Administrative Notice
January 25, 2024

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

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

Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars

Assurance of the quality of biosimilars has been indicated in the Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (PSEHD/PED) Notification No. 0204, Ministry of Health, Labour and Welfare (MHLW), dated February 4, 2020). Additionally, Questions and Answers on the guideline has also been indicated in the Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (PSEHD/PED Administrative Notice dated February 4, 2020). We have partially revised the Q&A as shown in the following old and new comparative tables based on scientific knowledge at the present time, and we would like to ask you to please disseminate this document to the relevant business operators under your jurisdiction.

With the release of this Administrative Notice, we abolish the Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau (PFSB/ELD) Administrative Notice, MHLW, dated July 21, 2009), the Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (PFSB/ELD, Administrative Notice, MHLW, dated March 31, 2010), the Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (PSEHD/PED, Administrative Notice, MHLW, dated December 15, 2015), and the Questions and Answers (Q&A) on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (PSEHD/PED, Administrative Notice, MHLW, dated February 4, 2020).

Description

Administrative Notice dated January 25, 2024 (New)	Administrative Notice dated February 4, 2020 (Old)
No.9 Q. What quality information is required to be presented in the materials attached to the initial clinical trial notification for a biosimilar? A. In addition to the materials indicated in the response to Q27 of "Revision of Questions and Answers (Q&A) on Submission of Drug Clinical Trial Plan and Implementation of the Clinical Trials "(Office Memorandum dated August 31, 2022), a summary of the results of the comparative study of quality attributes with the reference product used in the clinical trial should be attached as supporting data. It is recommended that sponsors consult with PMDA regarding the quality comparability evaluation prior to the initial clinical trial notification.	No.9 Q. What quality information is required to be presented in the materials attached to the initial clinical trial notification for a biosimilar? A. In addition to the materials indicated in the response to Q11 of "Revision of Questions and Answers (Q&A) on Submission of Drug Clinical Trial Plan and Implementation of the Clinical Trials "(Office Memorandum dated December 14, 2015), a summary of the results of the comparative study of quality attributes with the reference product used in the clinical trial should be attached as supporting data. Consulting the PMDA is recommended regarding the quality comparability evaluation prior to the initial clinical trial notification.
No.10 Q. Is it acceptable to use data from clinical trials conducted in non-Japanese subjects that confirm the equivalence of PK and efficacy (including PD) with original biopharmaceuticals for approval application? A. Clinical trials of biosimilars are intended to confirm the equivalence of PK and efficacy (including PD) to original biopharmaceuticals. Therefore, if the ethnic factors of subjects do not affect the study results, data from clinical trials conducted overseas in non-Japanese subjects may be used, and it is acceptable not to conduct a clinical trial that includes Japanese subjects. If the sponsors conduct global clinical trials with Japanese subjects and the ethnic factors of subjects are considered to affect the study results, Method 1 and Method 2 as indicated in the "Basic Principles on Global Clinical Trials" (Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and	No.10 Q. If you have a basic idea about the acquisition of clinical data on Japanese, please indicate it. A. At least either the clinical trial to verify PK equivalence with original biopharmaceuticals or the clinical trial to verify efficacy (including PD) equivalence with the original biopharmaceuticals must be realized with the clinical trial with Japanese subjects. Method 1 and Method 2 as indicated in the "Basic Principles on Global Clinical Trials" (Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) cannot be directly applied to the number of Japanese cases when the study is conducted as an international joint clinical trial that includes Japanese subjects. However, the plan should be such that it can be explained that there is no discrepancy between the results of the Japanese population and those of the overall population.

Welfare) cannot be directly applied to the number of Japanese. However, the plan should be such that it can be explained that there is no discrepancy between the results of the Japanese population and those of the overall population with reference to the above notification.	
No.11 Q. In Q&A10, it stated that if the ethnic factors of subjects are not expected to affect the clinical trial results, how do you evaluate this? A. For example, it is possible to identify ethnic factors and their impact based on the original biopharmaceuticals and to confirm the results of Japanese subgroup analysis of clinical trials from currently available evidence of original biopharmaceuticals. Additionally, if some differences of quality attribute between a biosimilar and the original biopharmaceutical was observed, it is important to evaluate ethnic factors and their impact focusing on the differences.	(Newly established)
No.12～No.37	No.11～No.36

Questions and Answers on Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars (Q&A)

No.	Corresponding part of the text	Question (Q)	Answer (A)
1. Introduction			
1	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.	Are original biopharmaceuticals not allowed unless they have been approved as a drug containing a new active ingredient? For example, if the approval of a product with new active ingredients is withdrawn in the future, is there a possibility that a biosimilar with sufficient clinical experiential use could be allowed for use as an original biopharmaceutical?	As long as there are products approved as drugs with new active ingredients, the original biopharmaceutical will be selected from among them. However, in the future, a biopharmaceutical approved as a drug with new active ingredient may be withdrawn from the market due to approval cancellation. In such cases, there is a possibility that a biosimilar with sufficient clinical use results after marketing may be considered an original biopharmaceutical. We would like to leave this for future consideration.
2	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.	"Other relevant data" has been added. Is it correct to assume that publicly available information can also be used in the comparative evaluation?	The phrase "other relevant data" includes information that is publicly known. However, publicly known information is generally used as a reference during the review. While comparative study is not necessary for the primary structure, it is generally difficult to compare publicly known information with respect to quality attributes such as heterogeneity. In such cases, comparative studies by direct evaluations may be useful.
3	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.	Does the comparability evaluation of a biosimilar and the original biopharmaceutical refer to the same thing as the comparability evaluation before and after changes in the manufacturing process? Also, is comparability synonymous with biosimilarity?	"同等性／同質性" is a term used in the ICHQ5E Notification for the change in the manufacturing process of biopharmaceuticals as a Japanese translation of "comparability. The same concept can be applied to the comparative evaluation of the quality, efficacy, and safety of a biosimilar and an original biopharmaceutical as to the comparative evaluation of the quality, efficacy, and safety of the product before and after a change in the manufacturing method. Therefore, the same terminology is used for biosimilars. In the case of a comparability evaluation before and after a change in manufacturing process, the comparison is conducted in a situation where all information regarding the manufacturing method before and after the change and the specifications of the product manufactured by their method are known. In contrast, comparisons between a biosimilar and an original

			biopharmaceutical are made without information on the manufacturing process of the original biopharmaceutical and with limited information on the quality of the original biopharmaceutical. Therefore, the nature and extent of the comparative studies required are different. In Europe and the United States, the term “biosimilarity” is sometimes used for the “comparability” of a biosimilar and an original biopharmaceutical.
4	An application of a biosimilar will be able to be submitted after the expiry of the re-examination period of the original biopharmaceutical.	Regarding indications for which the re-examination period had not expired at the time of the approval application for approval of the biosimilars and are not subject to the application, should we apply for the application category as “1-(4) Drugs with new indications,” if we apply for additional indications after the expiry of the re-examination period?	When submitting an application for an additional indication, the application category should be "1-(7) Biosimilars."
5	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.	Given the remarkable progress in the science and technology related to biopharmaceuticals, is it appropriate to incorporate the latest analytical techniques including methods that were not available when the original biopharmaceutical was developed during the characterization of a biosimilar and comparative studies with original biopharmaceuticals? In addition, for example, even if there is a possibility that quality attributes of a biosimilar may differ from the original biopharmaceutical, is it reasonable to adopt a process that is considered safer, such as a serum-free cell-culture?	The incorporation of scientific progress is also a requirement for original biopharmaceuticals. When re-evaluating original biopharmaceuticals or listing them in the Japanese Pharmacopoeia, it is required to consider not only the requirements at the time of approval but also the state-of-the-art analytical techniques. A similar strategy is required in the development of biosimilars. It is desirable to select a manufacturing method that is considered safer for the development of biosimilars. However, it must be fully confirmed that the introduction of a new manufacturing method will not adversely affect the efficacy and safety of the product.
2. Scope			
6	Scope	Is it possible to refer to the concept of the Guideline for Ensuring the Quality, Safety, and Efficacy of Biosimilars when a product containing the same active ingredient as an approved biopharmaceutical using recombinant DNA technology is developed by chemical synthesis?	It is thought that decisions should be made on a case-by-case basis depending on the characteristics of the product, but in general, this guideline is considered to serve as a reference.
3. General Principles for the Development of Biosimilars			
3.1 Evaluation of comparability with original biopharmaceuticals			
7	In the development of biosimilars,	Please indicate where the quality	Comparative test results on quality

	the sponsors should demonstrate the comparability of the proposed product with the original biopharmaceutical through quality, nonclinical and clinical comparisons.	comparison data with original biopharmaceuticals should be included in the CTD.	should be included in CTD 2.3.R (Regional information).
8	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.	If there are detailed criteria or acceptable ranges for comparability evaluation of biosimilars, please let us know. Also, please indicate if there is an appropriate time to discuss and agree with the regulatory authorities on the establishment of an acceptable range.	With respect to the comparability evaluation of biosimilars, it is not appropriate to establish a uniform standard or acceptable range because it depends on the characteristics of the product and the test. Please consult us on an individual basis regarding the justification of the acceptable range through PMDA consultation services.
9	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.	What quality information is required to be presented in the materials attached to the initial clinical trial notification for a biosimilar?	In addition to the materials indicated in the response to Q27 of "Revision of Questions and Answers (Q&A) on Submission of Drug Clinical Trial Plan and Implementation of the Clinical Trials "(Administrative Notice dated August 31, 2022), a summary of the results of the comparative study of quality attributes with the reference product used in the clinical trial should be attached as supporting data. It is recommended that sponsors consult with PMDA regarding the quality comparability evaluation prior to the initial clinical trial notification.
10	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.	Is it acceptable to use data from clinical trials conducted in non-Japanese subjects that confirm the equivalence of PK and efficacy (including PD) with original biopharmaceuticals for approval application?	Clinical trials of biosimilars are intended to confirm the equivalence of PK and efficacy (including PD) to original biopharmaceuticals. Therefore, if the ethnic factors of subjects do not affect the study results, data from clinical trials conducted overseas in non-Japanese subjects may be used, and it is acceptable not to conduct a clinical trial that includes Japanese subjects. If the sponsors conduct global clinical trials with Japanese subjects and the ethnic factors of subjects are considered to affect the study results, Method 1 and Method 2 as indicated in the "Basic Principles on Global Clinical Trials"(Notification No. 0928010 dated September 28, 2007, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) cannot be directly applied to the number of Japanese. However, the plan should be such that it can be explained that there is no discrepancy between the results of the Japanese

			population and those of the overall population with reference to the above notification.
11	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 Q&A10, it stated that if the ethnic factors of subjects are not expected to affect the clinical trial results, how do you evaluate this?	For example, it is possible to identify ethnic factors and their impact based on the original biopharmaceuticals and to confirm the results of Japanese subgroup analysis of clinical trials from currently available evidence of original biopharmaceuticals. Additionally, if some differences of quality attribute between a biosimilar and the original biopharmaceutical was observed, it is important to evaluate ethnic factors and their impact focusing on the differences.
3.2 Original biopharmaceutical			
12	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 should be 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.	What is the definition of "identical product"? For example, even if the manufacturing process and the formulation of an original biopharmaceutical have been changed during the development of a biosimilar, can it still be considered an "identical product" if it has the same non-proprietary name, in principle?	Some approved products have the same non-proprietary name but different brand names. In this guideline, identical products here refer to products that have the same approval. However, the same product may be marketed by several companies under different brand names. In this case, either product may be used. Regarding the identity of domestically approved products and overseas-approved products, it is preferable to collect publicly available information such as each product's manufacturing facility because the information may be helpful. In assessing the comparability of a biosimilar and the original biopharmaceutical, the variation in the quality attributes of the original biopharmaceutical being compared should be taken into account. Although the manufacturing process of an original biopharmaceutical may change during development of biosimilar, it is possible to develop and apply for approval of a biosimilar using the product before the change in manufacturing process as the original biopharmaceutical.
3.3 Points to consider when developing manufacturing process and establishing a quality control strategy for biosimilars			
3.3 (i) Host cells			

13	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.	The guideline states "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,". For example, what degree of identity can be considered for "the same host cells"? Also, what is the meaning of "desirable"?	The phrase "same host cells" refers, for example, to CHO cells if the original biopharmaceutical was manufactured with CHO cells. It is considered unavoidable that the CHO cells in biosimilar development cannot be matched to the subspecies of the CHO cells of the original biopharmaceutical. Even if it is clear that an original biopharmaceutical is manufactured using a certain cell line, it is assumed that the sponsors may choose another cell line for immunogenicity or other factors. However, since post-translational modification may vary significantly, the justification must be determined based on these factors. Therefore, the word "desirable" is used.
14	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.	What does "different types of host cells" in the mention of "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 profiles of process-related impurities, including host cell impurities, and then submit the data" refer to, for example?	The term "different types of host cells" refers to cell lines of different origins. For example, an original biopharmaceutical is manufactured with NS0 cells and a biosimilar is manufactured with CHO cells.
3.3 (ii) Formulation development			
15	The administration route of a biosimilar should be the same as those of the original biopharmaceutical.	How should we think about the assortment of strengths and/or dosage forms for biosimilars?	Please refer to “Assortment of necessary strengths and/or dosage forms for generic drugs” (Health Policy Publication No. 0310001 dated March 10, 2006, Notice by the Director-General of the Health Policy Bureau) and related Q&A.
16	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.	Are there any points of attention when developing a biosimilar for a device that is different from the original biopharmaceutical? For example, the original biopharmaceutical is marketed only in a syringe formulation that can be self-administered, but the biosimilar will be developed in a pen formulation in addition to the syringe formulation.	When developing a device of a different type from an original biopharmaceutical, confirmation may be required regarding medical necessity and safety. Therefore, it is advisable to consult with regulatory authorities through PMDA consultation services.
3.3 (iii) Specifications			

17	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.	Is it possible to use an original biopharmaceutical as the reference material for a development product?	In the early stages of development, it may be unavoidable to use an original biopharmaceutical as the reference material. However, it is generally difficult to obtain all information on the quality of original biopharmaceuticals, and there is a limit to controlling their quality by oneself even if they are positioned as reference materials. Therefore, it is necessary to establish the in-house reference materials as early as possible.
18	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.	Is it acceptable to substitute a biological test used in an original biopharmaceutical by a more accurate test method?	Alteration is allowed if the justification of the test method is confirmed by considering the difference in principle, and the correlation with existing biological tests.
4. Comparative Studies of Quality Attributes			
19	Although international and national 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.	In addition to using the reference standard for calibration of biological activity, is it possible to use it as reference for the structural comparison?	As stated in the glossary of terms in the guideline, it is not appropriate to use reference standards for purposes other than the intended use. If a comparative study of structural and physical-chemical properties is performed using a reference standard distributed for potency standards as a control, the data obtained are meaningless.
4.1 Comparison of structure/physicochemical properties			
20	If the primary structure of the desired product is different from that of the original biopharmaceutical, the product is not regarded as a biosimilar.	In the development of a biosimilar of a monoclonal antibody, the lysine residue at the C-terminus of the heavy chain is completely missing, but the original biopharmaceutical contains a component with the lysine residue. In such a case, is the difference in the primary structure acceptable?	Structural heterogeneity due to the differences in the number of lysine residues at the C-terminus of heavy-chains in monoclonal antibody is usually observed because of post-translational modification. If it is reasonably determined that this structural difference does not affect safety and efficacy *in vivo*, then it could be acceptable as a biosimilar even if the primary structure is different.
4.2 Comparison of biological properties			

21	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.	Please provide any common considerations regarding the comparison of biological activities with the original biopharmaceutical in the development of a biosimilar of a monoclonal antibody.	Even if an original biopharmaceutical does not have the functional properties of the Fc region, it may provide useful information on the similarity of the higher-order structure. Therefore, it is recommended that the functional properties of the Fc region are evaluated in comparison with those of the original biopharmaceutical.
22	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.	Is there any overlap between biological activity testing in characterization and pharmacological studies?	A comparison of biological activity is important as a comparability evaluation. The comparison should also include an evaluation of the impact of glycans and heterogeneity. Therefore, the data should also be included in the Comparison of Quality Attributes section, even if it overlaps with the data from pharmacological studies.
4.3 Comparison of impurities			
23	In addition, impurities that are not contained in the original biopharmaceutical may be contained in the biosimilar. Therefore, appropriate analysis and evaluation are required.	Is a safety assessment required for all impurities in a biosimilar?	It is not necessary to conduct safety testing for all impurities. It is necessary to evaluate impurities as a part of the product characterization and ensure that they are within acceptable limits from a safety perspective, taking into account previous experience and information on impurities (e.g., experience in products using the same host or cell-culture process and data pertaining to the safety of process-related impurities).
5. Nonclinical Studies			
5.1 Nonclinical pharmacological studies			
24	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.	Please provide examples of cases requiring *in vivo* pharmacological studies.	For example, with epoetin, it is known that the higher the amount of sialic acid, the longer the half-life in the blood and the higher the *in vivo* pharmacological activity, but the receptor binding ability evaluated in *in vitro* tests is conversely reduced. In such cases, comparability evaluation by *in vivo* pharmacological studies is considered necessary.
6. Clinical Trials			

25	Where pharmacokinetic (PK) and/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.	Is it correct to understand that the description “where PK and/or PD studies are sufficient to assure comparability in the clinical endpoint of interest, the afore-mentioned, additional clinical trials to evaluate efficacy might be omitted” may also omit safety studies?	As stated in the guideline, it indicates the possibility of presumed comparability in terms of efficacy and does not refer to safety. Safety needs to be considered separately.
6.2 Comparison of clinical efficacy			
26	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.	Please provide us with any points to be considered in the comparability evaluation.	Regarding the comparability acceptable range, it is important not only from a statistical perspective but also in relation to clinical significance, and information on the original biopharmaceutical and other related information would serve as a useful reference. In assessing comparability, in principle, 95% confidence intervals should be used based on "Statistical Principles for Clinical Trials” (Notification No. 1047 of PMSB/ELD dated November 30, 1998). In principle, the significance level for hypothesis test in the comparability evaluation should be 2.5% for one-sided or 5% for two-sided.
27	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.	Please provide examples of what alternative endpoints might be considered in comparative clinical efficacy trials.	For example, response rates are expected to be used as an indicator for some anticancer drugs.
6.3 Confirmation of clinical safety			
28	If necessary, clinical trials to evaluate safety (including an immunogenicity evaluation) should be considered	In the confirmation of clinical safety, what is the reason for specifying immunogenicity testing as "including an immunogenicity evaluation”?	Immunogenicity is exemplified as an item of particular need for consideration because it may be of concern in biologics experientially. Therefore, it is necessary to collect information on immunogenicity and conduct appropriate risk management from the clinical trial stage.
29	The study methods used to evaluate anti-drug antibodies should be appropriately validated assays.	When comparing the immunogenicity of a biosimilar and an original biopharmaceutical within the same clinical trial, is it acceptable to evaluate anti-drug antibodies using the same assay? In addition, please provide any points to be considered when establishing the measurement method for anti-drug antibodies.	If the justification of the measurement method can be demonstrated, the evaluation can be performed with either the same or different measurement methods. In both cases, the method(s) must be demonstrated that the results obtained with the biosimilar and the original biopharmaceutical can be used for comparative evaluations. The analytical method used to evaluate anti-drug antibodies must be shown to

			be a method that can avoid false negatives, such as by setting cut-points properly for detecting positive samples, properly evaluating resistance to residual drugs in the sample, and adding pretreatment step(s) to avoid the effects of coexisting drugs as necessary.
30	The study methods used to evaluate anti-drug antibodies should be appropriately validated assays.	Please provide any points to be considered when evaluating the results of anti-drug antibody measurements.	When emergence of the antibodies is observed, it is necessary to characterize the anti-drug antibodies by evaluating their neutralizing activities, and the analysis on the class and specificity of the antibodies is also desired. Consideration should also be given to confirming the reduced efficacy and safety impact by the emergence of the antibodies. Furthermore, if the immunogenicity of the biosimilar shows a different trend from that of the original biopharmaceutical, antibody production against impurities and reactivity to specific glycan antigens should also be fully considered.
6.4 Grant of indications			
31	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).	Therapeutic monoclonal antibodies have a common mechanism of action of binding to an antigen for all indications. Therefore, if the efficacy of a biosimilar is comparable to that of an original biopharmaceutical for a certain indication, is it possible to extrapolate all the indications without conducting clinical trials for each indication?	Therapeutic monoclonal antibodies have various mechanism of actions, such as ADCC activity, CDC activity, and apoptosis induction activity, in addition to neutralizing activity against the antigen. Therefore, it is necessary to understand which action contributes to the efficacy for each indication of the relevant monoclonal antibody drug product. As a result of extensive studies on structural, physicochemical, and biological properties in quality and nonclinical studies, if a high similarity with the original biopharmaceutical is confirmed and it can be explained from information on the original biopharmaceutical and on the results of clinical trials conducted that comparable efficacy and similar safety can be expected for indications for which clinical trials were not conducted, it may be possible to obtain other indications without necessarily conducting clinical trials for those indications.

32	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).	Is it acceptable the situation where a biosimilar does not obtain some of the indications as well as dosage and administration that the original biopharmaceutical has, even after the re-examination period or patent term has expired?	In principle, the biosimilar should obtain all indications as well as dosage and administration for which the re-examination period has expired, among the multiple indications as well as dosage and administration for which the original biopharmaceutical has been approved.
33	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).	If the comparability of efficacy is confirmed for an indication as well as dosage and administration for which the re-examination period has not yet expired for an original biopharmaceutical, is it possible to use the clinical trial results for the approval application regarding the indication as well as dosage and administration for which the re-examination period has expired?	If the clinical trial results are appropriate for confirming the comparability of the biosimilar and the original biopharmaceutical in terms of an indication as well as dosage and administration, and if it is expected that the clinical trial results can be used to demonstrate that the efficacy of the biosimilar is comparable and the safety profile is similar to that of the original biopharmaceutical in terms of the indications as well as dosage and administration for which approval is sought, the application can be done based on the results of such clinical trials. However, it should be noted that the indication as well as dosage and administration for which the comparability verification study was conducted, cannot be obtained at the time of initial approval, and an application for partial changes must be conducted upon the expiration of the re-examination period for the original biopharmaceutical.
34	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.	If a new clinical trial is conducted for an indication that is not approved for the referenced original biopharmaceutical but is approved for another approved biopharmaceuticals or for a new indication, is it possible to apply for the additional indication?	It is considered possible to conduct an additional application for indications not included in the original biopharmaceuticals if a separate clinical trial is conducted.
7. Post-Marketing Risk Management			
35	In addition, when conducting additional pharmacovigilance activities, efficient and effective methods should be selected from various methods, such as use-results	Are there any cases in which additional pharmacovigilance activities or other activities are not required in the pharmaceutical risk management plan?	For example, for indications as well as dosage and administration, that have been shown to be highly similar to original biopharmaceuticals in quality and nonclinical studies, and for which

	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.		clinical trials with a sufficient number of subjects have shown no concerns about the efficacy and safety of the developed formulation, additional pharmacovigilance activities or other activities for such indications as well as dosage and administration may not be necessary.
36	When conducting additional pharmacovigilance activities, the reliability should be properly secured.	How exactly do we properly secure reliability?	For example, when conducting a use-results survey or other activities, appropriate measures should be implemented to ensure reliability with reference to the GPSP Ministerial Ordinance. In addition, when a disease registry is used, the Guideline for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases (dated March 31, 2014, Pharmaceuticals and Medical Devices Agency) may be used as a reference.
37	Furthermore, it is desirable to consider the appropriate method of publicizing the results.	What exactly do you mean by appropriate method of publicizing the results?	The information should be publicized in a manner that guarantees fairness and allows the information to be used by medical institutions and other related organizations. For example, submission of papers, conference presentations, and other appropriate means may be considered. The Guideline for Provision of Sales Information on Prescription Drugs" (dated September 25, 2018, Notification No. 0925-1 of PSEB, Pharmaceutical Safety and Environmental Health Bureau) should be referred to when releasing and providing information.