

**PFSB/ELD No.0304007**

**“Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics”**

**1. Introduction**

“Follow-on biologics” are drugs to be developed by different marketing approval holders as drugs having bio-equivalent/quality-equivalent quality, safety and efficacy as biotechnology-derived drugs already approved domestically as drugs with new active ingredients (hereinafter “originator biodrug(s)”). In general follow-on biologics can be developed on the basis of data obtained from a comparison with the originator biodrug demonstrating bio-equivalence/quality-equivalence in respect of quality, safety and efficacy; or similar data.

In this document “bio-equivalence/quality-equivalence” does not signify that the quality attributes of a follow-on biologic are completely identical with those of the originator biodrug, but that these are highly similar and, notwithstanding some variations, can be scientifically concluded to have no harmful effect on the safety or efficacy of the final product.

Given the quality attributes of follow-on biologics, such as their complex structure in being comprised from several function sites, bioactivity, instability and immunogenicity etc., unlike chemically synthesized drugs, it is often difficult in their development to verify the sameness with originator biodrugs of the active ingredient, and basically it appears that the same approach as with the generic products of chemically synthesized drugs (hereinafter “generic drugs”) cannot be applied. Therefore with follow-on biologics new evaluation guidelines different to those for generic drugs are required. In addition, applications shall be filed under a new marketing approval application category different to generic drugs (1 – (7) Follow-on biologics) (see footnote \*).

These guidelines set out the requirements to be considered for the development of the new application category of follow-on biologics and clarify the data required for approval applications.

Applications for follow-on biologics can be filed on the expiry of the reexamination period etc. of the originator biodrug. Accordingly, the development of

follow-on biologics is likely to commence once a certain period of manufacturing and marketing performance and clinical usage has elapsed since the development and approval of the originator biodrug. Given the likelihood during this period of rapid progress with the manufacturing process, analytical techniques or evaluation techniques relating to the target biotechnology-derived drug, data accumulated during this time and the latest scientific technologies should be fully incorporated into the development. In addition, the latest available safety data should be taken fully into account.

\* Follow-on biologics do not correspond to “Recombinant drugs with a different host-vector system to that used for the manufacture of approved recombinant drugs” given in the PAB/ERD Notification No. 243 dated March 30 1985 or to “Drugs with a different cell species to approved cell culture drugs” given in the PAB/ERD-1 Notification No. 10 dated June 6 1988 and shall also be in a different application category to generic drugs.

## **2. Scope of Application (Coverage)**

These guidelines cover recombinant protein drugs (including simple proteins and glycoproteins), polypeptides and derivatives thereof that have been produced using microorganisms or cultured cells, have been highly purified and can undergo quality characterization by means of a series of appropriate analytical procedures; and drugs based on their constituent ingredients (for example, conjugates).

The basic view set out in these guidelines may also be applicable to categories of drugs other than the above that have been highly purified and can undergo characterization, such as non-recombinant protein drugs produced using cell culture techniques or proteins and polypeptides that have been isolated from tissue or body fluids. The applicability should be discussed with the regulatory authorities for each individual product.

This document is not applicable to antibiotics, synthesized peptides and synthesized polypeptides, polysaccharides, vitamins, metabolic products of cells, nucleic acid-based drugs, 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**

In the development of follow-on biologics it is necessary to establish an independent manufacturing process and, as with new recombinant protein drugs, to give specific details of the respective quality attributes. In addition, it is necessary to demonstrate high similarity with the originator biologic of the quality attributes based on empirical data. Demonstration of bio-equivalence/quality-equivalence including from non-clinical study and clinical study data is in principle also required. Further, originator biologics should be drugs approved domestically and be the same product throughout the development period of the follow-on biologic (the entire quality, non-clinical and clinical development period).

For evaluating the bio-equivalence/quality-equivalence of follow-on biologics, it is considered necessary to conduct studies as appropriate based on the concept given in the ICH Q5E Guideline: “Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process”. In effect, bio-equivalence/quality-equivalence should be evaluated as appropriate through comparison with the originator biologic using a combination of physicochemical tests, bioactivity tests and also non-clinical and clinical study data.

The objective of evaluating the bio-equivalence/quality-equivalence of follow-on biologics is to demonstrate that their quality attributes are highly similar to those of the originator biologic and that even any variations found therein have no harmful effect on the safety and efficacy of the final product. Where the originator biologic substance is obtainable for tests to evaluate the bio-equivalence/quality-equivalence of quality attributes, tests using this shall be required.. However, in general it will often be difficult to obtain the originator biologic substance, and in such cases there may be no option other than to perform the investigations using the drug product.

Accordingly, although there may be limitations to current scientific techniques, or limitations to the evaluation of bio-equivalence/quality-equivalence of the quality attributes from data obtained using drug products, analyses should be conducted as far as possible using procedures demonstrated to be scientifically valid, and the data obtained submitted. However, depending on the product, literary materials or similar information may also be referred to for some bio-equivalence/quality equivalence evaluations of quality attributes.

The need for and scope of non-clinical and clinical study data will depend on the extent to which bio-equivalence/quality-equivalence with the originator biologic has

been established from a scientifically valid and rational evaluation of the quality attributes.

Non-clinical studies should be conducted after full characterization of the follow-on biologic. The type of study to conduct should be properly determined with reference to the results of the characterization of the quality attributes of the follow-on biologic per se and of the evaluation of bio-equivalence/quality-equivalence based on a comparison with the originator biologic of the quality attributes.

Clinical studies should be conducted with reference to the quality attributes of the follow-on biologic to be developed and to the results of the bio-equivalence/quality-equivalence evaluation results based on a comparison of the quality attributes of the originator biologic and follow-on biologic and the findings of non-clinical studies. In addition, the study must be designed as necessary and rational and the bio-equivalence/quality equivalence with the originator biologic of efficacy and safety evaluated with reference also to diverse information including literature on the originator biologic.

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

In the development of follow-on biologics, it is necessary to establish an independent and highly constant and robust manufacturing method. In addition, as with new recombinant protein drugs, the product obtained should be fully characterized and the data submitted. The manufacturing process should be optimized according to the characteristics of the active ingredient(s) of the follow-on biologic to be developed and as appropriate the results of the evaluation of bio-equivalence/quality-equivalence with the originator biologic in respect of the quality attributes. In addition to appropriate specifications and test procedures, it is necessary to set the process control method.

In addition, where there are changes in the manufacturing process during the development of a follow-on biologic, comparability should be evaluated in accordance with the ICH Q5E Guideline.

##### **4.1 Development of the Manufacturing Process**

It is envisaged that broad spectrum analysis of the originator biologic, foremost the dosage form, will be required in the development of follow-on biologics. However, normally it would be extremely difficult to obtain data on the

manufacturing process of a originator biodrug developed by a competitor or the drug substance per se.

In addition, it is likely that in many cases analysis of a originator biodrug product alone will only generate limited data on its manufacturing process. For example, although package inserts etc. may provide information such as whether serum or bioderived components have been used in the cell bank creation or culture process, or whether an antibody column etc. has been used in the purification process of the target active ingredient, such information is also likely to be extremely limited. Accordingly, in the development of follow-on biologics, it is necessary to develop and establish an independent manufacturing process of assured constancy and robustness. In addition, the bio-equivalence/quality-equivalence of the originator biodrug and follow-on biologic should be clarified after full consideration of such differences in the manufacturing process.

Given that the development of follow-on biologics will take place a considerable time after the approval of the originator biodrug, it is recommended that in developing the manufacturing process of a follow-on biologic, where safety measures etc. based on the latest knowledge at that time are applicable, these should be actively adopted. In other words, the development of follow-on biologics also demands proactive adoption of the latest safety measures etc. insofar as these do not affect efficacy. Accordingly, in some cases it may be more appropriate to search for a safer manufacturing method, such as non-serum culture.

### **Host-vector systems**

In the creation of cell bank systems for the manufacture of follow-on biologics, where the host cell of the originator biodrug has been disclosed it is preferable to proceed with the development using the same host cell. Should a different type of host cell be used for the development, quality and safety investigations focusing on the differences in the profile of process-related impurities including host-derived impurities should be conducted more thoroughly than where the same cell is used. The respective data should be submitted.

With glycoprotein drugs, it is often difficult to demonstrate bio-equivalence/quality-equivalence based on structural analysis data due to their significant glycan heterogeneity. In addition, even where the host is identical, glycan heterogeneity is known to fluctuate widely due to various factors such as the insertion site of the gene expression construct or the culture conditions. Given that in

the development of products that have significant glycan heterogeneity, it is in practice extremely difficult to set manufacturing conditions to obtain a high level of similarity in the glycan structure of originator biodrugs and follow-on biologics, it will probably be necessary to search for the optimum strategy through non-clinical and clinical studies that allow evaluation of the effects of glycan differences on safety and efficacy.

As with drugs containing new active ingredients, for clarification of the cell origin and history, it is preferable that information on the host cell is obtained as far as possible from an established research body. Where such information is unobtainable, information from literature or other sources will be acceptable. Similar requirements to those for new products are sought, including information on the establishment of the cell bank system and characterization of cell substrates as well as the culture history.

Given the shortage of available information on originator biodrugs, development using the same vector system is likely to be difficult. In particular, the development will probably have an independent strategy in respect of the promoter/enhancer and signal sequence etc. In accordance with the ICH Q5B Guideline “Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived. Protein Products”, it is necessary to analyze the gene expression construct in the production cells and to conduct studies on its stability throughout the manufacturing process.

### **Cell bank system**

Since it is unlikely that information on the originator biodrugs can be obtained concerning the formation of the cell bank system, more specifically on the cell culture method for the preparation of the master cell bank and working cell bank, the presence of serum and excipients and also the amplification method of the target gene, it is necessary to establish the cell bank system independently. The formation, characterization and management methods thereof should be based on the ICH Q5A Guideline “Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin”, the ICH Q5B Guideline and the Q5D Guideline “Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products”.

## **Culture and purification processes**

Since it will also be difficult to use the same culture, purification and other manufacturing processes as the originator biodrug, it is necessary to establish an independent manufacturing process. Accordingly, since the raw materials used in the serum and other culture process/purification process are likely to differ from those of the originator biodrug, the culture process-related and purification process-related impurities etc. are also expected to differ from those of the originator biodrug.

Product-related impurities and process-related impurities are also expected to impact significantly on safety. Further, in many cases identification of the similarity between an originator biodrug and a follow-on biologic of the impurity profile using a limit test or other measurement method will not always be easy. In such cases, it may be more logical to evaluate the effects on the safety of the product from an independently established manufacturing process and the characterization results rather than simply to compare the impurities. This does not require safety studies on all impurities but evaluation of the impurities as part of the product characterization and assurance of safety through the setting of the necessary and rational in-process controls and specifications and test procedures with reference to the elimination of impurities and the impurities-related experience and information.

### **4.2 Characterization (structural analysis, physicochemical properties, bioactivity etc.)**

For products manufactured with established manufacturing methods, characterization should produce data similar to that of new recombinant protein drugs.

Using the latest scientific technologies, characterization should fully elucidate items such as (1) structure and composition, (2) physicochemical properties, (3) bioactivity, (4) immunologic properties and (5) impurities.

With respect to impurities, product-related impurities and process-related impurities should be analyzed and evaluated with reference also to their elimination in the purification process. It will be difficult to demonstrate the bio-equivalence/quality-equivalence of the impurity profile with the originator biodrug. However, since there are concerns over the occurrence of immunogenicity or similar problems, where necessary the conduct of appropriate studies at the non-clinical stage and clinical stage of development should be considered.

### **4.3 Drug product design**

Follow-on biologic drug products should essentially have the same dosage form and route of administration as the originator biologic. Provided that efficacy and safety are not affected, in designing a drug product it is not essential for the pharmaceutical formulation to be the same as that of the originator biologic. It may be valid to select different excipients. Further, where necessary the conduct of non-clinical studies or clinical studies on *in vivo* kinetics etc. should also be considered.

### **4.4 Stability testing**

Long-term storage testing for the actual storage time and under actual storage conditions is also required for the development of follow-on biologics. The shelf life should be based on long-term storage test data. However test data for a period of six months or more may be submitted with the application for approval. In addition given that identical storage conditions and a shelf life to the originator biologic are not prerequisites, comparison therewith will not necessarily be required. Also, in principle stress and acceleration testing should be conducted to obtain useful data for evaluating the properties of follow-on biologic drug substances and drug products. These stability tests should follow the ICH Q5C Guideline on “Stability Testing of Biotechnological/Biological Products”.

## **5. Evaluation Studies of the Bio-equivalence/quality-equivalence of Quality Attributes**

In addition to fully elucidating the quality attributes of follow-on biologics manufactured with a constant and robust manufacturing method, the bio-equivalence/quality-equivalence of the necessary and feasible items concerning the quality attributes of the originator biologic and follow-on biologic should be evaluated. As well as an active ingredient per se that has glycan differences in the glycoprotein, differences in quality attributes including product-related substances and the impurity profile are highly likely to be found between follow-on biologics to be manufactured with a different manufacturing method and the originator biologic. Accordingly, where possible, the impact on efficacy and safety of any variations noted from the evaluation of the bio-equivalence/quality-equivalence of the quality attributes using several lots should be considered, and the non-clinical/clinical studies to be conducted selected on the basis of the results.

The acceptable range of quality attribute variations will vary widely according to such factors as the characteristics of the product and the purpose and method of use in medical practice. Information and literary materials obtained on the originator biologic should also be considered.

Given the anticipated difficulty of obtaining the originator biologic substance, it is also envisaged that for evaluation of bio-equivalence/quality-equivalence with originator biologics studies will be conducted using the originator biologic product directly or a sample equivalent to the target protein extracted and purified therefrom. When extracting and purifying from commercially obtainable drug products to prepare samples equivalent to the drug substance in order to evaluate bio-equivalence/quality-equivalence, a validated extraction and purification method should be used, and it should be ensured that the respective method can fully reflect the quality attributes of the originator biologic. However, although an official reference standard may be obtainable for some originator biologics, this cannot be used as the control in comparative studies of structural analyses and physicochemical properties.

For evaluating the bio-equivalence/quality equivalence of quality attributes, (1) comparative studies of the structural analysis and physicochemical properties and (2) comparative studies of bioactivity should be conducted where necessary, and (3) comparative studies etc. on immunogenicity etc. should also be considered.

**(1) Comparative studies of the structural analysis and physicochemical properties etc.**

Comparative studies of the variations in the structure and physicochemical properties etc. between originator biologics and follow-on-biologics should be conducted. The desired product shall not be assessed as a follow-on biologic where it has primary structural differences with the originator biologic. Where variations from the originator biologic in heterogeneity due to the processing of N- or C-terminal amino acids etc. are noted, it is necessary to ensure that these do not adversely affect efficacy and/or safety.

In many cases it will be difficult to discuss the similarity of the quality attributes based solely on a comparative study of structure and physicochemical properties etc. and it will be necessary to evaluate the impact of variations in heterogeneity from higher-order structures or posttranslational modifications in conjunction with the results of the analyses of bioactivity, *in vivo* kinetics and immunologic properties etc.

## **(2) Comparative studies of bioactivity**

Although it is vital to evaluate bio-equivalence/quality-equivalence with the originator biologic for higher-order structures as well as primary structures, test methods for higher-order structures cannot always be applied due to the unavailability of specimens or the difficulty of preparing samples for measurement. However, it is also vital to determine bioactivity in evaluating the bio-equivalence/quality-equivalence of higher-order structures since these are likely to be reflected therein. Accordingly, bioactivity is also regarded as vital data for evaluating the bio-equivalence/quality-equivalence of stereostructures or heterogeneity from posttranslational modifications. A test procedure accurate enough to assess the variations from the originator biologic in terms of efficacy and safety should be used. In comparative studies of bioactivity where a reference standard is available it is preferable to find the reference value to be determined using international or internal standard.

The bioactivity of originator biologics and follow-on biologics should be compared using several methods as far as possible. For example, comparative studies of cell proliferation and differentiation, receptor-binding activity, enzyme activity and other *in vitro* bioactivity closely linked to clinical effects are valuable.

At the same time, since glycan structures etc. impact significantly on *in vivo* kinetics, *in vitro* activity may have no correlation with clinical effects, and in such cases it is considered necessary to conduct *in vivo* bioactivity studies.

Where the clinical dosage of the originator biologic is weight-based, the specific activity in particular should be compared and its bio-equivalence/quality-equivalence verified. Where there are variations in the specific activity, their acceptability should be evaluated and the validity of using the same dose as the originator biologic explained.

## **(3) Comparative studies of immunogenicity etc.**

Factors affecting immunogenicity include posttranslational modifications and product-related impurities as well as process-related impurities. In addition, cases have also been noted not only of impurities that increase the immunogenicity (the adjuvant effect) but also of impurities that suppress these instead. Evaluation of immunologic responses in animals may produce valuable data for evaluating quality attributes including impurities.

## **6. Specifications and Test Procedures**

To assure product constancy, follow-on biologics also require the independent setting of specifications and test procedures based on the results of characterization or lot analysis etc. With biodrugs, in addition to specifications testing of the drug substance, it will often also be logical, depending on the manufacturing process control tests, to carry out quality controls, in which case the scientific validity of the specifications set including those for the manufacturing process control tests should be explained. In addition, where necessary the results of the evaluation of bio-equivalence/quality-equivalence with the originator biodrug should also be reflected as appropriate. In setting the specifications and test procedures, the ICH Q6B guideline on “Test Procedures and Acceptance Criteria for Biotechnological/Biological Products” should be followed.

In addition, where the originator biodrug is listed in official compendia such as the Japanese Pharmacopoeia, in principle it is preferable to base the specifications and test procedures on those listed therein. However, given that in the case of biodrugs the required specifications are not always fully stipulated in official compendia, it may also be necessary to set supplementary specifications and test procedures including the impurities profile and/or bioactivity etc. with reference to the results of the characterization or clinical use etc. of the target follow-on biologic.

## **7. Non-clinical Studies**

The development of follow-on biologics also requires that, at the minimum, safety for administration to humans has been verified prior to the commencement of clinical studies. More specifically, the non-clinical studies held to be required for the conduct of clinical studies should have been completed, including the acquisition of safety data. These non-clinical studies include cases where it is more logical to conduct studies on the follow-on biologic alone, as with studies to verify the safety of follow-on biologics with a different impurities profile to that of the originator biodrug, and cases where comparative studies on the originator biodrug are appropriate, as with verification studies of pharmacological action equivalence. However, it may also be valid to conduct comparative studies on the originator biodrug for safety verification in cases where the impurities profile is different. Where necessary it is appropriate to conduct these non-clinical studies with reference to the ICH S6 Guideline “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”

With some glycoprotein drugs glycan heterogeneity may significantly affect *in vivo* kinetics and it may be useful here to compare the non-clinical pharmacokinetics as part of the evaluation of the bio-equivalence/quality-equivalence of a follow-on biologic.

Further, the conduct of non-clinical studies is predicated on full quality characterization. In addition to the results of the evaluation of the bio-equivalence/quality-equivalence between the originator biodrug and follow-on biologic of the quality attributes, the usage of other drug products with the same desired product as the active ingredient and literary materials also have an important role in safety evaluation.

## 7.1 Toxicity studies

To identify the single-dose and repeat-dose toxicity of follow-on biologics, repeated dose toxicity studies on appropriate animal species are valuable for identifying the toxicity of follow-on biologics, and toxicokinetic investigations may also be useful given that these are protein drugs. In addition, local irritation as well as single-dose toxicity could also be evaluated in repeated dose toxicity studies.

Where the impurities profile differs due to variations in the culture process, purification process or other manufacturing processes, a direct comparison of the toxicity profile of the originator biodrug and follow-on biologic is also not always necessary. On the other hand, another option is to compare directly the toxicity profile of the originator biodrug and follow-on biologic after consideration of the variations found in the impurities profile.

In particular, where the impurities profile differs significantly or new impurities (antibodies used for affinity chromatography carriers etc.) not contained in the originator biodrug are found, as in cases where affinity chromatography is independently introduced, impurity-focused toxicity studies should be considered. In addition, where the product-related impurity profile differs significantly from that of the originator biodrug, studies focused on these differences may also be required in the course of the non-clinical and clinical development.

Where evaluating the production of antibodies in animals for direct comparison of the toxicity profile, clarification of whether or not the antibodies produced are neutralizing antibodies, or of whether or not they affect the pharmacokinetics may provide useful data in clinical practice.

Unless otherwise expressly deemed necessary from the results of repeated dose toxicity studies or data on the properties of active ingredients obtained on the originator biodrug, safety pharmacology studies, reproduction and developmental toxicity studies, genotoxicity studies, carcinogenicity studies and other ordinary non-clinical safety studies are unlikely to be required as non-clinical studies on follow-on biologics.

## 7.2 Pharmacological studies

For pharmacological studies bio-equivalence/quality-equivalence of the pharmacological action of the originator biodrug and follow-on biologic should be directly compared. However, where *in vitro* bioactivity studies (cell-based studies or receptor-binding activity etc.) closely related to the clinical effects are conducted as quality characterization studies and used for comparison of the originator biodrug and follow-on biologic, these may correspond to pharmacological studies. However, where, as with certain types of glycoprotein, *in vitro* activity does not correlate with the clinical effects, it will be necessary to verify the bio-equivalence/quality-equivalence with the originator biodrug of therapeutic efficacy and pharmacodynamics through *in vivo* pharmacological studies.

Where *in vitro* bioactivity etc. is fully assessable in bio-equivalence/quality-equivalence studies, *in vivo* comparative studies of pharmacodynamic effects may not be required. However, valuable information may often be obtained at the pre-clinical study stage from the conduct of *in vivo* pharmacological studies. Therefore where necessary the conduct of *in vivo* therapeutic efficacy or pharmacodynamic studies to verify the bio-equivalence/quality-equivalence of the follow-on biologic and originator biodrug should be considered.

## 8. Clinical Studies

Clinical studies are basically required for follow-on biologics since in general verification of their bio-equivalence/quality-equivalence with originator biodrugs from the quality attributes and the results of non-clinical studies alone will be difficult.

Further, although basically drug products used in clinical studies should have been produced through established processes, where there have been changes in the manufacturing process in the course of the development, comparability should be evaluated where necessary in accordance with the ICH Q5E Guideline.

Where data sufficient to assure bio-equivalence/quality-equivalence in the target endpoint has been obtained through the aforementioned pharmacokinetic (PK), pharmacodynamic (PD) or PK/PD studies, clinical studies on efficacy may be omitted.

Bio-equivalence/quality-equivalence evaluations based on clinical studies should be designed for the next study according to the data obtained and conducted step-wise. The type and content of the clinical studies required will vary widely according to the information on and properties of the originator biologic. Case-by-case handling based on the data obtained at the development stage of the scope of clinical studies required is necessary for each product and therefore it is preferable to consult with the regulatory authorities.

### **8.1 Pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD studies**

In principle, it is necessary to verify the PK bio-equivalence/quality-equivalence of an originator biologic with a follow-on biologic through an appropriately designed cross-over study. Since a cross-over study may not always be appropriate for medications with a long elimination half-life (antibodies, PEG-binding proteins etc.) or drugs that produce antibodies in humans, the study design should be investigated with reference to the properties of the follow-on biologic. Here, depending on the originator biologic and target disorder, it will sometimes be appropriate to conduct the study on healthy adults, and sometimes more appropriate to conduct it on patients. In addition, it is necessary to conduct the study using the same route of administration as that in the target indications of the originator biologic and, where multiple routes of administration exist, in principle, to study these individually. In principle the studies should be based on the recommended dosage of the originator biologic, but the selection of a scientifically valid dosage within the dosage range of the originator biologic is also possible. Although key PK parameters include the area under the blood concentration curve (AUC) and maximum concentration ( $C_{max}$ ), the acceptable bio-equivalence/quality-equivalence range (bio-equivalence/quality-equivalence margin) should be pre-specified. At the same time it is necessary to explain fully the validity of the acceptable range set.

In addition, it is necessary to conduct a PD marker-based comparison reflecting the clinical effects of the product. A PD marker-based comparison is particularly useful where PK studies are technically difficult to perform. Moreover, bio-equivalence/quality-equivalence should preferably be studied from analysis of the PK/PD relationship.

## **8.2 Comparison of clinical efficacy**

In cases where high similarity in terms of quality has been demonstrated through bio-equivalence/quality-equivalence evaluation studies on the quality attributes, but even the combination of PK, PD or PK/PD study results shows inconclusive bio-equivalence/quality-equivalence of clinical efficacy, it will be necessary to conduct clinical studies to verify that the efficacy of the follow-on biologic and originator biodrug in respect of the indications for which approval is sought is bio-equivalent/quality-equivalent. Studies to verify the bio-equivalence/quality-equivalence of the efficacy of the follow-on biologic with the originator biodrug should be appropriately designed and their validity explained. Specifically, the target number of cases should be set as necessary and valid, and the acceptable bio-equivalence/quality-equivalence range (bio-equivalence/quality-equivalence margin) pre-specified using clinically established endpoints. Where appropriate surrogate endpoints are available, the use of true endpoints will not always be required, but their validity should be fully explained on the basis of corroborative data or literature etc.

Where in the case of an originator biodrug with multiple indications and effects it can be explained that efficacy is equivalent to the originator biodrug in respect of certain indications and that a similar pharmacological action can be expected in the other indications and effects too, it may be possible to extrapolate to the follow-on biologic the other indications and effects approved for an originator biodrug used as the control. The extrapolability of indications and effects is confined to the indications of the originator biodrug used as the control and does not include the indications and effects of approved recombinant protein drugs with similar indications other than the originator biodrug.

However, where the respective indications and effects have a different mechanism of action or this mechanism of action is not clear, bio-equivalence/quality-equivalence of efficacy with the originator biodrug should be demonstrated for each indication and effect.

## **8.3 Verification of clinical safety**

Even where bio-equivalence/quality-equivalence of efficacy has been demonstrated, the safety profile of follow-on biologics may differ from that of originator biodrugs. Where necessary, the conduct of clinical safety studies

including a study of immunogenicity should be considered even where bio-equivalence/quality-equivalence has been demonstrated through PK, PD or PK/PD studies and clinical studies to evaluate efficacy are not conducted. In addition, for the conduct of clinical studies to compare efficacy, the study may be designed so as to investigate safety (the type of adverse event and incidence) at the same time.

Where the results of the impurity profile give rise to particular concerns over safety, the target number of cases should be set so as to ensure adequate investigation.

The conduct of repeat dose studies should be considered for drugs administered long-term.

Further, at an appropriate stage of the clinical development studies should be conducted that allow a scientifically valid determination of the occurrence of antibodies and other immunogenicity. Any antibodies detected should be analysed and identified as neutralizing antibodies or otherwise, and it is also preferable to analyze the class, affinity and specificity of the antibodies. In addition, consideration should also be given to identifying any reduction of efficacy or impact on safety from the occurrence of antibodies.

## **9. Post-marketing Surveillance**

Given that information on clinical studies is generally limited and in particular that biodrugs have different factors to generic drugs, such as immunogenicity issues, ongoing post-marketing surveillance of the safety profile etc. is required. For this it is necessary to foresee the risks that are not fully assessable in the evaluation of bio-equivalence/quality-equivalence at the development stage, and to formulate a post-marketing surveillance program appropriately designed with reference to these risks. The specific method and design of the post-marketing surveillance study and risk management plan should be discussed with the regulatory authorities and be submitted together with the application for approval. Further, the findings of the post-marketing surveillance should be reported to the regulatory authorities by an appropriate time following the approval of the follow-on biologic.

It is vital to assure the traceability of adverse events during the respective surveillance period, and notwithstanding any switch of the originator biologic or drug with similar indications to the follow-on biologic, their substitution or combined application should in principle be avoided throughout the treatment period.

### **ICH Guidelines for reference**

1. ICH Q2A Guideline: “Text on Validation of Analytical Procedures”
2. ICH Q2B Guideline: “Text on Validation of Analytical Procedures; Methodology”
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: “Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”

## **Glossary and Definitions**

### **1. Quality attributes**

Quality attributes are the molecular or product characteristics that are selected as appropriate for indicating the quality of the product and collectively define the identity, purity, potency and stability of the product and its safety with respect to adventitious agents etc. Specifications and test procedures measure a selected subset of the quality attributes. Product-related substances, product-related impurities and the type and abundance of process-related impurities are included in quality attributes as well as the potency, bioactivity and physicochemical properties etc. of the target active ingredient.

### **2. Product-related substances**

These are molecular variants of the desired product formed during manufacture and/or storage, which are bioactive and have no adverse affect on the safety and efficacy of the product. These molecular variants have properties comparable with those of the desired product and are not regarded as impurities

### **3. Impurities**

Components found in the drug substance or drug product other than the desired product, product-related substances and excipients. Some are process-related and some are 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. These 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 (for example, reagents and test solutions used in the downstream processing, leachable substances from chromatographic carriers etc.)

**6. (Official) Reference standards**

These refer to both international and domestic reference standards. For example, the international reference standards distributed by the National Institute for Biological Standards and Control (NIBSC) or the pharmacopoeia reference standards distributed by the Society of Japanese Pharmacopoeia fall into this category. These reference standards are for use in the respective potency assay or physicochemical test etc. and their application other than for the intended test is not appropriate.

**7. Acceptable range (bio-equivalence/quality-equivalence margin)**

In the conduct of comparative studies on follow-on biologics and originator biodrugs for the purpose of demonstrating bio-equivalence/quality-equivalence with the originator biodrugs, a confidence interval is shown for the comparison of two products in respect of the primary endpoint. The relationship of that interval to the preset unacceptable degree of inferiority.