Provisional Translation (as of April 19, 2013)[*]

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March 4, 2009

To: Prefectural Health Department (Bureau)

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

Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics

Unlike for chemically synthesized drugs, it is difficult to demonstrate that a biotechnological product is comparable with another product that has already been approved.

On the other hand, with the advances of manufacturing processes and analytical techniques, the development of follow-on biologics, which are claimed to be comparable to already approved biotechnological products, is ongoing in several foreign countries.

Taking the technological advances into account, the requirements for follow-on biologics have been discussed in the research project funded by the Health and Labour Sciences Research Grants: “Research on Evaluation of Quality, Efficacy, and Safety of Follow-on Biologics” (led by Dr. Toru Kawanishi, Principal Investigator, who is Director for Division of Drugs, National Institute of Health Sciences).

The current understanding based on the results of the above-mentioned research is outlined in the “Guideline for the Quality, Safety and Efficacy Assurance of Follow-on Biologics” (hereinafter referred to the “Guideline”), which is attached to this Notification. Please ensure the relevant organizations under your jurisdiction are thoroughly informed of the Guideline, along with the information provided below.

1. Scope

   For the submission of applications for drugs defined in Section 2.(7) of Part I of the Notification from the Pharmaceutical and Food Safety Bureau, MHLW (PFSB Notification

[*] This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

No. 0304004 dated March 4, 2009) (hereafter referred to as “follow-on biologics”), applicants should generate and collect data for submission in accordance with this Guideline.

2. Effective Date

The Guideline comes into effect as of March 4, 2009 and is applicable to applications (for follow-on biologics) that are submitted on this date or later.

As for biological products for which applications have already been submitted and are classified as follow-on biologics, the applicability of the Guideline is to be determined on a case-by-case basis.

3. Others

(1) The provisions of Article 7, Paragraph 1, Item 1, Sub-item *I*-1 and Article 17, Paragraph 1, Item 1, Sub-item *I*-1 of the Order for User Fees Provided for in the Pharmaceutical Affairs Act (Cabinet Order No. 91 of 2005) are to apply to the user fees for reviews.

(2) Review results for follow-on biologics are to be reported to the Drug Committees of the Pharmaceutical Affairs and Food Sanitation Council.

[Attachment]

"Guideline for the Quality, Safety and Efficacy Assurance of Follow-on Biologics[†]"

1. Introduction

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. 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.

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 sufficiently predictive to ensure that any differences in quality attributes have no adverse impact on the drug product or on its safety or efficacy.

Biotechnology-derived products generally have unique characteristics such as their structural complexity (e.g., proteins are composed of several functional domains), specific bioactivity, and quality attributes including stability and immunogenicity. For this reason, it is much more difficult to prove that the active ingredient of a follow-on biologic is identical to that of the original biologic as a reference product, unlike the case of a small molecule, chemically synthesized drug. Therefore, the generic approach used for small molecule, chemically synthesized drugs cannot be applied to follow-on biologics. To evaluate follow-on biologics, a new guideline which is different from that for generic drugs is required. In addition, applications for marketing approval should be submitted under a new application category (Application Category 1-(7) for follow-on biologics) to be established separately from that for generic drugs (see footnote [*]).

This guideline addresses the requirements and recommendations for the development of

[†] “Follow-on Biologics” in this guideline is a synonym for “Biosimilars.”

[*] The term “follow-on biologics” applies neither to "cell culture-derived products produced with a different cell seed than the approved cell culture-derived products" given in the PAB/ERD-1 Notification No. 10 dated June 6, 1988 nor to “recombinant protein products produced with a different host cell/vector than the approved recombinant protein products” given in the PAB/ERD Notification No. 243 dated March 30, 1984. A new application category is established separately from that for generic drugs.

follow-on biologics falling into the new application category and clarifies the data to be submitted in applications for the approval of those biologics.

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. Therefore, by the time the development of a follow-on biologic is commenced by a manufacturer after the development and approval of the original biologic, a certain amount of manufacturing, marketing, and clinical experience will have been accumulated. Since manufacturing processes, analytical techniques or evaluation 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.

2. Scope

This guideline covers recombinant proteins and polypeptide products (including simple protein and glycoprotein products), their derivatives, and products of which they are components, e.g., conjugates. Such proteins and polypeptides are produced from recombinant expression systems using microorganisms or cultured cells and can be highly purified and well-characterized using an appropriate set of analytical procedures.

The principles described in this document might also apply to other product types, such as highly purified and well-characterized proteins and polypeptides which are produced from nonrecombinant cultured cells or isolated from tissues and body fluids. Manufacturers are encouraged to consult with the appropriate regulatory authority to determine the applicability of the guideline on a product by product basis.

This guideline is not applicable to antibiotics, synthetic peptides/polypeptides, polysaccharides, vitamins, metabolic products of cells, nucleic acid products, allergen extracts, conventional vaccines based on antigens such as attenuated or inactivated pathogenic microorganisms and extracts, cells or whole blood/cellular blood components (blood cell components).

3. General Principles for the Development of Follow-on Biologics

For the development of a follow-on biologic, the manufacturing process should be established independently of that of the original biologic, and the quality attributes of the follow-on biologic should be thoroughly characterized, as in the case of new recombinant protein products. In addition, a high degree of similarity of the quality attributes with the original biologic should be demonstrated. As a general rule, comparability with the original biologic should be demonstrated through both non-clinical and clinical studies. Furthermore, 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.)

To evaluate the comparability of a follow-on biologic with the original product, comparability studies should be properly conducted according to the concept described in the ICH Q5E Guideline: “Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process”. Specifically, the comparability of the follow-on biologic to the original biologic as a reference will be evaluated based on the data from a combination of physicochemical tests, bioactivity tests and non-clinical/clinical studies, as appropriate.

The purpose of evaluating the comparability of a follow-on biologic with an original biologic is to demonstrate that their quality attributes are highly similar, and that any differences in the quality attributes of the two biologic products have no adverse impact upon safety or efficacy. If the drug substance of the original biologic is obtainable, the comparability studies should be conducted using the drug substance. However, since it is often difficult to obtain the drug substance of the original biologic, in such cases the sponsor can perform the study using the drug product, if applicable.

Although there may be limitations to current scientific techniques, or limitations to evaluating the comparability in quality attributes for the follow-on biologic in light of the data obtained from the studies using the drug product, data obtained from analyses performed with scientifically validated analytical procedures should be submitted. However, depending on the nature of the product, scientific literature or other public information may also be partially referred to for the comparability exercise in the study of quality attributes.

The requirements and scope for non-clinical and clinical study data to submit for a follow-on biologic depend on the extent to which comparability with the original

biologic has been established by scientific and rational evaluation of the quality attributes.

Non-clinical studies should be conducted after thorough characterization of the follow-on biologic. Also, it is required to design the non-clinical studies rationally and appropriately with reference to the results of the characterization of the quality attributes of the follow-on biologic per se and of the comparability exercise in comparison with the quality attributes of the original biologic.

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. In addition, it is required to design such a clinical study that is necessary and appropriate to evaluate the comparability of the follow-on biologic with the original biologics in terms of efficacy and safety, taking into account comprehensive information including literature on the original biologic.

4. Manufacturing Process and Quality Characterization of Follow-on Biologics

To develop a follow-on biologic, a highly consistent and robust manufacturing process should be established. As in new recombinant protein products, the quality attributes of the follow-on biologic under development should be fully characterized and the thus obtained data should be submitted. The manufacturing process should be suitably optimized based not only on the characteristics of the active ingredient(s) of the follow-on biologic but also the comparison of the relevant quality attributes with those of the original biologic. In addition, appropriate specifications and test methods as well as process controls should be established.

In addition, if any change is made to the manufacturing process during the development of the follow-on biologic, the comparability of the pre- and post-change products should also be evaluated in accordance with the ICH Q5E Guideline, as appropriate.

4.1 Development of the Manufacturing Process

It is envisaged that a comprehensive analysis of the original biologic including its formulation would be performed for the development of a follow-on biologic. In

practice, however, it will be difficult for a competing company to obtain data about the manufacturing process for an original biologic developed by another company (i.e., the innovator company), or even to obtain the drug substance itself.

In addition, in many cases the analysis of an original biologics product will only provide limited data on its manufacturing process. For example, although package inserts etc. may provide information such as whether serum or other components from animals have been used during the establishment of the cell bank system or culture process, or whether an affinity chromatography conjugated with specific antibodies, etc., has been used in the purification process of the active ingredient, such information is insufficient to fully understand the manufacturing process for the original biologic. Therefore, in the development of the follow-on biologic, an independent manufacturing process with assured consistency and robustness should be developed and established. The comparability of the follow-on biologic to the original biologic should be evaluated taking into full consideration such differences in the manufacturing processes for each product.

Since the follow-on biologic will be developed after a certain period of time from the approval of the original biologic, it is encouraged that the development of a manufacturing process for the follow-on biologic actively incorporates the safety measures based on the most up-to-date information, if applicable. This means that the most updated safety measures, etc. should be adopted for the development of the follow-on biologic, insofar as they have no adverse impact on efficacy. Therefore, in some cases it may be more appropriate to make manufacturing processes safer, such as by using serum-free culture media.

Host cells and vector system

To establish cell bank systems for the manufacture of follow-on biologics, where the host cell of the original biologic has been disclosed, it is desirable that the cell bank system be established using the same host cells. 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.

Since many glycoprotein products have significant heterogeneity at each glycosylation site, it is often difficult to demonstrate comparability based on the structural analysis alone. In addition, even if glycoprotein products are produced using the same host cell, the heterogeneity of glycosylation in each product is known to be significantly different due to various factors such as the insertion site of the gene expression construct or the culture conditions. In the case of a follow-on biologic for which glycosylation is highly heterogeneous, the development of an identical manufacturing process to ensure the high similarity in the carbohydrate structure between the follow-on biologic and the original biologic is virtually impossible. As a result, it will be necessary to search for an optimal development strategy by designing non-clinical and clinical studies where it is possible to detect whether or not any differences in glycosylation between the follow-on biologic and the original biologic affect safety and/or efficacy.

As with recombinant protein products containing new active ingredients, for clarification of the cell origin and culture history, it is recommended that information about the host cell is obtained from the organization at which the host cell has been established, wherever possible. If such information is not available, literature and other information will be acceptable. Not only information about culture history but also the procedures for establishing the cell bank system and characterization of cell substrates are included in the requirements, as with new protein products.

Since available information on an original biologic is limited, the development of a follow-on biologic using the same vector system is thought to be difficult. In particular, the follow-on biologic is likely to be developed using a gene expression construct in which the promoter/enhancer and signal sequence, etc. are different from those of the original biologic. In accordance with the ICH Q5B Guideline: “Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products”, the gene expression construct in the production cells and its stability throughout the manufacturing process should be analyzed.

Cell bank system

The cell bank system of a follow-on biologic should be established and justified independently, because it is unlikely that the sponsor of the follow-on biologic can obtain information on the cell culture method for establishing the master cell bank and

working cell bank, the use of serum and excipients, and the amplification method of the target gene for the original biologic. The establishment, characterization and control methods of the cell bank system for a follow-on biologic should comply with the ICH Q5A Guideline entitled “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin,” the ICH Q5B, and the Q5D Guidelines entitled “Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products”.

Cell culture and purification processes

Since it will also be difficult to utilize the same manufacturing processes such as the culture and purification of the original biologic, the manufacturing process for a follow-on biologic should be established independently. In this context, since the raw materials including serum and other components used for the culture and purification processes are likely to differ from those of the original biologic, impurities derived from the culture and purification processes are also expected to differ from those of the original biologic.

Certain product-related impurities or process-related impurities could have a significant impact on safety. Furthermore, in many cases the evaluation of similarity of the impurity profile in a follow-on biologic with that in an original biologic will be very difficult due to the limits of the tests and other measurement technologies. In such cases, it may be more rational to evaluate the safety for humans based on the data obtained from the independently established manufacturing process and the characterization of quality attributes rather than simply to compare the impurity profiles. 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 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.

4.2 Characterization (structural analyses, physicochemical properties, bioactivity, etc.)

For characterization of quality attributes of a follow-on biologic, full data about the

product which is manufactured with well-established manufacturing processes should be submitted, as with new recombinant protein products. The quality attributes of the follow-on biologic should be characterized and elucidated using the state-of-art scientific technologies, such as (1) structure and composition, (2) physicochemical properties, (3) bioactivity, (4) immunochemical properties and (5) purity, impurities and contaminants.

The impurities, such as product-related impurities and process-related impurities should be characterized and evaluated, taking into consideration their elimination data during the purification process. It will be very difficult to demonstrate that the impurity profile of a follow-on biologic is similar to that of the original biologic. Since some impurities could cause immunogenicity or other adverse effects, the conduct of appropriate studies at the non-clinical and clinical stages of drug development should be considered.

4.3 Drug formulation

In principle, the dosage form and administration route of a follow-on biologic should be the same as those of the original biologic. 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. In certain cases, it may be justified to select different excipients. Furthermore, the conduct of non-clinical studies or clinical studies on *in vivo* kinetics, etc., should also be considered, where necessary.

4.4 Stability testing

The sponsors of follow-on biologics are required to conduct long-term, real-time, real-condition stability studies. A recommended storage period should be justified according to the long-term, real-time, real-condition stability studies. A minimum of 6 months stability data at the time of submission should be submitted. 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. It is suggested that stability testing be conducted on the drug substance and drug product under accelerated and stress conditions, in order to obtain useful data for evaluating the properties of both drug substance and drug product for follow-on biologics. The stability testing should be conducted in accordance

with the ICH Q5C Guideline: “Stability Testing of Biotechnological/Biological Products”.

5. Evaluation Studies of the Comparability of Quality Attributes

The quality attributes of follow-on biologics which are manufactured with stable and robustly-established manufacturing processes should be thoroughly characterized. At the same time, comparability of quality attributes of a follow-on biologic with those of the original biologic should be evaluated, whenever possible and applicable. It is highly likely that there are differences in quality attributes not only of the active ingredient, such as the heterogeneity of glycosylation in proteins, but also product-related substances and the impurity profiles between the follow-on biologic and the original biologic. 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.

The acceptable criteria for differences in quality attributes will vary depending on the characteristics of the product and the intended use and dosing regimen in clinical practice. Public information and literature about the original biologics should also be considered.

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. If samples for the comparability exercise are prepared from the marketed original biologic product, the extraction methods and purification methods will be validated and confirmed to adequately determine the quality attributes of the original biologic. Although international and national standards for some original biologics may be obtainable, these standards cannot be regarded as a suitable reference product in comparative studies of structural analyses and physicochemical properties.

Comparative studies of (1) the structural analyses and physicochemical properties and (2) bioactivity, should be conducted, if necessary; and then (3) comparative studies on

immunologic responses, etc., should be considered for the comparability exercise of quality attributes.

(1) Comparative studies of the structural analyses and physicochemical properties

The structural and physicochemical properties between an original biologic and a follow-on-biologic should be compared. If the primary structure of the follow-on biologic is different from that of the original biologic, the product is not regarded as a follow-on biologic. Where there are any variations from the original biologic in terms of heterogeneity due to the processing of N- or C-terminal amino acids or other causes, it should be demonstrated that the variations have no adverse impact on efficacy and/or safety.

In many cases, it is difficult to evaluate the similarity in the quality attributes of biological products based solely on data from comparative studies of structural and physicochemical properties, etc. Therefore, the impact of variations in either higher-order structure or heterogeneity of posttranslational modifications should be evaluated in conjunction with the results of the analyses of bioactivity, pharmacokinetics, immunologic properties, etc.

(2) Comparative studies of bioactivity

It is important to evaluate the comparability of a follow-on biologic with the original biologic in terms of higher-order structure as well as primary structure. However, the analytical techniques for conformational structure cannot always be applied due to the unavailability of specimens or the difficulty in preparing samples for measurement. On the other hand, since changes of higher-order structure in a biological product could alter its bioactivity, the analysis of bioactivity is very useful as a means of evaluating the comparability of higher-order structure. Therefore, bioactivity is also a very important factor to evaluate the comparability in terms of conformation or heterogeneity of posttranslational modifications. Analytical methods should be justified to ensure that they have sufficient sensitivity and accuracy to detect the variations from the original biologic in terms of efficacy and safety for human use. In comparisons of bioactivity, it is desirable that bioactivity be calibrated against international or national reference standards, where available.

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.

On the other hand, in some glycoprotein products, carbohydrate moiety has a significant impact on pharmacokinetics; *in vitro* bioactivity of such products may have no correlation with clinical efficacy. In such cases, a bioassay to measure *in vivo* bioactivities is necessary.

Where the clinical dose of the original biologic is described by weight, the specific activity should be compared to assess comparability. 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.

(3) Comparative studies of immunogenicity etc.

Immunogenicity is affected by several factors such as process-related impurities, posttranslational modifications and product-related impurities. In addition, it is noted that some impurities have not only caused increases in immunogenicity (e.g., adjuvant effect) but also suppress them instead. Studies on immunological responses in animals may provide useful data for evaluating quality attributes including impurities.

6. Specifications and Test Procedures

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. Generally, in addition to performing testing of the drug substance and drug product, in-process tests to carry out quality controls will be rational in many cases. The specifications and test procedures, and acceptance criteria for in-process tests should be scientifically justified. Furthermore, specifications for the drug substance and drug product should be set, taking into account the results of the comparability exercise versus the original biologic, where necessary. To set the specifications and test procedures, the ICH Q6B Guideline: "Test Procedures and Acceptance Criteria for

Biotechnological/Biological Products" should be consulted.

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. However, since the specifications for biologics are not always fully set out in official compendia, it may also be necessary to develop supplementary specifications and test procedures to test the impurities and/or bioactivity with reference to the results of the characterization or clinical use of the target follow-on biologic.

7. Non-clinical Studies

As a minimum requirement, the sponsor should evaluate the safety of a follow-on biologic for human use prior to entering into clinical trials. Namely, the sponsor should ensure that non-clinical data, including safety data, have been obtained from non-clinical studies which need to be completed prior to initiation of clinical studies. There are some approaches to conduct non-clinical studies. Since the impurity profile of a follow-on biologic may be different from that of the original biologic, it is more rational to evaluate the safety in non-clinical studies of impurities in the follow-on biologic alone. On other hand, the comparability studies may be useful and appropriate to verify the similarity of pharmacological effects between the follow-on biologic and original biologic. However, comparative studies on the safety may also be appropriate to evaluate the safety of impurities, even though the impurity profiles are different between the follow-on biologic and original biologic. It is encouraged to follow the ICH S6 Guideline: “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals,” as appropriate.

The heterogeneity of sugar chains in some glycoprotein products may significantly affect *in-vivo* drug disposition, such as pharmacokinetics. It may then be useful to compare the non-clinical pharmacokinetics as part of the comparability exercise between the follow-on and original biologics.

Furthermore, the quality attributes of follow-on biologic should be fully evaluated prior to the conduct of non-clinical studies. In addition to data from the comparability studies on quality attributes between the follow-on biologic and original biologic, information

on use results or scientific literature on other products containing the same or similar (related) protein as the active ingredient may also play an important role in the safety evaluation of the follow-on biologic.

7. 1 Toxicity studies

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.

Although the impurity profile between the follow-on and original biologics may differ due to variations in the manufacturing processes, such as culture process or purification process, a direct comparative study of the toxicity profile may not always be necessary. On the other hand, another option is to directly compare the toxicity profile between the follow-on and original biologics based on the assumption of the difference in the impurity profile.

In particular, where the impurity profile differs significantly or where there are new impurities not contained in the original biologic, as in cases where an independent affinity chromatography process is introduced, toxicity studies focused on these impurities should be considered. In addition, where the product-related impurity profile of a follow-on biologic significantly differs from that of the original biologic, studies focused on the differences might be also necessary throughout the non-clinical and clinical development.

Where evaluating the production of antibodies in animals for direct comparison of the toxicological profile, clarification of antibody response (e.g., the production of neutralizing antibodies or the effect on pharmacokinetic/pharmacodynamic parameters) may provide useful information for the clinical study.

Unless considered as necessary based on the results of repeated dose toxicity studies of the follow-on biologic or data on the properties of the active ingredients in the original biologic, other general non-clinical safety studies including safety pharmacology studies, reproductive and developmental toxicity studies, genotoxicity studies, carcinogenicity

studies are generally unnecessary for follow-on biologics.

7. 2 Pharmacological studies

Comparability of the pharmacological action of a follow-on biologic and the original biologic should be directly evaluated in pharmacological studies. However, if the bioactivity between the follow-on and originator biologics is compared by conducting, as part of the characterization of quality attributes, *in vitro* bioactivity studies (cell-based studies or receptor-binding activity etc.) which is closely related to the clinical efficacy, the studies may be utilized as pharmacological studies. On the other hand, 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 original biologic through *in vivo* pharmacological studies.

As stated above, where the similarity of bioactivity between a follow-on biologic and the original biologic is fully evaluated by *in vitro* comparability studies, *in vivo* comparative studies of pharmacodynamics may not be necessary. However, useful information may often be obtained through *in vivo* pharmacological studies conducted at the stage prior to clinical study. Therefore, in order to evaluate the comparability of the follow-on biologic with original biologic, studies to evaluate *in vivo* therapeutic efficacy or pharmacodynamics should be considered, where necessary.

8. Clinical Studies

In general, it will be difficult to verify the comparability of a follow-on biologic with the original biologic based on the data on quality attributes and the results of non-clinical studies alone. Therefore, the sponsor should evaluate the comparability of a follow-on biologic through the clinical studies. Further, the follow-on biologic product used in clinical studies (investigational product) should generally be produced through well-established manufacturing processes. Where the manufacturing process is changed during the development of the follow-on biologic, the sponsor should evaluate the comparability of the follow-on biologic before and after the changes in accordance with the ICH Q5E guideline.

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.

In clinical studies intended to evaluate comparability, the studies explained in Sections 8.1 to 8.3 should be designed based on the data obtained from each study, and should be conducted in a step-wise approach. The type and contents of necessary clinical studies will vary widely according to available information and the properties of the original biologics. Since the scope of clinical studies necessary for the follow-on biologic under development should be determined on a case-by-case basis, taking into account the data obtained at each stage of development, the sponsor is encouraged to consult with the regulatory authorities.

8. 1 Pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD studies

In principle, the sponsor should conduct the comparability exercise for cross-over PK studies which are carefully designed to evaluate comparability between the follow-on and original biologics. However, since a cross-over study may not always be applicable to clinical studies for biologics with a long half-life (e.g., antibodies, PEG-binding proteins) or biologics that may produce antibodies in humans, the clinical study should be designed according to the properties of the follow-on biologic (e.g., parallel-group design). In this context, depending on the original biologic and/or target disease, it may be appropriate to conduct a clinical study in healthy adults, while a clinical study enrolling patients is sometimes more appropriate. 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. Also, clinical studies should be conducted using the approved dosage of the original biologic, while a scientifically rational dosage within the dosage range of the original biologic may also be chosen. While key parameters of a PK study include the area under the blood concentration curve (AUC) and maximum concentration (C_{max}), 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.

Furthermore, if possible, it is necessary to select PD marker(s) for clinical efficacy and to conduct the comparability studies between the follow-on biologic and original

biologics using the appropriate PD marker. A comparative study with PD marker is particularly useful, if PK studies are technically difficult to conduct. Moreover, it is suggested that, based on the analysis of the PK/PD studies, the comparability between the follow-on and original biologics be evaluated.

8. 2 Comparison of clinical efficacy

Even though high similarity in quality has been demonstrated through comparability studies on the quality attributes, an analysis of all data from the PK, PD or PK/PD studies might not demonstrate the comparability of clinical efficacy. In this case, it is necessary to conduct clinical studies to verify that the efficacy of the follow-on and originator biologics in respect of the indications of the product for which approval is sought are comparable.

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. 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 basis of supportive data or literature, etc.

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 have 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.

8. 3 Evaluation of clinical safety

Although comparability of efficacy has been demonstrated, in certain cases the safety profile of a follow-on biologic may still differ from that of the original biologic. If necessary, clinical studies to evaluate safety, including an immunogenicity study should be considered, even where comparability has been demonstrated through PK, PD or PK/PD studies and further clinical studies to evaluate efficacy are not required. However, when clinical studies are conducted to compare the efficacy of the two products, the studies may be designed such that safety (types of adverse events and their incidence) can be assessed as well.

If the results of the impurity profile give a rise to particular concerns about safety, the number of patients should be sufficient to perform a thorough investigation of the safety of the follow-on biologic.

Repeat dose studies on the follow-on biologic should be considered in the case of chronic administration.

Further, at an appropriate stage of the clinical development, studies should be conducted to evaluate antibody formation and other immunogenicity, thus leading to a scientifically justifiable conclusion. Any antibodies detected should be analyzed and identified to assess whether the antibodies neutralize the biological activity or not. It is also preferable to analyze the class, affinity and specificity of the antibodies in a scientifically rigorous way. Any reduction in efficacy or impact on safety arising from antibody formation should be considered. It is suggested that antibody formation against impurities or immune responses to specific carbohydrate antigens of the follow-on biologics should also be fully considered.

9. Post-marketing Surveillance

Since information obtained from clinical studies is generally insufficient and in particular, a follow-on biologics may raise specific concerns, such as potential immunogenicity issues, unlike generic drugs, the clinical safety of follow-on biologics should be followed up and monitored on an ongoing basis during post-marketing surveillance. Therefore, it is necessary to design a post-marketing surveillance program

to identify and monitor the risks that are not fully assessed during the comparability exercise at the clinical development stage. 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. Further, 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.

It is very important to assure the traceability of any adverse events arising during the surveillance period. Also, a follow-on biologic should not be substituted for or used alternately with the original biologic or other follow-on biologics in the same class for the same indication throughout a course of treatment.

References

1. ICH Q2A Guideline — Validation of Analytical Procedures: Text and Methodology

2. ICH Q2B Guideline — Validation of Analytical Procedures: Methodology (in Q2(R1))

3. ICH Q5A Guideline — Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

4. ICH Q5B Guideline — Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products

5. ICH Q5C Guideline — Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

6. ICH Q5D Guideline — Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

7. ICH Q5E Guideline — Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

8. ICH Q6B Guideline — Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

9. ICH S6 Guideline — Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

Glossary and Definitions

1. Quality attributes

A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes. Product-related substances, product-related impurities and the type and contents of process-related impurities are included in quality attributes, as well as the potency of active ingredient, bioactivity and physicochemical properties.

2. Product-related substances

Molecular variants of the desired product formed during manufacture and/or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

3. Impurities

Any component present in the drug substance or drug product which is not the desired product, a product-related substance, or excipient. It may be either process- or product-related.

4. Product-related impurities

Molecular variants of the desired product (for example, precursors, degradation products formed during manufacture and/or storage) other than product-related substances

5. Process-related impurities

Impurities derived from the manufacturing process. They include impurities derived from cell substrates, impurities derived from cell culture, or impurities derived from the downstream processing, i.e., extraction, separation, processing and purification of the desired product (e.g., reagents and test solutions used in the downstream processing, eluted substances from chromatographic carriers).

6. Standards

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

7. Acceptable range (comparability margin)

An acceptable range is the pre-defined limit of a confidence interval used for the comparability exercise in the comparative studies conducted for the purpose of demonstrating comparability between a follow-on biologic and an original biologic. The confidence interval is given for the comparison of the two products in respect of the primary endpoint.