Questions and Answers (Q&A) regarding the Guideline for the Quality, Safety, and Efficacy Assurance of **Follow-on Biologics (Biosimilars)** (3)			
No.	The relevant part of the guideline Page (line)	Question (Q)	Answer (A)
3. General Principles for the Development of **Follow-on Biologics**			
1	The original biologic should be already approved in Japan and be the same product throughout the development period of the follow-on biologic (i.e., during the entire period from characterization of quality attributes through non-clinical and clinical studies.)	In case where there is a product approved in foreign countries (hereinafter "product with overseas approval") considered to be identical to the original biologic that has been approved also in Japan (hereinafter "product with Japanese approval"), is it acceptable to use the relevant product with overseas approval as the comparator in quality tests, non-clinical studies, and clinical studies which will be conducted both in Japan and overseas?	As a general rule, the product with Japanese approval should be used as the comparator. However, if it can be explained that the product with Japanese approval and the product with overseas approval are regarded identical on the basis of results of the comparative studies for quality attributes, it is acceptable to use the product with overseas approval as a comparator. In such a case, it is desirable to collect public information for each product related to the manufacturing facilities, etc. which will sometimes serve as a useful reference for the identity between the product with Japanese approval and the product with overseas approval.
	(Page 2, section 3, line 5)		
2	The quality attributes of the follow-on biologic of interest, the results of the comparative studies of relevant quality attributes between the follow-on biologic and the original biologic, and the findings of non-clinical studies should be considered to conduct clinical studies.	With respect to quality attributes, what kind of information should be provided and included in the attachment document for the initial clinical trial notification of the **follow-on biologic**?	In addition to the information described in the Question and Answer section 11 of "Revision of Questions and Answers (Q & A) on Clinical Trial Notification and Conducting Clinical Trial for Drugs" (PMDA Administrative Notice, December 14, 2015)[#], a summary of the results of the comparative study of quality attributes between the follow-on biologic and the comparator used in the study should be included. It is recommended to have a consultation with PMDA in related to the evaluation of comparability of quality attributes prior to submission of the initial clinical trial notification.
3		We would like to know the basic principles when obtaining data from Japanese subjects.	It is necessary to enroll Japanese subjects either in the clinical study to verify PK comparability with the original biologic or the clinical study to verify efficacy comparability (including PD) with the original biologic. Regarding the number of Japanese subjects in a global clinical study, Method

			1 and Method 2 described in "Basic Principles on Global Clinical Trials" (September 28, 2007, PFSB/ELD Notification No. 0928010) cannot be applied directly. It is necessary to design a study plan in which can be explained the absence of inconsistency between the results from the Japanese population and those from the entire study population.
	(Page 3, section 3, line 15)		
5 Evaluation Studies of the Comparability of Quality Attributes			
4	It is strongly recommended that a comparison of the bioactivities between an original biologic and a follow-on biologic be made using multiple methods as far as possible. For example, it is useful to compare the two biologics through bioassays of cell proliferation and differentiation, receptor-binding activity, enzyme activity and other *in vitro* bioactivity parameters that are closely related to clinical efficacy.	Please show us points in common to be considered relating to the comparison of bioactivity with the original biologic in the development of a **follow-on biologic** of a monoclonal antibody.	In general, it is required to compare antigen-binding activity, as well as neutralizing activity (e.g. suppressive activity of cytokine-enhanced cell proliferation in case where the antigen is the cytokine or its receptor that mediates to enhance cell proliferation), affinity to Fcγ receptor, binding affinity to embryonic Fc receptor and complement C1q, ADCC activity, and CDC activity, etc. using the original biologic and the follow-on biologic. The functional characteristic of the Fc region will provide useful information regarding similarity of high-order structure. Therefore, even if the original biologic has no functional characteristic of the Fc region, it is recommended to compare the functional characteristics of the Fc region for both the original biologic and the follow-on biologic.
	(Page 7, section 5 (ii), line 10)		
6. Specifications and Test Methods			
5	For the purpose of assuring product consistency, specifications and test procedures for follow-on biologics should be set based on the results of characterization or lot analysis.	Is it acceptable to use the original biologic as a reference standard for the development of a follow-on biologic?	There would be the case where to use the original biologic as a reference standard is considered to be inevitable at the early stage of development of the follow-on biologic. However, in general it is difficult to obtain all the information with respect to the quality attributes of the original biologic, and furthermore there is a limitation to control the quality of the original biologic at its own, even though it is destined as the reference standard. Therefore, it

			is necessary to establish an in-house reference standard as early as possible.
	(Page 8, section 6, line 1)		
7. 1. Toxicity studies			
6	In order to evaluate both single-dose and repeated-dose toxicity of follow-on biologics, repeated dose-toxicity studies in relevant animal species may be valuable. Since the active ingredient of a follow-on biologic is a protein, toxicokinetic studies may also be useful. In addition, both single-dose toxicity and local tolerance could be evaluated in repeated dose toxicity studies.	Is it acceptable to waive toxicity studies if no difference is observed between the original biologic and the follow-on biologic in quality and pharmacological studies?	In addition to obtaining the characteristics of the **follow-on biologic**, it is necessary to compare the follow-on biologic and the original biologic in quality and pharmacological studies. Toxicity studies will be waived, as the case may be, in the event that a high degree of comparability to the original biologic is shown by the above-mentioned comparative studies, and the absence of safety concerns through administration of the follow-on biologic in human subjects can be explained with sufficient evidence. This should be discussed through consultation for each case.
	(Page 9, section 7.1, line 1)		
8. 1. Pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD studies			
7	In addition, it is necessary to conduct a clinical study using the same route of administration as that in the approved indications of the original biologic. Where multiple routes of administration are allowed, in principle, each route of administration should be studied.	Please show any case where it is not necessary to examine the comparability of PK for all administration routes.	For example, if the original biologic has an approval to be administered through both intravenous and subcutaneous routes, and the elimination process can be evaluated through subcutaneous administration, it is acceptable to conduct only the study with subcutaneous administration.
	(Page 11, section 8.1, line 6)		
8	While key parameters of a PK study include the area under the blood concentration curve (AUC) and maximum concentration (Cmax), the acceptable range of data from the comparability exercise (comparability margin) should be determined before the study.	Please let us know points to be considered when setting the acceptable range of comparability in PK study.	It is necessary to set the acceptable range of comparability based on the characteristics of each product. However, if a 90% confidence interval of the difference of the mean value of the log of PK parameters between the original biologic and the **follow-on biologic** fall within a range of log (0.80) to log (1.25), it is generally acceptable to consider that the PK profile is comparable.
	(Page 11, section 8.1, line 10)		
8. 2. Comparison of clinical efficacy			

9	To evaluate the comparability of the efficacy of the follow-on biologic with that of the original biologic, comparative clinical studies should be appropriately designed and justified. Specifically, it is necessary to determine the necessary and adequate number of patients to be enrolled, and pre-specify the margins defining clinical comparability (comparability margin) using clinically established endpoints.	Please let us know points to be considered with respect to comparability evaluation.	The comparability margin is important not only from a statistical point of view, but also from medical standpoints with respect to the clinical significance. Such an information on the original biologic is considered to serve as a reference for this purpose. For the evaluation of comparability, it is necessary to apply the 95% confidence interval in principle, as stipulated in the document "Questions and Answers Regarding Statistical Principles for Clinical Studies" (November 30, 1998, Iyakushin Notification No. 1047).
10		Please let us know points to be considered when setting the study subject as well as the dosage and administration for the clinical study to verify the comparability of efficacy, if available.	As a general rule, a clinical study to verify the comparability of efficacy has to be conducted within the scope of the indication as well as dosage and administration that have been approved for the original biologic. It is recommended to select and set the study population in which the difference in efficacy between the **follow-on biologic** and the original biologic can easily be detected, if such a difference exists.
11		In case the comparability of efficacy has been verified in relation to the indications as well as the dosage and administration of the original biologic for which the re-examination period has not expired, is it acceptable to submit the results of the relevant clinical study for the purpose of registration approval for the indication as well as the dosage and administration for which the re-examination period has expired?	If the relevant clinical study results with regard to the indication as well as the dosage and administration are appropriate for verification of the comparability between the **follow-on biologic** and the original biologic, and it can be explained by the relevant results that the comparability of efficacy and the similarity of the safety profile between the **follow-on biologic** and the original biologic are assumed as well, it is possible to use and submit the relevant clinical study results for the registration approval (of the indication for which re-examination period has expired.). However, it should be noted that it is necessary to submit the application as a partial change for post-approval once the re-examination period of the original biologic expired, because it is not possible to endorse initial approval for the indication as well

			as the dosage and administration for which evaluation studies of the comparability were conducted.
	(Page 11, section 8.2, line 5)		
12	In the case of an original biologic with more than one indication, if the efficacy and pharmacological effects of the follow-on biologic have been demonstrated to be comparable to one of the indications of the original biologic and comparability of pharmacological effects on the other indications can be expected, then in certain case, it may be possible to extrapolate from one approved indication to the other approved indications of the original biologic used as the reference product. The extrapolation of indications is limited to the indications of the reference original biologic and does not include the indications of other approved recombinant protein products with similar indications. However, where each relevant indication has a different mechanism of action or the mechanism of each indication remains unclear, the comparability of efficacy with the original biologic should be demonstrated for each indication, without extrapolation.	In case of monoclonal antibody drug products, all indications attribute to a common mechanism of action with binding to antigen. Therefore, if the efficacy of a follow-on biologic is comparable to that of the original biologic with regard to a certain indication, is it possible to extrapolate it for other indications without conducting a clinical study?	Since monoclonal antibody drug products have other various activities such as ADCC activity, CDC activity, apoptosis-inducing activity, etc. than neutralizing activity against antigen, it is necessary to clarify which activity contributes to the efficacy for each indication of the relevant monoclonal antibody drug. Having that said, the approval for other indications may be obtained without necessarily conducting a clinical study for each indication only when a high level of comparability between the original biologic and follow-on biologic is verified by comprehensive examinations of the structure, physicochemical and biological properties in quality tests and non-clinical studies, and it can be explained that the comparability in efficacy and safety, with respect to the indications for which clinical studies were not conducted, is highly predictive on the basis of information on the original biologic and the existing clinical study results.
	(Page 11, section 8.2, line 12)		
9. Post-marketing Surveillance			
13	The data obtained from the post-marketing surveillance should be reported to the regulatory authorities at an appropriate time after the approval of follow-on biologics.	Is it acceptable to report the results of the post-marketing surveillance only after the completion of the surveillance?	It is requested to submit report according to the schedule predefined in the protocol of the post-marketing surveillance. Since only limited information is available at the time of approval and it is required to develop a risk-management plan for a **follow-on biologic**, the marketing authorization holder is given instructions upon approval to submit periodic reports during

			the post-marketing surveillance so that the obtained data can be communicated without delay.
	(Page 12, section 9, line 6)		

In that document, it is described the following information are to be provided at the time of notification. 1)Flow chart of manufacturing process of investigational drugs 2) information as to whether cell banks are not contaminated with infectious organisms (virus, bacteria, and so on). 3) information as to whether harvested culture media before purification has not contaminated with pathogens such as bacteria, virus, etc.4) compatibility to the standards of bio-originated materials, in case of human or animal origin. 5) safety of investigational drugs in terms of viral contamination. 6) tentative test standards for safety in relation to, but not limited to endotoxin test, etc.

Important notes:

1. In this document, the term “follow-on biologic” stands for “biosimilar product”.
2. In this document, “comparability” does not signify that the quality attributes of a follow-on biologic are identical to those of the original biologic, but it means that they are highly similar and that existing knowledge is significantly predictive to ensure that any differences in quality attributes have no adverse impact on the drug product or on its safety or efficacy.