be $AUC_{(0\text{-}inf)}$ and C_{max}, or only $AUC_{(0\text{-}inf)}$ for intravenous administration. Secondary endpoints such as t_{max}, volume of distribution and half-life should also be evaluated. For a repeat-dose pharmacokinetic study, primary endpoints can be partial AUC ($AUC_{(0\text{-}t)}$) and steady site dosing interval AUC ($_{AUC\tau}$) and secondary endpoints can be steady state C_{trough} and C_{max}.

In case that comparability on quality and non-clinical study is

demonstrated, a drug interaction study (with a drug that is highly likely to be co-administered) or a pharmacokinetic study in a specific population (e.g., children, the elderly, patients with renal or hepatic impairment) is generally not required.

A pharmacokinetic evaluation for peptide or protein products has a limitation due to the limitation of analytical methods. Thus, extra care should be taken for the analytical method used and its analytical ability. Such a method should be able to detect analytes (drug and metabolite) within a qualitative range with the appropriate specificity, sensitivity, precision and accuracy, and to detect a trend of change over time. The same single analytical method should be used to measure the concentration of the biosimilar product and the reference product in the blood.

The presence of measurable concentrations of endogenous protein may substantially affect the measurement of the concentration-time profile of the administered exogenous protein. In such cases, the applicant should describe and justify the approach to minimize the influence of the endogenous protein on the results. In the event that establishment of the pharmacokinetic equivalence is not feasible or not meaningful due to the nature of a substance, the route of administration, or high pharmacokinetic variability, clinical comparability should be supported by pharmacodynamics, immunogenicity, or additional clinical parameters.

7.2. Pharmacodynamic Study

In general, a pharmacodynamic study can be conducted in a combination of pharmacokinetics-pharmacodynamics, and the selection of pharmacodynamic endpoints should be based on the correlation with clinical effects. Since the concentration-reaction relation as well as pharmacokinetics of a biological product may vary by product to product, pharmacokinetic-pharmacodynamic study data are

useful for evaluating the comparability between two products. Particularly, when multiple dose levels are used, such a study can provide helpful information on the relation between doses, exposure in the body, and effect(s). In the event a pharmacokinetic study cannot be appropriately conducted, pharmacodynamic endpoints play an even more significant role.

A comparative pharmacodynamic study should be conducted with a dose level selected out of the steep range in a dose-response curve in a suitable study group to detect any potential difference between a biosimilar product and reference product. The pharmacodynamic effects can be compared and evaluated in health volunteers using well-established pharmacodynamic endpoints.

Examples of pharmacodynamic surrogate markers that are related to clinical efficacy include:

· Granulocyte colony-stimulating factor (G-CSF): absolute neutrophil count

· Alfa-interferon: early virus concentration reduction in chronic hepatitis C

· Insulin: euglycaemic clamp study

· Beta-interferon: magnetic resonance imaging (MRI)

7.3. Confirmatory Pharmacodynamic-Pharmacokinetic Study

In general, an efficacy study should be conducted to demonstrate clinical comparability of the biosimilar product. However, comparative pharmacodynamic-pharmacokinetic study may suffice in some cases.

In addition to analytical and non-clinical comparability evaluations, a comparative pharmacodynamic and/or pharmacokinetic study are appropriate to demonstrate similar clinical performance between the biosimilar productand reference product under the following conditions:

- Pharmacodynamic markers reflect the mechanism of action of the drug
- Pharmacodynamic markers are sensitive enough to detect any expected difference between the biosimilar and the reference product
- The pharmacodynamic marker assay has been well-validated
- The dose-exposure relation of the reference product, pharmacodynamic endpoints, and response-efficacy relation are well established

The applicant should consider the option of using pharmacodynamic properties between the reference product and the biosimilar product with multiple pharmacodynamic markers. Even when relevant pharmacodynamic markers are not available, sensitive pharmacodynamic endpoint may be assessed if such assessment may help reduce residual uncertainties about comparability.

In a confirmatory pharmacodynamic-pharmacokinetic study, sensitive and well known study group and dose level to allow for the observation of any potential differences between a biosimilar product and a reference product should be considered. Otherwise, the relevant dose range needs to be investigated to demonstrate that the study model is able to observe any difference. The margin to demonstrate comparability in pharmacokinetic and pharmacodynamic endpoints should be predefined and reasonably established as well.

7.4. Efficacy Study

A comparative efficacy study may not be necessary if sufficient evidence of similarity is obtained from other parts of comparability exercise such as quality, non-clinical, and confirmatory pharmacodynamic-pharmacokinetic studies. If an efficacy trial of the biosimilar product and the reference product is deemed necessary, then

it is expected to be an adequately powered, comparative clinical trial.

For a biosimilar product, a separate dose-finding study is not required because the administration regimen and dosage of a reference product will be used.

When conducting a comparative clinical study between a biosimilar product and reference product, the study should be performed via a randomized, parallel clinical study with the appropriate power. It is desirable to conduct a clinical study in a double-blinded manner, and if not feasible at least the evaluator should be blinded. In the event blinding is not used in any form, it should be demonstrated that the study result has no bias.

To extrapolate the comparative efficacy result of a biosimilar product to other indications of a reference product (including extrapolation to other dose levels), demonstration should be generally based on the equivalence design rather than a non-inferiority design. However, with reasonable scientific justification and with consideration of the safety, tolerability, dose range and dose- response relationship of the reference product, the non-inferiority design may be acceptable. The non-inferiority design can be applied only when exclusion of possibility of efficacy superiority is ensured, in which prior discussion with the MFDS is recommended.

Comparability margin of a clinical study should be predefined and reasonably established within the range where it is clinically considered that no clinical difference from a reference product would exist.

A potential difference between a biosimilar product and reference product should be studied in a sensitive and well-established model. For example, regarding hormones, patients with a hormone deficiency can be the optimal study group.

The purpose of a biosimilar product efficacy study is to detect any clinically significant difference compared to a reference product that already has its efficacy clinically established rather than to demonstrate the efficacy of the biosimilar product itself. Although there may be a specific guideline presenting clinical criteria for efficacy per disease regarding establishment of efficacy endpoints, a different approach (selection of endpoints, endpoint analysis time points) from those specified in such a guideline may need to be applied for evaluation of biosimilar comparability. When such a different approach is to be applied, it should be scientifically justified.

7.5. Safety

Pre-licensing comparative safety data should be obtained from a sufficient number of healthy volunteers and/or patients. Safety data can be captured from pharmacokinetic/pharmacodynamic and clinical efficacy studies. If clinical development is limited to a confirmatory pharmacokinetic/pharmacodynamic study, a risk assessment should be performed to determine whether additional safety data needs to be secured.

In the event impurities that are not present in a reference product are included in a biosimilar product, additional safety data may be provided or, if not necessary, scientific justification should be provided.

Safety data obtained from clinical studies is often about frequent adverse reactions that develop within a short period of time. Comparison with a reference product should include the type, frequency, and severity of the adverse reactions. As for all medicinal product, further safety monitoring is required for a biosimilar product at the post-marketing phase.

7.6. Immunogenicity

Even though the safety and efficacy shows comparable between a biosimilar product and reference product, there may be a difference in immunogenicity. The immune response of a biotherapeutic product can occur due to various causes, including characteristics of active substance, impurities, excipients, container-closure system, product stability, route of administration, administration regimen (dosage), patient- or disease- related factors.

Immunogenicity outcomes also vary from no clinical relevance to a serious level or life-threatening level. For example, the development of a neutralizing antibody may affect the pharmacodynamics and a binding antibody may affect the pharmacokinetics. Thus, formation of an anti-drug antibody can greatly affect the product safety.

An immunogenicity assessment should be conducted as a part of the clinical evaluation between the study drug and the reference product. However, immunogenicity study may be exempted if scientific justification is provided based on the physicochemical comparability between the biosimilar product and reference product, and a complete risk assessment data on the clinical outcome and unexpected immunogenicity of the reference product.

An immunogenicity study should comprehensively evaluate quality and clinical considerations as appropriate for the characteristics of each product. Risk assessment should include accumulated immunogenicity information, quality aspects (attributes, complexity of active substance, expression system, glycosylation status, product- and process-related impurity, aggregation), excipients, container-closure system, product stability, route of administration, administration regimen, and patient- and disease-related factors (immune condition, immunomodulator use status) of the reference product. Particularly, a difference due to product-related factors (purity by new expression system, new excipient) may greatly affect risk assessment outcomes.

Risk assessment can also be performed according to the characteristics of a product. For example, a product having an endogenous protein may have a high risk. In this case, extra care should be taken for the possibility of serious adverse reactions occurring with the endogenous protein and its unique biological function due to immune response. On the contrary, for a well characterized biotherapeutics (e.g., insulin, somatropin, filgrastim, teriparatide) for which sufficient literature and clinical information demonstrating no effect of immunogenicity on the safety and efficacy are available, an immunogenicity study may not be required if the biosimilar product and reference product are highly similar to each other and the risk assessment result shows a low risk level.

An anti-drug antibody study strategy needs to be specifically described, e.g., selection of antibody analysis method, evaluation, information on characteristics, appropriate blood sampling time points, volume of samples, sample treatment and storage, and selection of the statistical analysis method for data analysis. The method of anti-drug antibody analysis should be validated, a screening analysis with sufficient sensitivity should be used for antibody exploration, and neutralizing antibody analysis (if there is any neutralizing antibody) should be available to additionally identify antibodies. Interferences that may be incurred by circulating antigens should be considered along with the antibody analysis.

If anti-drug antibody development increases in a biosimilar product compared to a reference product, the potential effects on pharmacokinetics, safety, and efficacy should be evaluated. Extra care should also be taken for the possibility that an immune response has a serious effect on homeostasis in the body related to the endogenous protein itself and its unique biological function.

The duration of required to investigate immunogenicity should be of sufficient to allow for the observation of meaningful antibody

development and should be determined with consideration of the treatment course, and the period during which anti-drug antibody development is expected. For a chronically administered drug, the investigation period should be of sufficient duration to allow for the evaluation of anti-drug antibody development and persistence status, antibody titer change over time, antibody response property change status, and the possibility of clinical effect.

When applying for marketing authorization, immunogenicity data up to the end of a clinical study that evaluates the efficacy must be submitted, and if necessary, follow-up data must be additionally submitted. Data for the immunogenicity evaluation before marketing authorization are limited. Particularly at the investigation phase before marketing authorization, anti-drug antibody-related serious adverse reactions that are not generally found may rarely occur. Therefore, additional data regarding immunogenicity may be required as post-marketing surveillance. after marketing authorization.

7.7. Extrapolation of Indication

If comparability of efficacy and safety is demonstrated between a biosimilar product and reference product for a specific indication, extrapolation of other indications of the reference product for which the re-examination period has expired may be accepted provided that all of the following are satisfied:

- Attributes can be compared through quality and non-clinical in vitro studies using various analytical methods that are sensitive to the mechanism of action and/or relevant receptors
- A sensitive clinical study model that is able to detect a potential difference between a biosimilar product and reference product is used

Indication extrapolation of a biosimilar product should be considered

based on the totality of evidence regarding comparability with the reference product and potential uncertainties in addition to the above conditions. For example, if a reference product binds to the same receptor, no additional study for extrapolation of indications is required even though individual different target cells show different effects due to a difference in the signaling pathway. However, if indications of a reference product involve different active sites or different receptors of the target cell or if there is a difference in safety profile between indications, additional justification for indication extrapolation may be required. If necessary, independent demonstration for each proposed indication may be required. Also, for safety extrapolation, patient-related factors such as concomitant drugs, comorbidity(ies) and immune conditions and disease-related factors such as target cell-related response (e.g., tumor cell lysis) should be considered.

8. Terminology

Terminologies used throughout this guideline are defined as below and those not defined in this guideline are subject to the Regulations on Product Authorization and Review of Biological Product (Ministry of Food and Drug Safety Public Notice):

① 'Biosimilar product' refers to a biotherapeutic product for which the quality, non-clinical and clinical comparabilities have been demonstrated with a product that has already been granted marketing authorization or import marketing authorization.

② 'Pharmaceutical form' refers to a pharmaceutical class depending on the physical and morphological (presentation) attributed for a drug that has the same agent (e.g., injections) and administration route. For example, a liquid injection and a lyophilized injection have different pharmaceutical forms for the same drug solution.

③ 'Reference product' refers to a product for which full registration dossier required for marketing authorization have been submitted and the approval has been obtained. It is used as a comparator to demonstrate comparability in quality, non-clinical, and clinical studies of a biosimilar product.

④ 'Comparability' refers to scientific evaluation in a comparative manner to determine no detectable difference between a reference product and a biosimilar product in quality, non-clinical, and clinical studies.

⑤ 'Clinical equivalence' refers to comparability evaluated based on primary clinical endpoints, including no clinical relevance of any difference observed.

⑥ ‘Immunogenicity’ refers to the ability of a substance to trigger immune response, including formation of a specific antibody, T-cell response, allergy, and anaphylactic reaction.

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발 행 일 2022년 7월

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