

広島県 収受	
第	号
- 6.3.12	
処理期限	月 日
分類記号	保存年限

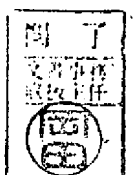
事務連絡
令和6年3月12日

各都道府県衛生主管部（局）薬務主管課 御中

厚生労働省医薬局医薬品審査管理課

バイオ後続品の品質・安全性・有効性確保のための指針
の英訳版について

標記について、「バイオ後続品の品質・安全性・有効性確保のための指針」（令和2年2月4日付け薬生薬審発第0204第1号厚生労働省医薬・生活衛生局医薬品審査管理課長通知）において、バイオ後続品の品質等の確保に関する取扱いを示してきたところ、当該指針の英訳版を別添のとおり作成したので、御了知の上、活用が図られるよう貴管内関係業者に対し周知方御配慮願います。



PSEHD/PED Notification No.0204-1
February 4, 2020

To: Prefectural Health Department (Bureau)

From: Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

(Official seal omitted)

Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars

Regarding the assurance of the quality of biosimilar products, the handling has already been shown in *Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics* (PFSB/ELD Notification No. 0304007, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 4, 2009). This guideline has been compiled as attached. We ask you to inform manufacturers and sellers placed under your administration.

This guideline is a summary of the basic concepts based on scientific knowledge at the present time. Therefore, it does not necessarily require adherence to the strategy shown here as long as the chosen method has a rational basis that reflects scientific progress.

Guideline for Ensuring Quality, Safety, and Efficacy of Biosimilars

Table of Contents

1. Introduction
2. Scope
3. General Principles for the Development of Biosimilars
 - 3.1 Evaluation of comparability with original biopharmaceuticals
 - 3.2 Original biopharmaceutical
 - 3.3 Points to consider when developing manufacturing process and establishing a quality control strategy for biosimilars
 - (i) Host cells
 - (ii) Formulation development
 - (iii) Specifications
 - (iv) Stability (storage condition/shelf life)
4. Comparative Studies of Quality Attributes
 - 4.1 Comparison of structure/physicochemical properties
 - 4.2 Comparison of biological properties
 - 4.3 Comparison of impurities
 - 4.4 Comparison of quality attributes related to immunogenicity
5. Nonclinical Studies
 - 5.1 Nonclinical pharmacological studies
 - 5.2 Nonclinical safety studies
6. Clinical Trials
 - 6.1 Clinical pharmacokinetic (PK) and pharmacodynamic (PD) studies
 - 6.2 Comparison of clinical efficacy
 - 6.3 Confirmation of clinical safety
 - 6.4 Grant of indications
7. Post-Marketing Risk Management

1. Introduction

A biosimilar is a product comparable with regard to quality, safety, and efficacy to a biotechnology-derived product already approved in Japan as a pharmaceutical with new active ingredients (hereinafter “original biopharmaceutical”), which is developed by a different marketing authorization holder. A biosimilar can generally be developed on the basis of data that demonstrate comparability with the original biopharmaceutical with respect to quality, safety, efficacy, or other relevant data. Biosimilar was previously referred to as follow-on biologic in Japan.

In this guideline, “comparability” means that the quality attributes of a biosimilar are highly similar to those of the original biopharmaceutical and it can be scientifically justified that any differences in the quality attributes have no adverse impact on clinical safety or efficacy based on the results of nonclinical studies and clinical trials.

Biopharmaceuticals (including biosimilars) have inherent degree of structural heterogeneity because biosynthetic processes by living organisms are used in their manufacturing process. The active ingredients of biopharmaceuticals (including biosimilars) have complex structures and heterogeneity associated with post-translational modification. Therefore, it is difficult to demonstrate the identity of the active ingredients of the original biopharmaceutical and the biosimilar. In addition to the possibility that the heterogeneity of active ingredients may affect the pharmacokinetics and pharmacological effects, there are issues such as immunogenicity whose relationship to quality attributes has not been fully elucidated, leading to the feature that clinical evaluation is required. Therefore, the approach similar to the generic drug of the chemical entities having the same structure as the original drug cannot be applied to the development of biosimilars.

This guideline addresses the points to be considered during the development of biosimilars and clarifies the data to be submitted in applications for the approval of those products. An application of a biosimilar will be able to be submitted after the expiry of the re-examination period of the original biopharmaceutical. Therefore, by the time the development of a biosimilar is commenced by a manufacturer after the development and approval of the original biopharmaceutical, a certain amount of manufacturing, marketing, and clinical experience will have been accumulated. Since manufacturing processes, manufacturing techniques, or evaluation techniques related to the original biopharmaceutical may be advanced and improved quickly in this intervening time, data accumulated during this period and state-of-the-art scientific technologies should be fully incorporated into the development of the biosimilar. In addition, the latest available safety data should be fully taken into account.

2. Scope

This guideline covers recombinant proteins (including unmodified simple protein and glycoprotein), recombinant peptides, their derivatives, and products of which they are components (e.g., polyethylene glycol-conjugated proteins and antibody-drug conjugates). These proteins and peptides are produced from recombinant expression systems using microorganisms or animal cells and can be highly purified and well characterized using an appropriate set of analytical procedures.

The principles described in this guideline might also apply to other product types, such as non-recombinant protein produced by cell culture technology or proteins and peptides isolated from tissues or body fluids, if they are highly purified and well-characterized. Applicants are encouraged to consult with the regulatory authority to determine the applicability of the guideline on a product-by-product basis.

This guideline does not cover antibiotics, synthetic peptides, polysaccharides, vitamins, cell metabolites, nucleic acid products, allergen extracts, conventional vaccines based on antigens such as attenuated or inactivated pathogenic microorganisms their extracts, cells, and whole blood and cellular blood components (blood cell components).

3. General Principles for the Development of Biosimilars

It will be difficult for sponsors to obtain data about the manufacturing process for an original biopharmaceutical developed by another company. Therefore, it is necessary to independently develop and establish a manufacturing process that ensures high consistency and robustness in the development of biosimilars. The comparability of the biosimilar to the original biopharmaceutical should be evaluated taking into full consideration such differences in the manufacturing processes for each product.

Since the biosimilars will be developed after a certain period of time from the approval of the original biopharmaceutical, it is encouraged that the development of a manufacturing process for the biosimilar actively incorporates the safety measures based on the most up-to-date information, if applicable, as they have no adverse impact on efficacy.

3.1 Evaluation of comparability with original biopharmaceuticals

In the development of biosimilars, the sponsors should demonstrate the comparability of the proposed product with the original biopharmaceutical through quality, nonclinical and clinical comparisons. The extent and necessity of nonclinical studies and clinical trials data required for the demonstration of comparability will differ depending on the extent to which similarity of the biosimilar with the original biopharmaceutical has been demonstrated by scientific and rational evaluation of the quality attributes in a comparative analytical study (refer to Chapters 4, 5, and 6).

Nonclinical studies should be conducted after thorough characterization of the biosimilars. Also, it is necessary to design nonclinical studies rationally and appropriately with reference to the results of the characterization of the biosimilar itself and of the comparison with the quality attributes of the original biopharmaceutical.

When conducting clinical trials, the quality attributes of the biosimilar, as well as the results of comparability evaluation of the original biopharmaceutical and the biosimilar via comparative analytical and nonclinical studies should be considered. In addition, it is necessary to design a clinical trial that is necessary and appropriate to evaluate the comparability of the biosimilar with the original biopharmaceuticals in terms of clinical efficacy and safety, taking into account comprehensive information that includes the literatures on the original biopharmaceutical.

3.2 Original biopharmaceutical

In principle, the original biopharmaceutical used as a reference product for quality, nonclinical studies, and clinical trials must be a biopharmaceutical approved in Japan. When test results using a drug product approved overseas (hereinafter referred to as an “overseas approved product”) as the reference product are used to the approval applications for biosimilars in Japan, it is necessary to justify that the domestically approved product and the overseas approved product can be regarded as identical based on the results of comparative analytical studies of both.

3.3 Points to consider when developing manufacturing process and establishing a quality control strategy for biosimilars

In the development of a biosimilar, similar to the development of biopharmaceuticals containing new active ingredients, development of the manufacturing process, quality characterization, and drug formulation design should be carried out with reference to the related guidelines such as ICH Q5, Q6B, Q7, and Q8 to Q11. Moreover, an appropriate control strategy should be established for the biosimilar to enable consistent production of the drug product that meets the desired product quality profile throughout the product life cycle. When developing biosimilars, it is expected that the numbers of clinical trials conducted, and the number of lots manufactured before approval applications are smaller compared to the case for biopharmaceuticals containing new active ingredients. However, in principle, since the quality target

product profiles (QTPPs) of the biosimilar are considered the same as the original biopharmaceutical, the lot analysis results of the original biopharmaceutical are important as information when identifying the critical quality attribute (CQA) and setting the acceptable ranges.

From the perspective of ensuring consistent quality, it is important to establish in-house reference materials as soon as possible. When changing manufacturing process, evaluations of the pre- and post-change products should be performed in accordance with the ICH Q5E guideline. In addition, it is important to confirm the adequacy of the control strategy established at the development stage on an ongoing basis even post-approval phase.

(i) Host cells

It is known that host cells used for producing a recombinant protein affect the post-translational modification such as glycosylation and the profile of host cell proteins. Where the host cells of the original biopharmaceutical have been disclosed, it is desirable for the cell bank system to be established using the same host cells. However, different types of host cells (cells of different origin including the originating species) may be used for safety and other reasons. When conducting development using different types of host cells, it should be justified. Moreover, in the case of the different types of host cells, it is required to conduct thorough examinations regarding quality and safety than in the case of the same host cells by focusing on the profile of process-related impurities, including host cell impurities, and then submit the data.

Even if glycoprotein products are produced using the same host cells, the heterogeneity of glycosylation in each product is known to be significantly different because of such various factors as the insertion site of the expression construct or culture conditions. When establishing a cell line used for the production of a biosimilar and developing the manufacturing process, the similarity of the glycosylation structure of the biosimilar with that of the original biopharmaceutical should be noted. Furthermore, the effects of different glycosylation on safety and efficacy should be evaluated through nonclinical studies and clinical trials.

(ii) Formulation development

The administration route of a biosimilar should be the same as those of the original biopharmaceutical. However, a different dosage form than the original biopharmaceutical may be acceptable in a certain justified case. For example, it may be acceptable that the biosimilar uses a liquid form, while the original biopharmaceutical uses a freeze-dried form. As long as there are no adverse effects on efficacy and safety, it is not necessary for the formulation of the biosimilar to be the same as that of the original biopharmaceutical. For example, a formulation using safer excipients is acceptable. It is desirable for the concentration of the active ingredient in the formulation of a biosimilar to be the same as that of the original biopharmaceutical. However, if it is possible to administer the same amount of the active ingredient using the dosage and dose regimen of the original biopharmaceutical, the same active ingredient concentration is not essential.

(iii) Specifications

Among the quality attributes of a biosimilar, specifications should be established regarding test items required for the drug substance and drug product (e.g., items required for identification of the active ingredients, items that are likely to change during storage, and items that are difficult to evaluate during the manufacturing process), in addition to the control by the relevant process parameters in the manufacturing process. Since it is usually difficult to obtain information on the specifications of the original biopharmaceutical, it is not essential to be the same as the specifications of the original biopharmaceutical.

(iv) Stability (storage condition/shelf life)

As with the original biopharmaceuticals, the sponsors of biosimilars are required to conduct long-term

stability studies under real-time and real-condition. The proposed shelf life should be justified according to the result of long-term stability study. A minimum of six months' stability data should be submitted at the time of approval applications. Since identical storage conditions and shelf life to the original biopharmaceuticals are not a prerequisite for biosimilars, a comparability exercise versus the original biopharmaceuticals will not necessarily be required in this regard. However, if the shelf life of the biosimilar is extremely shorter than that of the original biopharmaceutical, it may cause confusion in clinical practice. In that case, it is advisable to discuss with the regulatory authorities separately. On the other hand, it is also acceptable to set the longer shelf life for a biosimilar than for the original biopharmaceutical based on data obtained under actual storage conditions. It is also suggested that stability testing should be conducted under accelerated and stress conditions in order to obtain useful data for evaluating the quality attributes of both the drug substance and the drug product for biosimilars.

4. Comparative Studies of Quality Attributes

Comparative studies of quality attributes between a biosimilar and the original biopharmaceutical are an important step in verifying quality similarity and designing nonclinical studies and clinical trials. The quality attributes of biosimilars manufactured with well-established consistent and robust manufacturing processes should be thoroughly characterized using state-of-the-art analytical technologies. At the same time, comparative studies of quality attributes between a biosimilar and the original biopharmaceutical should be conducted regarding necessary and evaluable items. In this case, it is important to use an analytical method with sufficient performance to detect the difference in quality attributes between a biosimilar and the original biopharmaceutical. For example, it is advisable to perform multidimensional evaluations by multiple orthogonal analytical methods having different principles in order to analyze complicated quality attributes such as aggregates. The biosimilar product used in comparative studies should generally be produced through manufacturing processes for commercial products. Where the manufacturing process is changed during the development of the biosimilar, the sponsors should evaluate the comparability of the biosimilar before and after the changes in accordance with the ICH Q5E guideline.

It should be noted that it is highly likely that there are differences in quality attributes not only of the active ingredient, such as the heterogeneity of glycosylation in proteins, but also the profile of product-related substances, product-related impurities and process-related impurities between the biosimilar and the original biopharmaceutical produced by different manufacturing processes. The degree of similarity of quality attributes should be clarified by comparing quality attributes using multiple lots of the drug substance or the drug product, the impact of observed differences on efficacy and safety should be assessed, and nonclinical studies and clinical trials should be designed and conducted on the basis of the assessment results.

The impact of differences in quality attributes on efficacy and safety depends on the mechanism of action of the active ingredient, the indication of the product, and other factors. Therefore, the acceptable criteria for differences in quality attributes will vary depending on the characteristics of the product, the intended use and dosing regimen in clinical practice, and other factors. For example, where considering the effects of changes in each quality attribute on biological activity, pharmacokinetics, immunogenicity, and safety, it is considered that the greater the influence of the quality attributes have on these, the narrower the range in which the difference from the original biopharmaceutical is allowed, but the quality attribute having little influence on these would be allowed to have a wide acceptance range. In addition, in the case of products with multiple biological activities, such as antibodies and fusion proteins, the range of acceptable differences in quality attributes closely related to the mechanism of action for efficacy and safety among biological activities would be narrower. In the process of considering the impact of each of the quality attributes on efficacy and safety, the knowledge obtained from the original biopharmaceutical and from the information in the scientific literature is also useful.

When making comparisons regarding quality attributes, comparative studies on the structural and physicochemical properties, biological activity, and impurities should be conducted, and consideration should be given to the possibility of differences in clinical efficacy and safety, including immunogenicity based on the results of these comparisons. Although international and national reference standards for some original biopharmaceuticals may be obtainable, these standards cannot be regarded as a suitable reference product in comparative studies since the standards are set for the purpose of being applied to a specific use and are not substitutes for the original biopharmaceutical.

4.1 Comparison of structure/physicochemical properties

The structural and physicochemical properties such as amino acid sequence, disulfide bonds, glycan structures, other post-translational modifications, and subunit structure of the biosimilar should be compared with those of the original biopharmaceuticals. If the primary structure of the desired product is different from that of the original biopharmaceutical, the product is not regarded as a biosimilar. Where there are any variations from the original biopharmaceutical in terms of heterogeneity due to post-translational modification, such as processing of N- or C-terminal amino acids, it should be demonstrated that the variations have no adverse impact on efficacy and/or safety. In addition, it is useful to compare secondary structures and to compare tertiary structures as a higher-order structure evaluation. The analytical techniques for high-order structure cannot always be applied because of the unavailability of samples or the difficulty in preparing samples for measurement. It is considered that the similarity of the higher-order structure can be evaluated, including the comparison of biological activity, since the higher-order structure is considered to be reflected in the biological activity. Regarding properties such as the amino acid sequence of the desired product of the original biopharmaceutical, it is possible to refer to the scientific literature or other information.

4.2 Comparison of biological properties

It is strongly recommended that a comparison of the biological activities between an original biopharmaceutical and a biosimilar is conducted using multiple methods as far as possible. For example, it is useful to compare *in vitro* biological activities closely related to clinical efficacy, such as cell proliferation and differentiation, receptor-binding activity, enzyme activity, and others. In particular, in the case of a protein with multiple functional domain structures, the functions of the whole molecule can be compared by comparing the biological activities of each domain. In general, in the case of a biosimilar of antibodies, in addition to the antigen-binding activity, neutralizing activity, binding activity with Fc γ receptors, neonatal Fc receptor, and complement component 1q, antibody-dependent cellular cytotoxicity (ADCC) activity and complement dependent cytotoxicity (CDC) activity of the biosimilar and others should be compared with those of the original biopharmaceutical. On the other hand, the results of the *in vitro* biological activity may not correlate with that of clinical efficacy because of the significant influence of glycan structure or other factors on pharmacokinetics. In such cases, a comparison of *in vivo* biological activity would be necessary.

The comparison result of biological activity is important as one of the rationales that the comparable efficacy and safety as the original biopharmaceutical can be expected. Therefore, for items that may have an impact on biological activity among the attributes for which a difference was found in the comparison of structure and physicochemical properties, the extent to which the difference affects biological activity should be clarified as well as the effects on efficacy and safety, considering the mode of action of the product.

Where the clinical dose of the original biopharmaceutical is described by weight, the specific activity should be compared to assess comparability. Where there are some variations in the specific activity, their acceptability, that is, they have no impact on efficacy or safety, should be evaluated, and the use of the

same dose as in the original biopharmaceutical must be justified.

In comparisons of biological activity, it is desirable that the biological activity be calibrated against international or national reference standards, where available, because it becomes possible to compare it with publicly known information.

4.3 Comparison of impurities

For product-related impurities, the types and amounts should be compared, and the impacts on efficacy and safety should be considered. Representative examples of the product-related impurities include truncated forms and aggregates. Aggregates are impurities suggested to be associated with immunogenicity and may be of various sizes and shapes. Therefore, it is considered useful to make comparisons using multiple analytical methods having different principles.

Since process-related impurities differ depending on the manufacturing process, it is not always necessary to compare with the original biopharmaceutical. However, it is useful to compare the impurities commonly contained in the original biopharmaceutical and the biosimilar and demonstrate that the residual amount is less than that of the original biopharmaceutical. However, note that the results of a comparison of the biosimilar and the original biopharmaceutical whose constituent proteins differ from the biosimilar using the same analytical method such as host cell protein studies using ELISA may not reflect the difference in the actual residual amount because of the difference in the specificity of the analytical method. In addition, impurities that are not contained in the original biopharmaceutical may be contained in the biosimilar. Therefore, appropriate analysis and evaluation are required.

4.4 Comparison of quality attributes related to immunogenicity

The quality-related factors that may cause the difference in immunogenicity between the original biopharmaceutical and a biosimilar may include the desired product with the post-translational modification, product-related impurities, and process-related impurities. Immunogenicity is difficult to evaluate in nonclinical studies and needs to be evaluated in clinical trials. Therefore, clarifying the differences in quality attributes that may affect immunogenicity in quality comparison studies is also useful in examining clinical trial plans.

5. Nonclinical Studies

As a minimum requirement, the sponsors should evaluate the safety of a biosimilar for human use prior to entering into clinical trials. There are some approaches to conducting nonclinical studies.

Non-clinical studies include cases in which it is more reasonable to conduct studies only on a biosimilar, such as studies to confirm the safety of a biosimilar that has a different impurity profile from the original biopharmaceutical, and cases in which studies are appropriate for comparison with the original biopharmaceutical, such as comparative pharmacological studies.

The heterogeneity of sugar chains in some glycoprotein products may significantly affect the drug pharmacokinetics *in vivo*. It may then be useful to compare the nonclinical pharmacokinetics as part of the comparability study between a biosimilar and the original biopharmaceutical.

Furthermore, the quality attributes of the biosimilar should be fully evaluated prior to conducting nonclinical studies. In addition to data from the comparative studies on quality attributes between a biosimilar and the original biopharmaceutical, information on use results or scientific literature of other similar products may also play an important role in the study design for the safety evaluation of the biosimilar.

5.1 Nonclinical pharmacological studies

The pharmacological action of a biosimilar and the original biopharmaceutical should be directly

evaluated in pharmacological studies. If *in vitro* biological activity studies (e.g., cell-based studies or receptor-binding activity) that are closely related to clinical efficacy are required, and the biological activity between a biosimilar and the original biopharmaceutical has been compared in quality while taking the mechanism of action into account, these studies may be utilized also as nonclinical pharmacological studies. In case full evaluation can be obtained by *in vitro* comparative studies, *in vivo* comparative studies of pharmacodynamics may not be necessary. However, when *in vitro* biological activity does not correlate well with clinical efficacy as in some types of glycoproteins, it will be necessary to evaluate the comparability of therapeutic efficacy and pharmacodynamics with the original biopharmaceutical through *in vivo* pharmacological studies. If there is no suitable *in vitro* evaluation system, an *in vivo* evaluation is required.

5.2 Nonclinical safety studies

Whether or not nonclinical safety studies on biosimilars are necessary should be examined based on the results of quality studies and pharmacological studies.

If a biosimilar has a high similarity to the original biopharmaceutical by the results of these studies, and no safety concerns in conducting clinical trials can be sufficiently explained, nonclinical safety studies can be omitted.

On the other hand, when a biosimilar has safety concerns that differ from those of the original biopharmaceutical based on the quality and pharmacological studies, nonclinical safety studies should be conducted based on the information with reference to the ICH S6 guideline and others. Nonclinical safety studies of biosimilars can usually be evaluated in repeated-dose toxicity studies in single relevant species. The study design (e.g., animal species, duration of animal dosing, and dose) should be selected in consideration of the toxicity profile of the original biopharmaceutical, the target disease and others.

6. Clinical Trials

In general, it will be difficult to verify the comparability of a biosimilar with the original biopharmaceutical only based on the data on quality attributes and the results of nonclinical studies. Therefore, the sponsors should evaluate the comparability of a biosimilar through clinical trials.

Furthermore, the biosimilar product used in clinical trials (investigational product) should generally be produced through manufacturing processes for commercial products. Where the manufacturing process is changed during the development of the biosimilar, the sponsors should evaluate the comparability of the biosimilar before and after the changes, as appropriate, in accordance with the ICH Q5E guideline. Where pharmacokinetic (PK) or pharmacodynamic (PD) studies described below are sufficient to assure comparability in the clinical endpoint of interest, additional clinical trials to evaluate efficacy might be omitted.

In clinical trials intended to evaluate comparability, the subsequent studies should be designed based on the data obtained from the earlier studies and should be conducted in a step-wise approach. The type and contents of the necessary clinical trials will vary widely according to the available information and the properties of the original biopharmaceutical. Since the scope of clinical trials necessary for the biosimilar under development should be determined on a case-by-case basis, taking into account the data obtained at each stage of development, the sponsors are encouraged to consult with the regulatory authorities.

6.1 Clinical pharmacokinetic (PK) and pharmacodynamic (PD) studies

The sponsors should confirm the comparability of PK between a biosimilar and the original biopharmaceutical by clinical trials that are appropriately designed. A crossover design is desirable. However, it may not always be applicable to clinical trials for biopharmaceuticals with a long half-life (e.g., antibodies and polyethylene glycol-conjugated proteins) or biopharmaceuticals with a high risk of

immunogenicity, and parallel-group design is appropriate for these cases. The clinical trial should be designed according to the properties of the biosimilar. Furthermore, depending on the original biopharmaceutical, target disease and others, there is appropriate cases to conduct a clinical trial in healthy adults, or in patients. Considering the control mechanism of PK (target-mediated drug disposition, elimination by PK-related receptors) and the clinical factors that change them, enroll subjects where the differences in PK caused by differences in the quality attributes are easy to detect.

In addition, it is necessary to conduct a clinical trial using the same route of administration as that in the approved indications of the original biopharmaceutical. Where multiple routes of administration are allowed, in principle, each route of administration should be studied. However, it may not be necessary to examine all administration routes. For example, where the original biopharmaceutical supports a two-dosage regimen, intravenous and subcutaneous administration with the same dosage form, and it is possible to investigate the elimination process during intravenous administration by evaluation during subcutaneous administration, then it is sufficient to perform the studies by subcutaneous administration alone. Also, clinical trials should be conducted using the approved dosage of the original biopharmaceutical, while another scientifically rational dosage may also be chosen.

While the key parameters of a PK study are considered to be the area under the blood concentration curve (AUC) and maximum concentration (C_{max}), the acceptable range of data from the comparability exercise (equivalence margin) should be determined before the study. The acceptable range should be considered based on the characteristics of the individual product. Although the set acceptable range should be well justified, it is generally acceptable that the PK is judged to be comparable, where the 90% confidence interval of the difference between the mean values of the logarithmic value of the PK evaluation parameters of a biosimilar and the original biopharmaceutical is within the range of $\log(0.80)$ to $\log(1.25)$.

In some cases, a difference occurs in the binding property with the binding reagent used for the drug concentration analysis due to the difference in the quality attributes between both, and then the calibration curves of the original biopharmaceutical and a biosimilar do not match. Therefore, validated bioanalytical methods should be used to measure the concentration in biological samples.

In some cases, the evaluation of efficacy, safety, or immunogenicity can be performed together with the PK evaluation. In addition, a PD marker that reflects the clinical effect of the product is selected, and a comparison is performed using the PD as an index if possible. Especially where the PK study is difficult because of technical problems, a comparison using PD markers is useful.

6.2 Comparison of clinical efficacy

In addition to high similarity in quality has been demonstrated through comparability studies on the quality attributes, analyses of all data from the PK or PD studies might not demonstrate the comparability of clinical efficacy. In this case, it is necessary to conduct clinical trials to verify that the efficacy of the biosimilar and original biopharmaceuticals is comparable.

When conducting clinical trials to compare efficacy, comparative clinical trials should be appropriately designed and justified to confirm the comparability of the biosimilar with that of the original biopharmaceutical. Specifically, it is requisite to determine the necessary and adequate number of patients to be enrolled and to pre-specify the margins defining clinical comparability (comparability margin) using clinically established endpoints. The use of true endpoints will not always be required. Appropriate endpoints should be selected to detect the difference between a biosimilar and the original biopharmaceutical. Where the scientific rationale can be sufficiently explained and justified by taking into account the pharmacological effects and endpoints, it may be possible to utilize the study design to verify non-inferiority to the original biopharmaceutical.

In principle, clinical trials should be conducted within the approved indications, and dosage and administrations of the original biopharmaceutical. Furthermore, where there is a difference in efficacy between a biosimilar and the original biopharmaceutical, it is advisable to carry out studies using a population where the difference is easily detected.

6.3 Confirmation of clinical safety

Although comparability of efficacy has been demonstrated, the safety profile of a biosimilar may still differ from that of the original biopharmaceutical. If necessary, clinical trials to evaluate safety (including an immunogenicity evaluation) should be considered, even where comparability has been demonstrated through PK or PD studies and thus further clinical trials to evaluate efficacy are not required. When clinical trials are conducted to compare the efficacy of the two products, the studies may be designed such that safety (types of adverse events and their incidence rates) can be assessed as well.

If the analysis results of the impurity profile give rise to particular concerns about safety, a thorough investigation of the safety of the biosimilar must be considered.

Multiple dose studies on the biosimilar should be considered in the case of chronic administration. The period of a multiple dose study should be such that the safety profile can be confirmed, and it can be set based on well-known knowledge, such as anti-drug antibody production. In cases where comparability is demonstrated in terms of efficacy, it may be sufficient to confirm safety, including anti-drug antibody production, by no-control studies, not by comparative clinical trials.

Furthermore, at an appropriate stage of clinical development, studies should be conducted to evaluate the presence or absence of anti-drug antibody production and other immunogenicity, thus leading to a scientifically justifiable conclusion. The study methods used to evaluate anti-drug antibodies should be appropriately validated assays.

6.4 Grant of indications

When a biosimilar has high similarity in quality attributes to the original biopharmaceutical, comparability is demonstrated in nonclinical pharmacological studies and others, and it is judged that efficacy is comparable to the original biopharmaceutical in certain indications with no difference in the safety profile, the indications verified in clinical trials are granted to the biosimilar.

Furthermore, when the original biopharmaceutical used as a reference product has multiple indications, and if it can be expected that the pharmacological action similar to that of the original biopharmaceutical can be expected and there are no concerns in the safety profile, the indications that have not been verified in clinical trials can be granted to the biosimilar regardless of the same or difference in dosage and dose regimen or administration period for each indication (extrapolation). On the other hand, if the mechanism of action is different for each indication, or if the mechanism of action is not clear, other indications cannot be granted and a separate clinical trial may be required. For example, where a biopharmaceutical having an active ingredient composed of multiple domains acts through a multiple target molecules or receptors and their degree of contribution differs depending on each indication, this is considered to be the case.

The indications that can be granted without conducting clinical trials are limited to the indications of the original biopharmaceutical used as a reference product and the indications of other approved biopharmaceuticals with the similar indications other than the original biopharmaceutical are not included.

7. Post-Marketing Risk Management

Information on safety and efficacy obtained from clinical trials conducted prior to drug approval is generally limited. On the other hand, relatively enough information on safety and efficacy is generally obtained in the indication of drugs that have passed the re-examination period. However, biosimilars have characteristics different from those of generic drugs (e.g., immunogenicity) since they are biopharmaceuticals, and thus appropriate risk management and information provision considering the properties of the biosimilar are required during post-marketing stage. Therefore, in consideration of the items that could not be sufficiently evaluated in a comparability evaluation with the original biopharmaceutical in the development stage, the appropriate risk management plan for the drug should be

established, as well as clarifying the presence and content of post-marketing information to be collected.

When considering pharmacovigilance activities, the quality attributes of products, information obtained through clinical trials, their limitations and items that could not be fully evaluated, the characteristics of the assumed patient population, and post-marketing knowledge about the drug product obtained other countries/regions should be taken into consideration. In addition, when conducting additional pharmacovigilance activities, efficient and effective methods should be selected from various methods, such as use-results surveys, post-marketing database surveys, post-marketing clinical trials including multi-regional clinical trials, and other drug safety monitoring methods indicated in the ICH E2E guideline, depending on the purpose. It may be useful to construct and utilize a disease registry ensuring reliability by industry and/or academia, where the number of target patients is small, or where multiple companies sell biosimilars against the same original biopharmaceutical. When conducting additional pharmacovigilance activities, the reliability should be properly secured. In addition, a risk minimization plan should be prepared according to the content of the risk.

For the approval applications, it is necessary to submit a draft “Risk Management Plan” that includes whole the plans, and the details should be discussed with the regulatory authorities during the approval review process. In addition, after approval, the progress and results of these additional pharmacovigilance activities should be reported to the regulatory authorities at the time specified in advance described in the “Risk Management Plan”. Furthermore, it is desirable to consider the appropriate method of publicizing the results.

References

1. Validation of Analytical Procedures (ICH Q2A).
2. Validation of Analytical Procedures: Methodology (ICH Q2B).
3. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH Q5A).
4. Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products (ICH Q5B).
5. Stability Testing of Biotechnological/Biological Products (ICH Q5C).
6. Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Q5D).
7. Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH Q5E)
8. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Q6B).
9. Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH Q7)
10. Pharmaceutical Development (ICH Q8)
11. Quality Risk Management (ICH Q9)
12. Pharmaceutical Quality System (ICH Q10)
13. Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (ICH Q11)
14. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6)
15. Pharmacovigilance Planning (ICH E2E)
16. Statistical Principles for Clinical Trials (ICH E9)
17. *Guideline on Bioanalytical Method (Ligand Binding Assay) Validation* PFSB/ELD Notification No. 0401-1 dated April 1, 2014.
18. *Guidance for Quality Evaluation of Therapeutic Antibodies* PFSB/ELD Notification No. 1214-1 dated December 14, 2012.

Glossary and Definitions

Comparability

“Comparability” means that the quality attributes of a biosimilar are highly similar to those of the reference product and that it can be scientifically justified that any differences in quality attributes have no impact on clinical efficacy and safety of the product based on the results of nonclinical studies and clinical trials. However, differences in quality attributes that do not have adverse impact on safety or differences of a lower frequency of adverse reactions than reference product are acceptable.

Quality Target Product Profile (QTPP)

The QTPP is a prospective summary of the quality attributes of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8, 11)

Critical Quality Attribute (CQA)

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8, 11)

Quality attributes

Quality attributes are the molecular or product characteristics selected as items those are representative of the quality of the product. Collectively, the quality attributes define the identity, purity, potency, stability, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes. The quality attributes include not only the potency of the active ingredients, biological activity, and physicochemical properties but product-related substances, product-related impurities, and type and contents of process-related impurities.

Product-related substances

These are the molecular variants of the desired product formed during manufacture and/or storage that are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities. (ICH Q6B)

Impurity

An impurity is any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient. It may be either process- or product-related. (ICH Q6B)

Product-related impurities

Product-related impurities are molecular variants of the desired product (e.g., precursors or degradation products arising during manufacture and/or storage) other than product-related substances. (ICH Q6B)

Process-related impurities

These are the impurities derived from the manufacturing process. They may be derived from cell substrates, cell culture media, or the downstream processing, in other words, extraction, separation, processing, and purification of the desired product (e.g., processing or column leachables). (ICH Q6B)

Reference Standards

These refer to both international and national reference standards. For example, the international standards distributed by the National Institute for Biological Standards and Control (NIBSC) and the Japanese Pharmacopoeia Reference Standards distributed by the Society of Japanese Pharmacopoeia fall into this category. They are intended for use in the relevant potency assay or physicochemical assay etc. The standards should not be used for studies other than as intended.