Questions and Answers (Q&A) regarding the Guideline for the Quality, Safety, and Efficacy Assurance of **Follow-on Biologics (Biosimilars)** (1)			
No.	The relevant part of the guideline	Question (Q)	Answer (A)
1. Introduction			
1	A “follow-on” biologic is a biotechnological drug product developed to be comparable in regard to quality, safety and efficacy to an already approved biotechnology-derived product (hereinafter “original biologic”) of a different company.	Is a biologic product granted as an original biologic only for the biologic with a new active ingredient? For example, if the registration of the original biologic is withdrawn in future, is there a possibility that the follow-on biologic with sufficient experiences of clinical use can be granted as the original biologic?	As far as there exist biologics approved as drug products with new active ingredients, these drug products shall be selected as the original biologic among the relevant drug products. However, it may happen in future that the biologic product approved as the drug product with a new active ingredient will not be on the market due to the withdrawal of registration. In such case, there is a possibility that a **follow-on biologic** with enough experiences of clinical use would be considered as the original biologic. We would like to make this subject to future discussion.
2	A follow-on biologic can generally be developed on the basis of data that demonstrate the comparability with the original biologic with respect to quality, safety and efficacy, or other relevant data.	It is described that other relevant data can be used. Does this mean that public information and other information can be used for the purpose of comparability evaluation?	Other relevant data include public information as well. However, public information is much rather regarded as references than materials to be evaluated. Although a comparative study for some characteristic such as the primary structure is not necessary, it is of use to conduct a comparative study for other characteristics such as heterogeneity, on which it is generally difficult to compare with public information.
3	Since manufacturing processes, analytical techniques or evaluation	Considering the recent remarkable advance in science and technology with related to	It is also requested for the original biologic to incorporate new technologies through

	techniques relating to the target biotechnology-derived drug may be advanced quickly in this intervening time, data accumulated during this period and state-of-art scientific technologies should be fully incorporated into the development of the follow-on biologic. In addition, the latest available safety data should be fully taken into account.	biotechnology-derived drugs, should we include the newest analytical techniques, which were not available at the time of development of the original biologic, when conducting the characteristic analysis of a **follow-on biologic** and the comparability study with the original biologic? Is there a case where it is appropriate to apply the safer process of manufacturing by using a serum-free culture method, etc., even if there is a possibility that the difference in quality attributes between the follow- on biologic and the original biologic may come out?	scientific progress. In fact, we request the originator not only to meet regulatory requirements at the time of approval, but also incorporate the latest analytical techniques at the time when the original biologic is re-evaluated or listed in the pharmacopoeia. The same approach should be taken in the development of **follow-on biologic**. It is desirable to select safer manufacturing processes in the development of a **follow-on biologic**. However, it must be fully evaluated whether the introduction of a new manufacturing process has made no adverse impact on the efficacy and safety of the product.
3. General principles for the development of **follow-on biologics**			
4	Scope	Is it acceptable to refer to the "Guideline for the Quality, Safety and Efficacy Assurance of **Follow-on Biologics**" also when developing a drug product with chemically synthesized active ingredient identical to that of the already approved original biologic manufactured using recombinant DNA technology?	Although this subject should be discussed and judged on a case-by-case basis depending on the characteristic of the product, you can turn to this guideline as a reference in general.
5	In addition, a high degree of similarity of the quality attributes with the original biologic should be demonstrated.	We would like to know in which part of the CTD should be described the data demonstrating comparability of quality attributes with the original biologic.	It is desirable to describe the results of comparability studies of quality attributes in CTD2-3-R part (documents which are regionally required).
4.1. Development of the manufacturing process			
6	Host cell and vector system. To establish cell bank systems for the manufacture of follow-on biologics, where the host	It is described in the guideline that "…it is desirable to establish a cell bank system using the same host cells.".	For example, if CHO cells are used for production of the original product, "the same host cells" shall mean CHO

	cell of the original biologic has been disclosed, it is desirable that the cell bank system be established using the same host cells.	What level of identity is required as “the same host cell”? And what is an intention by the word “desirable”?	cells. But we are not requesting the conformity of subspecies. On the other hand, even if CHO cells are used for production of an original biologic, there would be possible to change the host cells from CHO to human cells from the standpoint of immunogenicity, etc. However, the usage of different type of host cells may cause substantial changes in the post-translational modification, which shall be taken into consideration in order to assess the appropriateness of the drug product. Therefore, we used the word “desirable”.
7	Host cell and vector system: If a different type of host cell is used for manufacturing, quality attributes and safety concerns should be evaluated more thoroughly than a case where the same cell is used, focusing on the differences in the profile of process-related impurities including host-derived impurities, and then the relevant data should be submitted.	Regarding the description on “If a different type of host cell is used for manufacturing, quality attributes and safety concerns should be evaluated more thoroughly than a case where the same cell is used, focusing on the differences in the profile of process-related impurities including host-derived impurities, and then the relevant data should be submitted.”, would you explain the definition of “a different type of host cell” by showing an example?	“A different type of host cell” means ‘a cell line from different origin’. For example, a **follow-on biologic** is manufactured using CHO cells, while the original biologic is manufactured using NS0 cells.
8	Cell culture and purification process. This does not mean the need to conduct a full safety study on impurities, but that it is required to evaluate the impurities as part of the product characterization, and establish necessary and	Regarding the description on “to evaluate the impurities as part of the product characterization, and establish necessary and rational in-process controls, and specifications and test procedures in light of the elimination of impurities during	The description, “in light of the accumulated experience and information” means that you may use data of other products as reference with respect to the safety of process-related impurities, if there is an experience of having manufactured products with

	rational in-process controls, and specifications and test procedures in light of the elimination of impurities during the purification processes and the accumulated experience and information about the relevant impurities, thereby securing safety.	the purification processes and the accumulated experience and information about the relevant impurities", would you explain this by showing an example?	the identical host cell and culture process.
4.3. Drug formulation			
9	In principle, the dosage form and administration route of a follow-on biologic should be the same as those of the original biologic.	Is it not allowed to develop a follow-on biologic in a clinically more convenient dosage form?	If deemed appropriate, the dosage form of a follow-on biologic can be different from that of the original biologic (for example, it can be changed from a freeze-dried formulation to a liquid formulation).
10	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.	Is it acceptable to develop a new formulation without using the excipients of biological origin in view of the safety?	It is also possible to use excipients with much safer profile (e.g. there is an alternative to consider a substitute to human serum albumin.).
4.4. Stability testing			
11	It is suggested that stability testing be conducted on the drug substance and drug product under accelerated and stress conditions.	Is it possible to use the data obtained from comparative stress and accelerated tests between the original biologic and the follow-on biologic as the data showing the similarity of changes such as degradation?	It may be possible to conduct comparative stress/accelerated tests between the original biologic and the follow-on biologic besides separate long-term stability studies, and to use the data obtained for the purpose of comparison of quality attributes (It may depend on the development strategy of the applicant how to translate and incorporate obtained data into the documents.).
5. Evaluation studies of the comparability of quality attributes			
5. (ii) Comparative studies of bioactivity			
12	In comparisons of bioactivity, it is desirable that bioactivity be calibrated against international	Should the comparative studies for bioactivity using the reference standard be conducted as well?	It is not always necessary to include studies using the reference standard in the

	or national reference standards, where available.		comparative studies for bioactivity. However, since the reference standards are used for the quantification of bioactivity for many biologics, the reference standards are often required to obtain quantitative values. In addition, when bioactivity is calibrated using a reference standard, the comparison with public information will be possible. Therefore, it is desirable to obtain bioactivity values that are calibrated using the reference standard in the studies.
13		Besides using the reference standard for calibration of bioactivity, is it possible to use the reference standard to obtain the data for the comparison of structure?	As described in the glossary of this guideline, the standards should not be used for other than the intended purposes. Meaningful data cannot be obtained when a commercially available reference standard reagents is used for a potency assay in order to compare the physicochemical characteristics.
14	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.	There seems to be some overlap between comparative bioactivity studies for the characteristic analysis and pharmacological studies.	Comparative studies of bioactivity are important for the evaluation of comparability. In addition, the effect of sugar chains and their heterogeneity should be also compared and evaluated. Therefore, it is desirable to include the data of comparative studies of bioactivity in the quality attributes section of dossier, even though they may overlap with the data of pharmacological studies.

5. (iii) Comparative studies of immunogenicity etc.			
15	Studies on immunological responses in animals may provide useful data for evaluating quality attributes including impurities.	Regarding the description on “Studies on immunological responses in animals may provide useful data for evaluating quality attributes including impurities.”, how do you differentiate “immunological responses” from ‘immunogenicity’? And what kind of “useful data” may be provided?	The purpose of studies on immunological responses is not to predict immunogenicity in humans, but to examine the immunological responses in animals as a part of the evaluation of quality attributes. For example, it may be possible to compare the antibody production induced by aggregates present in the product by using transgenic animals that have been prepared by introducing the gene of the relevant protein and do not recognize the relevant protein as foreign antigen. As the case may be, it would be possible to evaluate the difference in the impurities based on the difference in the time-course changes of antibody production in studies with normal animals.
7. Non-clinical studies			
16	Non-clinical studies	Should the drug product be used in non-clinical studies?	Although the non-clinical study is conducted with the drug product in principle, it will be possible to use other formulations than the drug product when conducting studies with a high dose or at the early stage of development.
7.2. Pharmacological studies			
17	Where *in vitro* bioactivity does not correlate well with clinical efficacy as in some types of glycoprotein, it will be necessary to evaluate the comparability of therapeutic efficacy and pharmacodynamics with the	Please show us an example of a case where *in vivo* pharmacological studies are necessary.	For example, as the case of Epoetin, an increase in the amount of sialic acid leads to a potentiation of *in vivo* pharmacological activity due to the longer half-life in blood. On the other hand, it is known that a decrease in receptor binding ability is observed in *in vitro*

	original biologic through *in vivo* pharmacological studies.		studies instead. In such a case, comparability evaluation by *in vivo* pharmacological studies are considered necessary.
8. Clinical studies			
18	Where pharmacokinetic (PK) and pharmacodynamic (PD) or PK/PD studies are sufficient to assure comparability in the clinical endpoint of interest, the afore-mentioned, additional clinical studies to evaluate efficacy might be omitted.	Regarding the description on "Where pharmacokinetic (PK) and pharmacodynamic (PD) or PK/PD studies are sufficient to assure comparability in the clinical endpoint of interest, the afore-mentioned, additional clinical studies to evaluate efficacy might be omitted.", does this mean that safety studies may also be omitted in some cases?	The description in the guideline solely indicates the possibility on assured comparability of efficacy, but it does not refer to the safety. Safety evaluation should be discussed separately.
8.1. Pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD studies			
19	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. In this case, the margin of the acceptable range set should be fully justified.	Please show us the actual acceptance range of PK parameters in clinical PK studies?	Since the acceptance range of each biologic product is considered to vary among products, it is difficult to show a certain acceptance range as for a chemically synthesized drug product. It is necessary to fully understand the characteristics of the **follow-on biologic** to be developed, and set a proper acceptance range of each biologic product. In such a case, it is required to show an adequate explanation using supportive data and literatures.
8.2. Comparison of clinical efficacy			
20	Where appropriate surrogate endpoints are available, the use of primary endpoints will not always be required. However, the choice of surrogate endpoints should be thoroughly justified on the	Please show us the example of surrogate endpoints in the studies for comparison of clinical efficacy.	For example, an increase in hemoglobin concentration can be used as a surrogate endpoint for erythropoiesis-stimulating agents (ESA).

	basis of supportive data or literature, etc.		
21	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.	Is it possible to submit the application for an additional indication when a separate clinical study is conducted regarding new indications or indication that have not been approved for the original biologic, but approved for other already approved biologics?	Regarding indications that were not included in the label of the original biologic, an application for a new indication is possible if a separate clinical study has been conducted.
8.3. Confirmation of clinical safety			
22	If necessary, clinical studies to evaluate safety, including an immunogenicity study should be considered.	Regarding the description on “including an immunogenicity study”, why is an immunogenicity study specified in the evaluation of clinical safety?	Immunogenicity is specified here as an item with a high importance of evaluation, because immunogenicity is a known safety factor of concern for some biologics. Therefore, the information regarding immunogenicity should be collected from an early stage of the clinical study. And, even for the original biologics, it is very difficult to address safety issues with a low frequency solely based on the information obtained from registration clinical studies. Therefore, the continuous monitoring of clinical safety parameters including immunogenicity is necessary during post-marketing surveillance.

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.