Questions and Answers (Q & A) regarding the Guideline for the Quality, Safety, and Efficacy Assurance of **Follow-on Biologics (Biosimilars)** (2)

No.	The relevant part of the guideline Page (line)	Question (Q)	Answer (A)
1. Introduction			
1	It is expected that an application for a follow-on biologic will be able to be submitted after the expiry of the re-examination period of the original biologic.	With respect to the indication that was not included in an initial application of the follow-on biologic because the re-examination period of the original biologic has not finished, should an application for the additional indication after completion of the re-examination period be submitted as “1-(4) Drug with new indication”? *Note: 1-(4) is the category as ‘Drug with new indication’ defined in the classification of pharmaceutical regulations.	Application for the additional indication should be submitted as “1-(7) Follow-on biologic.” **Note: 1-(7) is the category as ‘Follow-on biologic’ defined in the classification of pharmaceutical regulations.
	(Page 1, section 1, line 19)		
3. General Principles for the Development of **Follow-on Biologics**			
2	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.)	What is the definition of “the same product” here?	There could be the case where multiple products with the same generic name, but have different approvals (for example, different indication, etc.). Therefore, “the same product” mentioned here means the product which has obtained the same approval (the same approved labeling). In such a case where “the same product” is marketed by several companies under different brand names, either product of any of these companies may be selected and used.
		For example, if there is a change in the manufacturing method or drug formulation of the original biologic during the development of the **follow-on biologic**, can an original biologic be still regarded as	

		"the same product" as far as their generic name is the same?	Even if the manufacturing method of the original biologic is changed during the development period of the follow-on biologic, the follow-on biologic can be developed and applied for approval on the basis of its comparability to the original biologic which has been manufactured using the pre-change method. However, if possible, it is necessary to make it clear whether the original biologic, which was used in the evaluation of the comparability of the **follow-on biologic**, was manufactured by the pre-change method or the post-change method.
	(Page 2, section 3, line 5)		
3	The comparability of the follow-on biologic to the original biologic as a reference will be evaluated based on the combined data from physicochemical tests, bioactivity tests and non-clinical/clinical studies, as appropriate.	Please show us details on the criteria or an acceptance range in related to the comparability evaluation of the **follow-on biologic**, if available. In addition, please let us know the appropriate timing to discuss/agree with the regulatory authorities with respect to the setting of an acceptance range.	We think that it is inappropriate to set a fixed criteria or acceptance range for the comparability evaluation of a **follow-on biologic**. Because the standard and acceptance range may vary depending on the characteristics of the product. The appropriateness of the acceptance range for each product should be discussed during a consultation, etc.
	(Page 2, section 3, line 10)		
4.1. Development of the Manufacturing Process			
4	(For host cells and vector system,) it is desirable that the cell bank system be established using the same host cells.	It is described in the guideline that "for host cells and the vector system, it is desirable that the cell bank system be established using the same host cells.". However, it will be	As described in the section of "4.1 Development of the Manufacturing Process", there are cases where it may be more appropriate to seek manufacturing methods

		beneficial for patients to provide drug products which are manufactured based on the latest scientific knowledge and technologies with the use of different host cells from those for the original biologic and hereby have improved safety profiles. Therefore, the development of a follow-on biologic using the same host cells with the original biologic is not always considered to be appropriate. Please show us guidance or basic thoughts on changing host cells, if available.	which will enable safer product profile. If it is concluded that adapting different host cells is appropriate in terms of safety, it will be preferable to use different host cells as far as the change of host cells does not have an impact on the efficacy. In such a case, it is necessary to keep in mind that there is a possibility that not only the profile of process-related impurities, but also the heterogeneity of the objective substance will be different from those of the original biologic. The regulatory authorities will discuss this separately for each case.
	(Page 4, section 4.1 Host cells and vector system, line 2)		
4.2. Characterization (structural analysis, physicochemical properties, bioactivity, etc.)			
5	It will be very difficult to demonstrate that the impurity profile of a follow-on biologic is similar to that of the original biologic.	It is described that “It will be very difficult to demonstrate that the impurity profile of a **follow-on biologic** is similar to that of the original biologic.”. In such a case, is it acceptable that the specifications of a follow-on biologic are different from those of the original biologic?	Usually it is impossible to obtain the information with regard to the specifications of the original biologic. The specifications for a **follow-on biologic** must be defined on the basis of the results from analysis of quality attributes obtained through its own manufacturing process and lot analysis. Therefore, it is not necessary that the specifications of product-related impurities of a follow-on biologic are identical to those of the original biologic. However, with respect to the impurities identical to those of the original biologic

			according to the existing knowledge, it is desirable for the level of impurities to be same with or lower than that of the original biologic. In case where the original biologic is listed in an official compendium such as the Japanese Pharmacopoeia and the specifications of product-related impurities have been already set, this point will be addressed in future discussion.
	(Page 5, section 4.2, line 6)		
4.3. Drug formulation			
6	As long as there is no adverse effect on efficacy and safety, it is not necessary for the formulation of the follow-on biologic to be the same as that of the original biologic.	We would like to make sure whether the concentration of the active ingredient of the follow-on biologic does not have to be identical to that of the original biologic.	It is desirable that the concentration of the active ingredient of the follow-on biologic is identical to that of the original biologic. However, the concentration of the active ingredient of the follow-on biologic does not have to be identical to that of the original biologic, if it is possible to administer the follow-on biologic by which it will achieve the same level of biological activity or protein amount as that obtained by the approved dosage and administration of the original biologic.
	(Page 6, section 4.3, line 2)		
4.4. Stability testing			
7	Since identical storage conditions and storage period to the original biologics are not a prerequisite for follow-on biologics, a comparability exercise versus the original biologics will not necessarily be required in this regard.	Is it acceptable to develop the follow-on biologic that has a shorter shelf life than that of the original biologic due to the difference in the excipients, in case where the stability profiles between the original biologic and the	Although it is not required that the shelf life of the **follow-on biologic** has to be identical to that of the original biologic, a significant difference in the shelf life among biologic products may cause confusion in clinical practice. Therefore, it

		follow-on biologic are different? If the stability of the follow-on biologics has improved, is it granted to set a longer shelf life for the follow-on biologic than that for the original biologic?	is recommended to have an individual consultation with the regulatory authorities. On the other hand, it is acceptable to set a longer shelf life for the **follow-on biologic** than that for the original biologic, if the shelf life is determined on the basis of the data obtained under actual storage conditions.
	(Page 6, section 4.4, line 3)		
5.	Evaluation Studies of the Comparability of Quality Attributes		
8	The impact of observed differences in the quality attributes for the follow-on biologic and the original biologic should be assessed (using several lots of products, if possible), and then non-clinical/clinical studies should be designed and conducted on the basis of the assessment results.	Regarding the description on “using several lots of products, if possible,” is it also required that the original biologic be extracted from several lots of drug product and be evaluated? In such a case, should it be taken into account the possibility that several lots of drug product may be derived from an identical lot of drug substance?	There are some cases where it is desirable to use several lots of the original biologic considering the characteristics of the relevant **follow-on biologic**. Since it is difficult to identify whether several lots of drug product of the original biologic are derived from an identical lot of drug substance, it is acceptable to use several lots of drug product.
	(Page 6, section 5, line 6)		
9	When the sponsor plans to compare the quality attributes of a follow-on biologic with those of the original biologic, it is likely to be difficult to obtain the drug substance of the original biologic. Therefore, it is also envisaged that the comparability exercise versus an original biologic will be conducted using the drug product itself or the desired protein extracted from the product.	What are points to be considered in case where the drug substance is extracted from drug product of the original biologic and comparative studies are conducted using extracted samples?	It is needed to assess and confirm whether the applied extraction and purification methods reflect adequately the quality attributes of the original biologic. It is necessary for the applicant to have innovative ideas in this regard. For instance, it is conceivable to formulate the drug substance of the follow-on biologic by the same method with that for the original biologic, apply the extraction/purification methods developed, and then examine whether these methods are appropriate or

			not. However, we are not requesting the applicant to implement this approach.
	(Page 6, section 5, line 13)		
10	Where there are some variations in the specific activity, their acceptability should be evaluated, and the use of the same dose as in the original biologic must be justified.	There will be some cases where the specific activity is different between the follow-on biologic and the original biologic. In such a case, is the **follow-on biologic** approved if the dosage as titer unit is identical to that of the original biologic?	In case of glycoprotein, the specific activity can vary due to the difference in the sugar chain moiety. Although it depends on the degree of variation, the **follow-on biologic** with different specific activity can be approved when it is confirmed and concluded that the variation does not have an adverse impact on the efficacy and safety by appropriate non-clinical and clinical studies.
	(Page 8, section 5 (ii), line 3)		
6.	Specifications and Test Methods		
11	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 change the biological analysis method used for the original biologic to another method with higher accuracy of measurements?	This is acceptable, if the correlation between the new method and the existing method is confirmed and the appropriateness of the new method is verified.
	(Page 8, section 6, line 1)		
12	In addition, where the original biologic is listed in an official compendium such as the Japanese Pharmacopoeia, the specifications and the test procedures for the follow-on biologic should be set in accordance with the specifications and test procedures specified in the pharmacopeia.	If an original biologic is listed in the Japanese Pharmacopoeia, will a **follow-on biologic** also be listed in an official compendium? If yes, is it not necessary to validate the test method described in the official compendium for the original biologic?	Generally speaking, a follow-on biologic is considered to be the listed drug. However, we would like to make this a subject of future discussion, and encourage the applicant to consult the regulatory authorities. Since the test methods listed in the Japanese Pharmacopoeia have been already validated, further validation is not necessary. If there is a difference in

			impurities, and specification tests may be different, it is required to newly assess test methods including validation.
	(Page 8, section 6, line 9)		
7.1. Toxicity studies			
13	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.	Is the administration period for a repeated-dose toxicity study determined on the base of the period which depends on the clinical administration period in the same case like other biological drugs?	The administration period for a repeated-dose toxicity study can be determined in accordance with the guideline, by taking the clinical administration period and the target disease into consideration on the basis of the results from non-clinical studies of the original biologic.
	(Page 9, section 7.1, line1)		
8.2. Comparison of clinical efficacy			
14	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.	We would like to confirm that pre-specifying the margins for clinical comparability (comparability margin) does not mean to prove the non-inferiority or set the non-inferiority margins.	Since the purpose of pre-specifying acceptable ranges is to confirm the comparability, we are not requesting to prove the non-inferiority.
	(Page 11, section 8.2, line 7)		
15	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	Is it possible to extrapolate the other indications of the original biologic to the **follow-on biologic**, if the dosage/administration and administration period for each indication of the original biologic are different, but are exerted through the identical mechanism of action?	If it can be explained that similar effects on pharmacodynamics are expected, there would be the case where the extrapolation may be possible. However, if the dosage and administration as well as administration period are significantly different, and a different mechanism of action is envisaged, it is not appropriate to extrapolate other indications of the original to follow-on biologics.

	other approved indications of the original biologic used as the reference product.		Additional clinical studies would be required.
		On the contrary, is it acceptable the situation where a **follow-on biologic** will not obtain approval for some of the indications of the original biologic even after their re-examination period and patent expiration?	As a general rule, a follow-on biologic should obtain approval for all indications of the original biologic, of which the re-examination period has finished.
	(Page 11, section 8.2, line 12)		
8.3. Evaluation of clinical safety			
16	Repeat dose studies on the follow-on biologic should be considered in the case of chronic administration.	With regard to the simple protein (peptide) such as insulin, there would be the case where the comparability can be shown and confirmed by quality tests, a non-clinical study and a PK/PD study. In such a case, is it possible to omit the comparative clinical study for safety, even if it is highly likely that the insulin will be used in clinical practice for chronic administration?	If the comparability of efficacy has been demonstrated even for the **follow-on biologic** clinically used for chronic administration, the uncontrolled study on safety aspects including antibody formation may be examined instead of a comparative study. As the case may be, it will be requested to obtain safety data during post-marketing surveillance.
		We would like to know your opinions on the administration period of a repeated-dose study for a drug used for chronic administration.	We think that the administration period of a repeated-dose study should be set in order to verify the safety profiles. Therefore, it is not appropriate to set up a fixed period as study duration applied to all studies. It will be also possible to set an appropriate study duration for such as an antibody production based on the public information. This point should be discussed for each case through a consultation.
	(Page 12, section 8.3, line 9)		

9. Post-marketing Surveillance			
17	The specific method and design of the post-marketing surveillance study and risk management plan should be discussed with the regulatory authorities and included in the application submitted for approval.	Is it required to submit a detailed plan for post-marketing surveillance at the time of application for new approval?	At the time of submission of the application for approval, a specific plan of post-marketing surveillance based on the available data should be provided. However, it is acceptable to re-examine the issues afterwards and re-evaluate the plan of post-marketing surveillance during the application process.
	(Page 12, section 9, line 5)		

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.