가이드라인 관리번호
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식품의약품안전평가원
NATIONAL INSTITUTE OF FOOD AND DRUG SAFETY EVALUATION

이 가이드라인은 동등생물의약품의 비교동등성 평가에 대한 식품의약품안전처의 입장을 기술한 것으로, 대외적으로 법적 효력을 가지는 것이 아님

※ 가이드라인이란 대외적으로 특정한 사안 등에 대하여 식품의약품안전처의 입장을 기술한 것임(식품의약품안전처 지침등의 관리에 관한 규정(식약처 예규))

※ 본 가이드라인에 대한 의견이나 문의사항이 있을 경우 식품의약품안전처 식품의약품안전평가원 유전자재조합의약품과로 문의하시기 바랍니다.

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TABLE OF CONTENTS

1. INTRODUCTION 1

2. SCOPE 2

3. GENERAL CONSIDERATIONS 3

4. SELECTION OF REFERENCE PRODUCT 4

5. QUALITY EVALUATION 5

5.1. Manufacturing process 5

5.2. Comparability exercise for quality evaluation 5

5.2.1. Characterization study 7

5.3. Specification 10

5.4. Analytical methods 10

5.5. Stability studies 11

6. NON-CLINICAL EVALUATION 11

7. CLINICAL EVALUATION 14

7.1. Pharmacokinetic (PK) studies 14

7.2. Pharmacodynamic (PD) studies 17

7.3. Efficacy studies 18

7.4. Confirmatory PK/PD studies 19

7.5. Safety 20

7.6. Immunogenicity 20

7.7. Extrapolation of other clinical indications 22

8. DEFINITIONS 23

9. REFERENCES 23

GUIDELINES ON EVALUATION OF BIOSIMIALR PRODUCTS

1. INTRODUCTION

Since the authorization of recombinant human insulin for the treatment of diabetes, the use of recombinant protein products have been extended to include variety of disease such as anti-arthritic and anti-cancer drugs. Biological products cause relatively lower incidence of adverse events (AEs) and show a higher efficacy based on the targeted therapy as compared with chemically synthesized drugs. However, their cost has been excessive, thereby limiting their access to patients. From mid 2000s, it became possible to develop 'biosimilar products' whose quality, safety and efficacy have been demonstrated to be comparable to their original products due to the expiration of patents. It is expected to reduce the burden of medical expenses from public health perspectives.

Chemically synthesized drugs have been regulated under as generic drugs where their chemical structures can be manufactured equivalent to original products whose patent or data protection is no longer valid for protection.

However, biological products are generally protein compounds with a large molecular weight with very complex chemical structure. Therefore, their structures and activities are greatly subject to the types of cell lines and the manufacturing process. Even when the same manufacturers produce the same products, there would be no guarantee that the same products can be produced if there is a modification of manufacturing method. This explains why the 'comparability exercise' should be conducted to assess the quality, safety, and efficacy. Therefore, approach established for generic drugs is not suitable for

regulation of biosimilar products.

From these perspectives, the European Medicines Agency (EMA) legislated regulations and guidelines for biosimilar products in 2005. In addition, the World Health Organization (WHO) also published the international guidelines for the assessment of biosimilar products in 2009. This was followed by the introduction of local guidelines based on the WHO guideline in other overseas regulatory authorities. Regulatory guidelines for the approval of biosimilar products have also been prepared in Korea. With reference to the WHO guidelines as well as being harmonized with EMA guidelines, the first Korean biosimilar guideline was published in 2009. Thereafter there has been a consensus on the necessity to revise the current guideline based on the development of biosimilar products, the relevant clinical and regulatory experiences and the global regulatory harmonization. This has eventually led to revision to the current guideline.

2. SCOPE

The current guideline contains the principles and guidance in association with the assessment of dossiers for the approval of biosimilar products specified on the 'Regulations on Review and Authorization of Biological Products (MFDS notification)' (See Appendix 1) (Chapter II, Clause 1, Article 8).

In principle, biosimilar products can be applied to all types of biologics (hereinafter 'biological products'). But they are defined specifically as protein agents whose major constituents have been well characterized protein products. They should also be products whose comparability can be verified through a comparative exercise of the results from characterization studies as well as non-clinical or clinical studies.

In the current guideline, attempts are made to describe principles of the comparability exercise between a reference product and a biosimilar product in terms

of quality, non-clinical and clinical studies. But it does not apply to biological products for which the regulatory approval is attempted solely based on the bioequivalence.

3. GENERAL CONSIDERATIONS

Biosimilar products are defined as a biological product that is comparable to already marketed reference products in terms of quality, safety and efficacy. It would therefore be mandatory to demonstrate their comparability to a reference product through an extensive comparability exercise of the quality, non-clinical and clinical studies.

The development of a biosimilar product is based on a stepwise-approach where comprehensive analytical comparability are the basis for possible data reduction in the non-clinical and clinical development. Therefore, it is recommended that a comparability exercise should be sufficiently performed in terms of characterization including structure and physicochemical and biological properties. And the analytical method should employ the state-of-the-art technology.

So as to other types of biological products, biosimilar products should be evaluated based on the results obtained from their quality evaluation and non-clinical/clinical studies. It is expected that a smaller amount of dossiers are submitted to a regulatory authority as compared with new drugs. But this may be the case when their similarity is anticipated by the sufficient quality evaluation. Moreover, assessment criteria would vary depending on the characteristics of a reference product.

If differences between the biosimilar product and the reference product are found, their potential impacts on safety and efficacy should be evaluated and justified. Differences arising from safety-related improvements (*e.g.* improved purity or immunogenicity) maybe acceptable from perspectives of comparability. But this should be accompanied by the sufficient justification. Moreover, posology and route of administration of a biosimilar product should be same to a reference product. If there

are differences in product composition, it would be mandatory to justify such differences. It would not be appropriate to develop biosimilar products if there is a deliberate improvement in the efficacy.

Extrapolation of indications is a major advantage of biosimilar products. If comparability between the biosimilar product and the reference product has been fully demonstrated in terms of quality, safety and efficacy, extrapolation of all therapeutic indications of the reference product could be accepted.

4. SELECTION OF REFERENCE PRODUCT

A reference product is used for the development of biosimilar products, and it should also be served as a biological product which has already been authorized in Korea. However, *i.e.*, if it is not possible to purchase a reference product or if it is difficult to obtain a sufficient amount of it, it is allowed to purchase reference products from overseas countries. In this case, it would be mandatory to submit the data demonstrating the equivalence of a purchased foreign reference product that is marketed in Korea (*e.g. via* analytical comparability).

During the development of biosimilar products, it is required to use the same reference product throughout the comparability exercise. The dosage form, posology and route of administration of reference product and biosimilar product should be same. The final formulation and container of biosimilar products are not necessarily identical to those of a reference product but the impact on biosimilarity should be appropriately justified.

To be qualified as a reference product, the safety and efficacy data should be accumulated based on the sufficient clinical experience. Due to this fact, biosimilar products cannot be used as a reference product.

5. QUALITY EVALUATION

The quality of biosimilar products should be evaluated in two manners: the evaluation of the quality of biosimilar products themselves and comparability to a reference product. Both evaluation should meet the ‘Regulations on Review and Authorization of Biological Products. (MFDS Notification)’ and other relevant guidelines.

5.1. Manufacturing process

Biosimilar products are produced through their own manufacturing process for both drug substance and the drug products. The manufacturing process should demonstrate the quality assurance through in compliance with the Good Manufacturing Practice (GMP). Dossiers should include the quality control and the management and validation of manufacturing process.

In addition, if there are manufacturing changes of biosimilar products, it would be mandatory to perform the relevant comparability tests in compliance with the ‘Guideline on Comparability of Biological Products subject to Changes in Manufacturing Processes’ or ICH Q5E. This should also be accompanied by the assessment of comparability between and after changes during the manufacturing process.

5.2. Comparability exercise for quality evaluation

It is extremely important to compare the characteristics of quality between the biosimilar product and the reference product. Appropriate test and comparison should be made considering the possible effects on the safety and efficacy. All the data of analysis of the characteristics including the comparability to a reference product should be submitted for the regulatory approval. For the comparability exercise, it

would be mandatory to use representative batches for which the consistency of manufacturing process has been validated.

The purpose of comparability exercise is to verify the comparability in the quality, safety and efficacy. If there are any differences in the quality attributes, it would be required to provide the justification of the possible effects of such differences on the safety and efficacy. But if there are differences in the quality attributes associated with safety and efficacy, it is probable that the corresponding drugs might not be approved as biosimilar products because it is difficult to demonstrate the comparability to a reference product.

A comparability exercise should be performed in a manner that a direct head-to-head comparison of the biosimilar product and the reference product at the drug product level. In case that direct comparison in drug product level is not available, drug substance may need to be isolated from a drug product. But this should be accompanied by the submission of data demonstrating a lack of changes in the characteristics of isolated drug substance as well as the validation of the process of sample isolation. The final comparability should be determined considering non-clinical or clinical data as well as the quality.

The acceptable range of comparability should be set based on sufficient amount of data of reference product. The quantitative range should be based primarily on the measured quality attribute ranges of the reference product and should not be wider than the range of variability of the representative reference product batches, unless otherwise justified. Descriptive statistical approach may be needed to set criteria for acceptance. The manufacturing process of a reference product may be improved during its life cycle. As a result, there might be changes in the specific quality attributes. The range of changes in the quality seen between before and after such changes is representative of a reference products. Therefore, it can be used for a comparability exercise for the level of quality.

In demonstrating the comparability in the quality between the biosimilar product and the reference product, the state-of-the-art technology should be used to

detect its difference. This should also be accompanied by the application of validated assay methods. In addition, critical process parameters, validity of manufacturing process and the necessity of additional non-clinical or clinical data should be considered.

In submitting the data of comparability exercise, it would be mandatory to attach an outline of results from the comparability exercise. This should also be accompanied by the description of assay methods, acceptance criteria and test materials. It would also be mandatory to specify the trade name, formulations, composition, dosage, the source of a reference product, the number of batches, batch number and the date of manufacture (or expiry date).

5.2.1. Characterization study

To determine the comparability in the quality between the biosimilar product and the reference product, an extensive characterization studies should be performed using the state-of-the-art technology. Characterization studies should be performed for physicochemical, biological and immunological characteristics, purity (process- or product-related impurities), potency and content (Note: The characterization studies may be performed in accordance with the 'Guidelines on Specifications of Biotechnological/Biological Products' or ICH Q6B.). Characterization studies should be performed in direct comparison with a reference product. If there are differences found in characterization studies between the biosimilar product and the reference product, it would be mandatory to consider the significance of such differences. This may be followed by additional characterization studies.

- **Structural and physicochemical properties**

  The physicochemical characterization should include the determination of composition, physicochemical properties, and primary and higher order structures of the active ingredient of the biosimilar product. If the

appropriate higher order structural information cannot be obtained, a relevant biological activity assay may indicate a correct conformational structure. In such instances, the analytical procedures for determination of biological activity should have appropriate precision and accuracy. In addition, if process- and product-related impurities are generated or if degradation products are identified through stress and accelerated stability studies, such impurities and/or degradation products should also be evaluated.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process. Therefore, the biosimilar product may contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate and identify such forms.

- **Biological properties**

Protein constituents, used as biological products, show a very diverse feature of biological properties, and they reflect a mode of action and clinical effects. Therefore, a variety of functional assay methods should be used to evaluate individual biological activities for biological products with a complex biological activity.

Biological activity should be performed to measure the functions of proteins; it is also used to determine whether any changes in the quality of a product arose from active product-related materials or inactive impurities. Moreover, because it can be used to confirm the high-dimensional structure of proteins, it is efficient in adjusting results of physicochemical test. Accordingly, if there are attempts to use biological test methods with an appropriate level of accuracy and precision, it would become possible to justify difference in the function between the biosimilar product and the reference product. Based on the characteristics of biological test, however, there might be a high degree of variation.

Therefore, it is necessary to consider the possibility of not detecting such variability.

Biological activity test results should be expressed as an adjusted active unit when there are international or MFDS reference standards. Moreover, compendial method can be applicable, if exist.

- **Immunological properties**

It is required to identify the immunological characteristics of biosimilar products especially for monoclonal antibodies. If there are attempts to include the immunological properties in the characterization studies (antibodies or antibody-derived products), the specificity, affinity, binding activity, Fc functions and other components as compared with a reference product should be assessed.

- **Purity(Impurities)**

With the use of a variety of assay methods for both biosimilar products and reference products, quantitative and qualitative analyses to characterize impurity should be performed. It would be recommended to perform a comparative study in accelerating or degrading conditions (stress conditions), which is essential for sufficiently confirming the types of impurities. Moreover, the possibility of post-translational modification should also be considered.

Product-related impurities should be evaluated using the state-of-the-art technology in comparison with a reference product. If applicable, more than one assay technology should be applied to each impurity.

Biosimilar products are produced from their own manufacturing process. This leads to the speculation that there might be differences, whether they are qualitative and quantitative, in manufacturing process-related impurities between the biosimilar product and the reference product. A quantitative

comparison may not be justified for a comparability exercise. However, the relevant effects to safety and efficacy should be justified.

Impurities should be appropriately controlled based on specification or action limit during manufacturing process. Any new impurities should be evaluated for the potential effects on the safety and efficacy.

5.3. Specifications

Specifications for drug substance or drug product of the biosimilar product should be established for routine quality controls. Product-specific tests to be included in the specifications should be selected to assure the quality of the biosimilar product and should comply with the requirements as specified in the relevant regulations or guidelines.

Each specification should be established and justified based on data obtained from representative lots (such as data obtained from lots used in non-clinical and/or clinical studies, data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data, and data obtained from the comparability exercises [quality, safety and efficacy]). The analytical methods should be appropriately validated.

5.4. Analytical methods

In order to demonstrate that the quality of the biosimilar product is comparable to the reference product, extensive characterization studies should be applied using the state-of-the-art technology.

Given the complexity of the protein and its inherent heterogeneity, more than one analytical technology may be required for each quality attribute, in order to sufficiently characterize the physicochemical and biological properties.

Although validated analytical procedures are not necessarily required for characterization, analytical procedures should be scientifically sound and be able to produce reliable results. Therefore, procedures should be sensitive and specific enough to detect even the slight differences between the biosimilar product and the reference product.

It is required to validate the test methods used in routine quality control of drug substance and the drug product in compliance with the 'Regulation on Review and Authorization of Biological Products (MFDS Notification)' and 'Guideline on Evaluation of Quality, Safety, and Efficacy for Recombinant Protein Products.'

5.5. Stability studies

To determine the valid period of use and storage conditions of drug substance and the drug product of biosimilar products, a long-term stability study should be performed. Stability study should be performed in such a condition that actual containers and storage conditions can be generated in compliance with 'Guidelines on Stability Study of Biological Products' and ICH Q5C.

6. NON-CLINICAL EVALUATION

In order to establish the safety and efficacy of a biosimilar product, non-clinical and clinical evaluations are usually required, in addition to comprehensive quality evaluation.

In principle, non-clinical studies should be conducted with the representative batches of commercial scale. However, if it is not possible to perform non-clinical studies with such batches (toxicity studies requiring administration of high dose), minimal modifications may be made within the justifiable range so as to allow the

performance of non-clinical studies.

Since non-clinical studies of a biosimilar product are conducted as a part of the comparability exercise, they should be designed to comparative manners with reference products and biosimilar products. Such non-clinical studies may be conducted in accordance with existing guidelines (such as ICH S6 document). Design of non-clinical study requires a clear understanding of the product characteristics. Results from analytical comparability should be considered from the point-of-view of potential impact on efficacy and safety.

Throughout the non-clinical and clinical study, the same reference product should be used. In addition, it should also be identical to that has been used for the assessment of the quality.

As mentioned below, both *in vitro* and *in vivo* tests should be considered depending on the characteristics of each product on a case-by-case basis. This should also be accompanied by the sufficient validation of the study.

In vitro studies

In general, to determine the comparability in the biological and pharmacodynamic properties between the biosimilar product and the reference product, receptor binding or other cellular level findings should be evaluated (*e.g.* cell proliferation assay). These data are generally described based on the biological properties for the assessment of quality or may also be used as a reference for non-clinical studies.

In vivo studies

Animal studies should be designed to select species which are qualified for a test material and to obtain a sufficient amount of data (*e.g.* animal species with pharmacodynamic and toxicologic activity against a reference product). This should also be accompanied by the use of the

state-of-the-art technology. In general, the following matters should be considered for an *in vivo* study.

- Biological and pharmacodynamic activity relevant to the clinical application
  These data should usually be available from biological assays described in the quality evaluation and these studies can be made in the non-clinical part of the dossier, if feasible.
- Non-clinical toxicity as determined in at least one repeat-dose toxicity study in a relevant species and including toxicokinetic study

  If possible, these measurements should include determination and characterization of anti-drug antibody responses. The duration of the studies should be sufficiently long to allow detection of potential differences in toxicity and antibody responses between the biosimilar product and the reference product. Although the value of animal models for immunogenicity in humans is considered low, data from immunogenicity studies in animal models are useful in interpretation of toxicokinetic data and assessment of overall comparability exercises.

  In addition, the comparative repeat dose toxicity study is useful in predicting any “unexpected” toxicity during clinical study of the biosimilar product. Repeat-dose toxicity study with representative batches of commercial scale will, in principle, allow for detection of potential toxicity associated with the active ingredient and product- and process-related impurities.
- Local tolerance study

  Local tolerance study may be performed depending on the administration route of the biosimilar product. If this study is included in repeat dosse toxicity, additional study will not be necessary.
- Other toxicological studies

  For comparability exercise, other toxicity studies such as safety

pharmacology, reproductive toxicity, genotoxicity and carcinogenicity should not be necessary. According to what is known, however, additional toxicity studies may also be required depending on the toxicological characteristics (*e.g.* adverse effects arising from a reference product against reproductive functions) or results of repeat-dose toxicity study.

7. CLINICAL EVALUATION

Pivotal clinical data should be generated using the product derived from the final manufacturing process. If the manufacturing process of the drug products used in clinical studies is different from the final manufacturing process for which marketing authorization is sought, such differences should be justified and additional data may be required.

The clinical comparability exercises include pharmacokinetic, pharmacodynamic, and efficacy studies. If the comparability can be demonstrated by confirmatory pharmacokinetic/pharmacodynamic data, an efficacy study may be omitted.

7.1. Pharmacokinetic (PK) studies

For the development of biosimilar products, comparative pharmacokinetic (PK) studies should be performed. The comparative PK study is designed to demonstrated similar PK profile of the biosimilar product and the reference product in terms of key PK parameters. In principle, PK studies should generally be performed for all proposed routes of administration and dose should be selected within the recommended therapeutic dose range of the reference product.

PK studies should be comparative in nature to demonstrate the comparability of the biosimilar product and should be designed to enable detection of potential differences between the biosimilar product and the reference product. In general, this

is achieved effectively by performing single-dose PK studies in a sensitive and homogenous study population and by using dose sensitivity enough to detect differences to reach its maximum value. For example, for a drug product with saturable absorption (saturation kinetics), the lowest therapeutic dose would be most appropriate, provided that the employed assay can measure the resultant drug plasma levels with sufficient accuracy and precision.

The choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population should be justified. The cross-over design may not be appropriate for biological products with a long half-life or for proteins immunogenic which formation of anti-product antibodies is likely. Therefore, if the cross-over design is adopted, it is necessary to demonstrate that the half-life, antibody formation, and other characteristics do not affect the PK profiles. If the parallel design is selected, careful attention should be paid to avoid potential imbalances between groups. In PK studies for demonstrating comparability, healthy volunteers could be considered as a sensitive and homogenous population for study if considered ethical. If it is not possible to conduct PK studies in healthy volunteers, it can be done with patient groups. When a patient group is selected as a subject in a PK study, the most sensitive model/patient group that is able to minimize any major inter-individual or time-dependent variation. In clinical efficacy studies, PK studies could be performed additionally to evaluate the influence of major target-mediated clearance, high immunogenicity, high variability of PK parameters and other PK properties on clinical aspects. This can be validated through a study of PK profile in a subgroup of patient or population PK study. At the time of specimen collection, the level of anti-drug antibody is measured in conjunction with pharmacokinetic studies.

If the approved route of administration of the reference product is either an intravenous or subcutaneous route, absorption and elimination could be observed. Once the comparability in respect to absorption and elimination of the subcutaneous route is demonstrated, it may not be necessary to conduct the comparability exercise for the intravenous route.

To demonstrate the pharmacokinetic comparability between the biosimilar product and the reference product, acceptance range should be defined and then justified. Unless otherwise noted, acceptance range of 80-125% may be used as they have been used for standard bioequivalence studies. If there are attempts to broaden the margin of comparability, the justification should be made considering their potential effects on the efficacy and safety.

Pharmacokinetic endpoints may be considered depending on the study design. For example, in a single-dose PK study, the primary endpoint parameters are the $AUC_{(0\text{-}inf)}$ and C_{max}. For intravenous administration, only $AUC_{(0\text{-}inf)}$ is the primary endpoint parameter. Secondary endpoint parameters such as t_{max}, volume of distribution, and half-life, should be estimated. In a repeat-dose PK study, the primary endpoint parameters should be the truncated AUC after the first administration until the second administration AUC($AUC_{(0\text{-}t)}$) and AUC over a dose interval at steady state AUC(AUC_{τ}). Secondary endpoint parameters are C_{trough} and C_{max} at steady state.

If there is evidence of comparability from the quality and non-clinical studies, other PK studies, such as interaction studies (with drugs highly likely to be used concomitantly) or studies in special populations (*e.g.*, children, the elderly and patients with renal or hepatic insufficiency) are usually not required for a biosimilar product.

Due to limitations of analytical techniques, a pharmacokinetic study for peptide or protein compounds has been performed in a limited scope. Therefore, special attention should be paid to the methods and performance of assay. Moreover, test materials (drugs or metabolites) should be detected within the range of quantification based on the optimal specificity, sensitivity, precision and accuracy. Furthermore, time-dependent changes should also be detected.

If the active ingredient of a biosimilar product is an endogenous protein and the concentration of the endogenous protein is measurable, the concentration-time profile of the administered exogenous protein may be substantially affected. In these cases, it would be mandatory to describe valid methods for the purpose of minimizing the effects of exogenous protein.

7.2. Pharmacodynamic (PD) studies

In general, the pharmacodynamic (PD) study can be performed in combination with the pharmacokinetic study. Pharmacodynamic parameters should be served in association with clinical effects. Biological products may show a variability in the dose-response relationship as well as PK parameters between the products. Therefore, both pharmacodynamic and pharmacokinetic data might be useful in assessing the comparabiltiy between the biosimilar product and the reference product. In particular, these studies would provide useful information about the dose-response relationship and *in vivo* exposure-response relationship if performed at varying doses.

In the comparative PD studies, PD effects should be investigated in a suitable patient population using one dose within the steep part of the dose-response curve in order to detect potential differences between the biosimilar product and the reference product in most sensitive manner. If it is possible to use PD markers well established in healthy volunteers, the comparative evaluation of PD effects may be conducted using healthy volunteers.

Usually, the clinical comparability of the biosimilar product and the reference product should be demonstrated in the efficacy studies. However, if similar PD profiles are obtained, the equivalence in efficacy trials can be expected.

There are pharmacodynamic surrogate markers that are associated with the clinical efficacy as shown below:

- **Granulocyte-colony stimulating factor (G-CSF):** Absolute neutrophil counts
- **α-interferon:** Initially decreased viral concentrations in patients with chronic hepatitis C
- **Insulin:** Euglycaemic clamp test
- **β-interferon:** Magnetic resonance imaging (MRI) scans of the lesions

7.3. Efficacy studies

Posology and route of administration of a reference product should be applied to those of a biosimilar product. Therefore, it is unnecessary to conduct dose-finding study for biosimilar products.

To adopt posology and route of administration and to accept extrapolation of indications of reference product, it is recommended to design the efficacy trial with equivalence study rather than non-inferiority study. Equivalence design is more desirable than non-inferiority design. Non-inferiority test could only be considered if provided with valid scientific evidence and when safety and tolerance, dosage range, dose-response relationship of the reference product and others are justifiable. Non-inferiority design could be applied when the likelihood of superiority in efficacy is excluded with certainty. To proceed further with non-inferiority design of a test, it is recommended to have consultation with MFDS beforehand.

Comparability margin should be pre-defined and appropriately justified. The margin should be selected within the range that would not show clinical differences from the reference product.

Similar efficacy of the biosimilar product and the reference product should be demonstrated in an adequately powered, randomized, and parallel group clinical trial (equivalence trials). Such clinical studies should preferably be double-blind or at a minimum observer-blind. In the absence of any blinding, careful justification is required to prove that trial results are free from significant bias.

It would be mandatory to examine potential differences between the biosimilar product and the reference product using a sensitive, well-established experimental model. For the case of hormone products, patients with hormone deficiency could be served as the most sensitive group

Efficacy study of biosimilar products does not aim to demonstrate clinical efficacy *per se* but to detect any clinically significant differences between the biosimilar product and the reference product. Product-specific guidelines, which

recommend clinical designs for the demonstration of clinical efficacy by product type, could guide the choice of clinical endpoints. However, in certain circumstances, different methods (the choice of clinical endpoints, time points of analysis of endpoints) for biosimilar comparability exercises, which deviate from the scope of this guideline, may be applied. If such changes to endpoints are applied, the applicant should justify that the changes in endpoints is scientifically valid.

7.4. Confirmatory PK/PD studies

In general, for the demonstration of the efficacy of biosimilar products, clinical trials should be conducted. In the following cases, however, a comparative PK/PD may be alternatively performed.

- A reference product with well-established pharmacodynamic and pharmacokinetic characteristics
- More than one PD surrogate marker that is indicative of the efficacy
- A reference product with well-established dose-exposure relationship, PD parameters and response-efficacy relationship

Even in a confirmatory PK/PD study, it is necessary to consider the study group and dose which are both sensitive and reliable in identifying potential differences between the biosimilar product and the reference product. Otherwise, it would be mandatory to evaluate the range of dose for the purpose of demonstrating whether it is possible to detect differences in experimental models. Moreover, it would also be mandatory to define and then to validate acceptance range for the comparability in major pharmacodynamic and pharmacokinetic parameters.

7.5. Safety

To determine the safety of biosimilar products, clinical safety data should be obtained from a sufficient number of patients before authorization.
Safety data is obtained from clinical trials, and it is mainly based on adverse events (AEs) that occur frequently for short periods of time. A comparison of the safety profile between the biosimilar product and the reference product should be made based on the types, incidence and severity of AEs. It is generally acceptable to submit the safety data of biosimilar product from clinical trials when licensing, nevertheless careful monitoring should be required from post-marketing surveillance (PMS) study.

7.6. Immunogenicity

Although there is a comparability in the safety and efficacy between the biosimilar product and the reference product, there is a possibility that there might be a difference in the immunogenicity between the two products. Immune reactions against biological products may occur due to various causes such as the characteristics of drug substance, impurities, excipients, stability of product, route of administration, posology (dose) and patient- or disease-related factors. Immunogenic outcomes also display a broad spectrum of outcomes from no clinical relevance to life-threatening cases. For instance, neutralized antibodies and binding ones may affect pharmacokinetic and pharmacodynamic characteristics of the product, respectively. This suggests that anti-drug antibodies may considerably affect the safety of products.
Therefore, it is required to make a comparison of the frequency and pattern of antibody formation and clinical effects arising from the immune reactions between the biosimilar product and the reference product before authorization.

Generally, human immunogenicity cannot be predicted from animal experiments. It should therefore be evaluated from human subjects from clinical styudy.

The antibody-testing strategy, including the selection, assessment, and characterization of assays, identification of appropriate sampling time points, sample volumes and sample preparation/storage as well as selection of statistical methods for data analysis should be described in detail. Antibody assays need to be validated for their intended purpose. A screening assay with 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 there is an increase in the formation of antibodies against the biosimilar product as compared with the reference product, it would be mandatory to assess its potential effects on the pharmacokinetics, safety and efficacy. In addition, special attention should be paid to the possibility that immune responses might have a serious effect on endogenous proteins themselves and homeostasis associated with their unique biological functions.

The required observation period for immunogenicity testing should be specified in the manner of allowing observation of clinically significant antibody formation. The period usually depends on the intended duration of therapy and the expected time of antibody development. In the case of chronic administration, investigation should be conducted for the sufficient period to evaluate antibody incidence, their persistence, development of antibody titers over time, potential changes in the character of the antibody response and the possible clinical implications.

When application for product authorization is submitted, the immunogenicity data obtained till the completion of efficacy studies should be provided and, if necessary, follow-up data should be additionally submitted. Since pre-authorization immunogenicity data are often limited, further characterization of the immunogenicity profile may be necessary for post-marketing, particularly, if rare antibody-related serious adverse events may occur that are not likely to be detected in the pre-marketing phase.

7.7. Extrapolation to other therapeutic indications

If similar quality, efficacy and safety of the biosimilar product and the reference product have been demonstrated for a particular therapeutic indication, extrapolation of these data to other indications of the reference product for which post-marketing surveillance was completed in korean market could be possible if all of the following conditions are fulfilled:

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

Other than the above conditions for extrapolation of therapeutic indications for biosimilar products, extrapolation should be considered in the light of the totality of evidence, which is the overall evidence of comparability data and potential uncertainties. For example, if the biosimilar product binds to the same receptor that reference product dose, it does not require additional studies for extrapolation even if they elicit different responses at different target cells due to differences in signaling pathway. However, if each therapeutic indication of the reference product interacts with different active site/receptor(s) of a target cell or if there are any significant differences in safety profile, additional data may be required for extrapolation of indications. In certain cases, justification for each application of therapeutic indications may be required. In addition, for the extrapolation of the safety, it is necessary to consider concomitant drugs, comorbidities, patient-related factors, such as immune status, and disease-related factors, such as target cell-related response (*e.g.* lysis of tumor cells).

8. DEFINITIONS

Glossaries used in the current guideline are defined as shown below. Any undefined matters are subject to ‘Regulation on Review and Authorization of Biological Products (MFDS Notification).’

① A "biosimilar product" is a biological product that is comparable to already marketed reference products in terms of quality, safety and efficacy.

② A "reference product" is a drug product already authorized by MFDS on the basis of full regulatory submissions. The reference product is used in demonstrating the comparability of a biosimilar product through quality, non-clinical and clinical studies

③ "Comparability" is scientific comparison of a biosimilar product with a reference product with the goal to establish that no detectable difference exists in terms of quality, safety and efficacy.

④ "Clinical equivalence" is the state of being equal or virtually identical in major clinical endpoints of interest. In addition, any observed differences are of no clinical relevance.

⑤ "Immunogenicity" is the ability of a substance to trigger an immune response or reaction, such as development of specific antibodies, T-cell response, allergic or anaphylactic reaction.

9. REFERENCES

1) Regulations on Review & Authorization of Biological Products (MFDS Notification)
2) Regulations on Validation of Drug Products (MFDS Notification)
3) Guidelines on Safety Studies of Biological Products (MFDS, 2013)
4) Guidelines on Comparability of Biological Products subject to Changes in

Manufacturing Processes (MFDS, 2009)

5) Guideline on Evaluation of Quality, Safety, and Efficacy for Recombinant Protein Products (MFDS, 2014)
6) Guidelines on Validation of Analytical Procedures for Drug Products (MFDS, 2004)
7) Handbook for Interpretation and Application of the Guidelines on Validation of Analytical Procedures for Drug Products (MFDS, 2012)
8) Guideline on similar biological medicinal products (EMA/CHMP/437/04 Rev. 1, 2014)
9) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) (EMA/CHMP/BWP/247713/2012, 2014)
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12) Guideline on quality of biotechnological products: stability testing of biotechnological/biological Products (ICH Q5C, 1995)
13) Comparability of biotechnological/biological products subject to changes in their manufacturing process (ICH Q5E, 2004)
14) Guideline on specifications: test procedures and acceptance criteria for biotechnological/biological products (ICH Q6B, 1999)
15) Guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6, 2011)
16) Guideline on statistical principles for clinical trials (ICH E9, 1998)
17) Guideline on choice of control group and related issues in clinical trials (ICH E10, 2000)
18) Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (WHO Replacement of Annex 3 of WHO Technical Report Series, No. 814, 2013)

제·개정 이력

동등생물의약품 평가 가이드라인 영문판

제 · 개정번호	승인일자	주요내용
B1-2010-3-005	2010. 9	동등생물의약품 평가 시 품질, 비임상, 임상 분야의 고려 사항
B1-2015-3-008	2015. 10	동등생물의약품의 대조약 선정, 비교동등성 허용기준 설정 및 임상시험디자인 등 내용 추가 및 수정

동등생물의약품 평가 가이드라인 영문판

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발 행 인	바이오생약심사부장(직무대리) 홍성화
발행위원	박윤주, 정지원, 남경탁, 송치원, 백대현, 송 현, 김영은, 김진아, 박혜원, 김광제, 이정윤, 서수경, 엄준호, 김병철
발 행 처	식품의약품안전처 식품의약품안전평가원 바이오생약심사부 유전자재조합의약품과

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