

## **Guideline for the quality, safety and efficacy of follow-on biological medicinal products**

### **1. Introduction**

A follow-on biological medicinal product (hereinafter referred to as FOBMP) is considered as a new biotechnological medicinal product developed to be similar in terms of quality, safety and efficacy to an already licensed, biotechnology medicinal product (hereinafter referred to as reference biological product or RBP) developed by a different marketer-manufacturer in Japan. A FOBMP should be developed based on data showing the comparability in terms of quality, safety and efficacy with the RBP. In this guideline, “comparability” does not mean that the quality attributes of a FOBMP are completely the same as those of the reference biological product, but means that the quality attributes of a FOBMP are highly similar to those of the RBP and even if there are any differences in the quality attributes, it can be scientifically considered that those differences have no adverse impact on the safety or the efficacy of the final or finished product.

In the development of a FOBMP, it is often difficult to demonstrate the equivalence of the active ingredient to that of the approved product because of the quality attributes including complex structures consisting of multiple functional domains, biological activities, instability and immunogenicity, unlike in the case of chemically-synthesized medicinal products. Basically, an approach similar to that used for the generic products of chemically-synthesized medicinal products is considered not to be applicable. Thus, a new guideline for evaluating FOBMPs that is different from that for generic products is required. In addition, a new application class for FOBMPs (or 1-(7) Bio-kozokuhin) that is different from that for generic products should be established.

(\* footnote)

This guideline aims at presenting the requirements considered for the development of FOBMPs classified into a new application class and at showing data required for application for approval.

Approval of a FOBMP may be achieved after the patent expiration of the RBP and the completion of re-examination period. Thus, a FOBMP is to be developed after the marketing and clinical experiences of the RBP for a given period have been obtained since it was developed and approved. During the period, the manufacturing process, analytical technologies or evaluation technologies will be rapidly advanced. Therefore, a FOBMP should be developed based on the information pooled during the period using new scientific technologies. Furthermore, new information concerning safety should be appropriately considered for development.

\* These products do not meet the class specification specified in the following notifications:

*“Recombinant drugs which have different host/vector system from those already licensed recombinant drugs” provided in the Notification No 243 of the First Evaluation and Regulation Division, PAB dated Mar 30, 1984 and “Drugs manufactured by cell culture technology of which seed cell strains are different from the licensed drug manufactured by cell culture technology” provided in the Notification No. 10 of the First Evaluation and Regulation Division, PAB dated June 6, 1988. Thus, a new application class different from that for generic drugs is to be established.*

## **2. Scope**

This guideline applies to recombinant DNA proteins (including simple proteins and glycoproteins), polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced using microorganisms and cultured cells and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this guideline might also apply to other product types such as non-recombinant proteins manufactured by cell culture technologies as well as proteins and polypeptides isolated from tissues or body fluids, if they can be highly purified and characterized. Manufacturers are advised to consult with the Regulatory Authority to determine applicability for each product.

This guideline does not apply to antibiotics, chemically synthesized peptides and chemically synthesized polypeptides, polysaccharides, vitamins, cellular metabolites, medicinal products containing nucleic acids, allergen extracts, conventional vaccines using attenuated or inactivated pathogenic microorganisms or the extracts as an antigen, cells or whole blood or blood cells (hemocytes).

## **3. General Principles for the development of follow-on biological medicinal products**

For FOBMPs, it is necessary to establish its own production method and clarify its quality attributes in detail just as in the case of a new recombinant therapeutic protein.

In addition, it should be demonstrated that the quality attributes are highly similar to those of the RBP. Furthermore, the comparability between a FOBMP and its RBP should be demonstrated based on non-clinical and clinical data. The RBP is a drug approved in Japan and should not be changed throughout the period of development of the FOBMP (throughout the entire period of quality, non-clinical and clinical development).

For comparability exercises of a FOBMP, adequate studies should be conducted based on the concept described in ICH Q5E guideline: “Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process”. That is to say, the comparability should be evaluated by a combination of physicochemical studies, bioactivity assays and non-clinical /clinical data for comparability exercises between a FOBMP and its RBP as comparator as necessary.

Comparability exercises for a FOBMP are generally performed to demonstrate it has highly similar quality attributes to its RBP, and even if there are any differences in the quality attributes, they have no adverse impact on the safety and the efficacy of the final or finished product. In the comparability study, if the active ingredient of RBP is available, the study should be conducted using the active ingredient. However, it is often difficult to obtain the active ingredient of the reference biological product, and in such a case, the study should be conducted with a drug product.

Therefore, there are limitations in evaluation of comparability of quality attributes due to limited scientific technologies and data from the drug product, however, the quality attributes should be analyzed as thoroughly as possible by using methods that have been scientifically validated, and the data obtained should be submitted. Depending on products, literature information etc. can be used as reference for a part of comparability exercises in terms of quality attributes.

The requirement and the range of non-clinical and clinical data vary depending on how much comparability between a FOBMP and its RBP has been demonstrated within a scientifically appropriate range by comparability exercises in terms of quality attributes.

Non-clinical studies of a FOBMP should be conducted after the characterization of the product. Considering the results of its characterization and comparability exercise based on the comparison of quality attributes with the RBP, a rational and appropriate study should be conducted.

For conducting clinical trials, the quality attributes of a FOBMP to be developed, and the results of comparability exercises between the FOBMP and its RBP based on the quality attributes and non-clinical data should be considered. In addition, a necessary and appropriate study should be designed based on various knowledge including literatures on the RBP, and comparability in terms of the safety and efficacy should be evaluated between the FOBMP and the RBP.

#### **4. Manufacturing process and characterization of a FOBMP**

For development of a FOBMP, the consistent and highly robust manufacturing process should be established by an independent approach. The characterization of the final or finished product should be appropriately conducted in a similar manner to that for new recombinant therapeutic proteins, and the data should be submitted likewise. The manufacturing process should be optimized based on the characteristics of the active ingredient of a FOBMP to be developed as well as the results of comparability exercises in terms of quality attributes between the FOBMP and the RBP, and the adequate specifications, test procedures and in-process control should be established.

When the manufacturing process of a FOBMP was changed during the development process, the comparability should be evaluated in accordance with ICH Q5E guideline.

##### **4.1 Development of manufacturing process**

In the development of a FOBMP, it is expected that the RBP will be sufficiently analyzed for various aspects including pharmaceutical formulation. However, it is usually difficult to obtain information on the manufacturing process and the active ingredient itself of the reference biological product developed by the other manufacturer.

In addition, limited information on the manufacturing process is usually obtained from analyses using only the drug product of the RBP. For example, information about whether or not sera or biological materials were used for preparation of cell banks or during the process of cell culture, or information about whether or not an antibody column etc. against the intended active ingredient is used during the process of purification may be obtained from the package insert etc. However, these kinds of information may be highly limited. Thus, a consistent and robust manufacturing process should be developed and established by using an independent approach for development of a FOBMP. Considering the difference in the manufacturing process between a FOBMP and its RBP, the comparability between these products should be validated.

A FOBMP is developed in a sufficient period of time after licensing of the RBP. Thus, it is recommended that safety measures based on the current knowledge, if available, are actively adopted for development of the manufacturing process of the FOBMP. Current safety measures that do not impact on the efficacy should be actively adopted. Therefore, it may be often adequate to consider a much safer manufacturing process including the one by serum-free culture, unlike that of the RBP.

#### **Host/vector system**

For establishment of a cell bank system used for manufacture of a FOBMP, when a host cell of the reference biological product is known, it is advisable to develop the FOBMP using the same host cells. When the different kind of host cells are used taking risks for development, the quality and the safety should be more thoroughly evaluated than that of the product developed using homologous cells, based on the difference in profiles of process-related impurities including host-related impurities, and the data should be submitted accordingly.

With respect to therapeutic glycoproteins, it is often difficult to demonstrate the comparability based on data from structural analyses due to the heterogeneous nature of the sugar chains. In addition, it has been known that the heterogeneous nature of the sugar chains may be largely changed by various factors including the insertion sites of expression construct and culture conditions even when homologous cells are used. When a product having highly heterogeneous sugar chains is developed, since it is actually very difficult to design manufacturing conditions which may produce high similarity in sugar chain structure of FOBMP and RBP, an optimum approach should be sought

through non-clinical and clinical studies which would allow evaluation of the effects of differences of sugar chains on the safety and efficacy.

Host cells should be obtained from an established research institute so that the origin of the cells and data on cell culture can be clearly known as in the case of medicinal products containing a new active ingredient. When such data are not available, literature information can be accepted. The requirements similar to those for a medicinal product containing a new active ingredient should be implemented for not only data on cell culture but also establishment of a cell bank system and characterization of cell substrates.

There is almost no available information on the RBP and it may be difficult to develop a FOBMP using the same vector system. Especially, promoters, enhancers and signal sequences may be developed by using an independent approach. In accordance with ICH Q5B guideline “Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products”, analyses of the expression construct in cells produced should be conducted and the genetic stability of the expression construct throughout the manufacturing process should be studied.

#### **Cell bank system**

For establishment of a cell bank system, cell culture methods used for preparation of master cell banks and working cell banks, presence or absence of sera and excipients and gene amplification methods should be determined by using an independent approach because there may be almost no available information on RBPs. Establishment of a cell bank system, the characterization, and the maintenance procedures should conform to ICH Q5A guideline “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin”, ICH Q5B guideline and Q5D guideline “Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products”.

#### **Cell culture and purification processes**

The manufacturing process including cell culture and purification processes should be established by an independent approach, because it is difficult to adopt the same process as that of the RBP. The raw materials used for the cell culture and purification processes, such as sera may be different from those of the RBP. Thus, it is expected that the culture process-related impurities and the purification process-related impurities may be different from those obtained during the manufacturing process of the RBP.

Some of the product-related impurities and the process-related impurities may have a considerable impact on the safety. In addition, it is often difficult to demonstrate the similarity of impurity profiles between a FOBMP and its RBP due to limitations of analytical techniques. In such a case,

it may be adequate to evaluate not only the similarity of impurity profiles but also the safety based on the manufacturing process established by an independent approach and the results of the characterization. This does not mean that impurity profiles should be evaluated by a full set of safety studies, but means that impurity profiles should be evaluated as a part of the product characterization, and necessary and appropriate in-process control, specifications and test procedures should be established based on the levels of removal of impurities, experience of and information on impurities in order to ensure safety of the product.

#### **4.2 Characterization (Structural analyses, physicochemical properties and biological activities etc.)**

Data from the characterization of the product produced by a validated manufacturing process similar to those of a new recombinant therapeutic protein should be required.

In characterization, 1. structure/composition, 2. physicochemical properties, 3. biological activities, 4. immunochemical properties, and 5. impurities should be fully elucidated by using new science technologies. The specifications and test procedures should be established based on the results of characterization.

With respect to impurities, product- and process-related impurities should be analyzed and evaluated based on the levels of removal of impurities during the purification process. It is difficult to demonstrate the comparability of impurity profiles between a FOBMP and its RBP, and problems of immunogenicity etc. may occur. Thus, the implementation of adequate studies during the non-clinical and clinical development processes should be considered as appropriate.

#### **4.3 Formulation design**

In principle, the dosage form and the route of administration of a FOBMP should be the same as those of the RBP. The pharmaceutical formulation should not need to be always the same as that of the RBP unless it impacts the efficacy and the safety. It is sometimes adequate to select different excipients. In addition, non-clinical and clinical studies on drug disposition should be conducted as appropriate.

#### **4.4 Stability testing**

A long-term storage test for the actual storage period under the actual storage condition should be required for development of a FOBMP. The expiration date should be established based on data from the long-term storage test. However, it is allowed to submit data from the long-term storage test for at least 6 months at the time of application for approval. The comparison with the reference biological product is not always required since the storage condition and the expiration date does not need to be the same as that of the RBP. Stress testing as well as accelerated testing should be

conducted in principle, because useful information may be obtained for characterization of the active ingredient and the drug product of a FOBMP. The stability testing should be conducted in accordance with ICH Q5C guideline “Stability Testing of Biotechnological/Biological Products”.

#### **5. Comparability exercise in terms of quality attributes**

Quality attributes of a FOBMP produced by a consistent and robust manufacturing process should be fully analyzed, and the comparability exercise in terms of necessary and possible quality attributes between the RBP and the FOBMP should be conducted. There may be some differences in the quality attributes including product-related substances and impurity profiles between a FOBMP and its RBP produced by a different manufacturing process. Thus, it should be considered how the difference observed impacts the efficacy and the safety in the comparability exercise in terms of quality attributes by using multiple lots if possible, and some kinds of non-clinical and clinical studies for implementation are required to be selected based on the results.

The acceptable range of differences in quality attributes varies considerably depending on the characteristics of the product, the intended use and the usage at clinical sites. The knowledge and literature information on the RBP should be also considered.

It may be difficult to obtain the active ingredient of the RBP for comparability exercises. Thus, the studies may be conducted using a drug product itself or the target protein extracted from the drug product. When a sample corresponding to the active ingredient is prepared by extraction from the available drug product and purification, a validated method for extraction and purification should be used, and it should be confirmed that the sample extracted and purified fully reflects the quality attribute of the RBP. Official reference standards of some RBPs may be available. However, they cannot be used as control substances for comparative studies on structural analysis and physicochemical properties.

For comparability exercises in terms of quality attributes, 1. comparative studies on structural analysis and physicochemical properties, 2. comparative studies on biological activities should be conducted in as required and 3. comparative studies on immunogenicity, etc. should also be studied.

#### **① Comparative study on structural analysis and physicochemical property**

A comparative study on structures and physicochemical properties should be conducted between a FOBMP and its RBP. When there is a difference in the primary structure between the target substance and the RBP, the target substance is not considered as a FOBMP. When there is a difference in heterogeneity due to the processing of N-terminal or C-terminal amino acids between the target substance and the RBP, it should be ensured that the difference has no adverse impact on the efficacy or safety profiles.

With respect to biological medicinal products, it is often difficult to indicate the similarity of quality attributes only by a comparative study on structures and physicochemical properties. Thus, the impact of the differences in heterogeneity due to higher order structures and posttranslational modification should be evaluated, considering the biological activities, drug disposition and immunochemical properties.

## ②. Comparative study on biological activity

It is important to evaluate the comparability in terms of not only the primary structure but also higher order structures between a FOBMP and its RBP. However, a test procedure for higher order structures is not sometimes applicable because of low availability of specimens and difficulty of preparation of samples for determination. While, it is considered that the biological activity reflects higher order structures and it is important to determine the biological activity for evaluation of comparability in terms of higher order structures. Thus, the data of biological activities may be important for comparability exercises in terms of heterogeneity of 3-D structures and posttranslational modification. Test procedures with a certain degree of accuracy by which differences from the RBP can be evaluated in terms of efficacy and safety should be used. It is advisable to obtain calibrated value with a reference standard for a comparative study on biological activities, if available.

Biological activities should be compared between a FOBMP and its RBP in terms of both the efficacy and safety by using multiple methods if possible. For example, it is useful to conduct a comparative study on biological activities including cell growth and differentiation, receptor binding activities and enzyme activities *in vitro* that are closely related to clinical efficacy.

While, *in vitro* biological activities are not sometimes related to clinical efficacy because the sugar-chain structures etc. considerably impact the drug disposition. In such a case, a biological activity assay should be conducted *in vivo*.

When, the clinical dose of the RBP is expressed per unit of weight, the comparability should be confirmed, especially by comparing the specific activity. If there are any differences in the specific activity, the acceptability of the differences should be evaluated and the use of the same dosage as that of the RBP should be validated.

## ③ Comparative study on immunogenicity

Factors having impacts on immunogenicity include process-related impurities as well as posttranslational modification and product-related impurities. It has been known that immunogenicity is increased or inhibited by some impurities (adjuvant effects). Useful information for evaluation of quality attributes including impurities may be obtained by studying

immunogenicity in animals.

## **6. Specifications and Test procedures**

In development of a FOBMP, specifications and test procedures should be established by using an independent approach based on the results of the characterization and lot analyses in order to ensure the consistency of the product. It is required to give scientific validity of establishment of the specification including in-process control tests since it is often rational to control quality through in-process tests in addition to the specification tests of APIs and drug products in the case of biological pharmaceuticals. The results of comparability exercises between a FOBMP and its RBP should be also adequately reflected to the specifications and test procedures as required. Establishment of specifications and test procedures should conform to ICH Q6B guideline “Test procedures and Acceptance Criteria for Biotechnological/Biological Products”.

When the RBP is listed in the official compendium such as Japanese Pharmacopoeia, it is advisable to establish specifications and test procedures in accordance with those listed in the official compendium in principle. For biological medicinal products, however, all specifications required are not always provided in the official compendium, and additional specifications and test procedures for impurity profiles and biological activities etc. should be sometimes established, considering the results of the characterization and the intended clinical application of the FOBMP.

## **7. Non-clinical study**

In development of a FOBMP, the safety for human should be confirmed before the initiation of clinical studies. Including safety data, essential non-clinical studies required for clinical studies should be completed before the implementation of clinical studies. Of these non-clinical studies, a safety study of the FOBMP with impurity profiles different from those of the RBP which is adequate for evaluation of only the FOBMP, while, an equivalence study on pharmacological actions is adequate for comparing with the RBP. Even when the impurity profile is different, a comparative study with the RBP is sometimes adequate for confirming the safety. These non-clinical studies should be conducted in accordance with ICH S6 guideline as appropriate.

With respect to therapeutic glycoproteins, heterogeneity of sugar chains may have a considerable impact on drug disposition, and it is sometimes useful to compare the pharmacokinetics in non-clinical studies as a part of comparability exercises of a FOBMP.

Characterization should be thoroughly conducted before implementation of non-clinical studies. Comparability exercises in terms of quality attributes between a FOBMP and its RBP as well as usage experiences of and literature information on other drug products with the same active ingredient as the intended product may have an important role for safety evaluation.

### **7.1 Toxicity study**

Repeated dose toxicity studies with adequate animal species are useful to evaluate the single and repeated dose toxicity of a FOBMP, and toxicokinetic studies may be also useful because a FOBMP is a therapeutic protein. Local irritability can be examined in a repeated dose toxicity study as well.

When impurity profiles are different between a FOBMP and its RBP because of differences in manufacturing processes including a cell culture process and a purification process, the direct comparison of toxicity profiles between these products is not always required. However, toxicity profiles may be sometimes directly compared between a FOBMP and its RBP, considering the difference in impurity profiles between these products.

When the impurity profile is considerably different from that of the RBP or when there are new impurities (antibody etc.) that are not contained in the RBP as in the case where affinity chromatography is introduced for purification, a toxicity study on impurities should be conducted. In addition, when the product-related impurity profile is considerably different from that of the RBP, studies on the difference should be sometimes required throughout the entire non-clinical and clinical development processes.

When antibody formation is evaluated in animals in order to compare directly the toxicity profile, it is useful for evaluation of clinical immunogenicity to demonstrate whether or not the antibody formed is neutralizing and whether or not it affects the pharmacokinetics.

A safety pharmacological study, reproductive toxicity study, genotoxicity study, carcinogenicity study, and other non-clinical safety studies are considered less needed as non-clinical studies of a FOBMP, unless otherwise required based on the information on the results of the repeated dose toxicity studies and the characterization of the active ingredient of the RBP.

### **7.2 Pharmacological study**

The comparability of pharmacological action should be evaluated by direct comparison between a FOBMP and its RBP. However, when an assay on biological activities (an assay using cells and that on receptor-binding activities) that are closely related to the clinical effect was conducted *in vitro* as a characterization study to compare between a FOBMP and its RBP, this biological activity assay might be sometimes used in place of a pharmacological study. However, when the *in vitro* activity of a FOBMP such as some glycoproteins does not correlate with the clinical effect, an *in vivo* pharmacological study should be conducted to confirm the comparability in terms of drug potency and pharmacodynamics between a FOBMP and its RBP.

When the *in vitro* bioactivity assay can fully evaluate the comparability, an *in vivo* comparative study on pharmacodynamic effects is not always required. However, useful information are often obtained in an *in vivo* pharmacological study before the implementation of clinical studies. Therefore, the implementation of a drug efficacy study and a pharmacodynamic study *in vivo* should be considered to confirm the comparability between a FOBMP and its RBP as appropriate.

## **8. Clinical study**

It is usually difficult to validate the comparability between a FOBMP and its RBP only based on quality attributes and the results of non-clinical studies, and in principle, the comparability should be evaluated by clinical studies. The drug product used for clinical studies should be manufactured by well-established manufacturing process in principle and when formulation changes are made during the development, comparability shall be evaluated according to ICH Q5E guideline.

When adequate data supporting the comparability in terms of the intended clinical endpoint can be obtained from the clinical pharmacokinetic (PK) study, pharmacodynamic (PD) study or PK/PD study, as described below, the further clinical studies on efficacy may be sometimes omitted.

Clinical studies on comparability should be designed and implemented step by step based on the data obtained from the preceding studies. The kinds and details of clinical studies required depend on the information on and the characteristics of the RBP. The range of clinical studies required for each product should be decided on a case-by-case basis, based on data obtained during the stage of product development, after consultation with the Regulatory Authority.

### **8.1 Clinical pharmacokinetic (PK) study, pharmacodynamic (PD) study and PK/PD study**

In principle, the comparability of pharmacokinetics between a FOBMP and its RBP should be confirmed by a well-designed crossover study. However, a crossover study is not always adequate for a drug with a long elimination half-life (antibody and PEG-binding protein etc.) or a medicinal product eliciting antibodies in human. Thus, a study design should be established considering the characteristics of the product. Depending on RBP and the target disease there are cases when healthy volunteers or patients may be adequate as the study subjects. The study should be conducted using the route of administration the same as that of the intended indication of the RBP. When multiple routes of administration are applicable, each route—should be studied in principle. The study should be conducted by using a recommended dose for the RBP in principle. However, a scientifically adequate dose can be selected within a range of dosage and administration of the RBP. Areas under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C<sub>max</sub>) are selected as main pharmacokinetic parameters, and the acceptable range for comparability (comparability margins) must be established before study and fully elucidated.

PD markers reflecting the clinical efficacy of the product are to be selected, and they should be compared between a FOBMP and its RBP, if possible. Particularly, when it is difficult to conduct a pharmacokinetic study due to a technology problem, the comparison of PD markers is useful. Furthermore, it is advisable to evaluate the comparability by PK/PD analyses.

### **8.2 Comparison of clinical efficacy**

When the comparability in terms of clinical efficacy cannot be confirmed based on the results of PK, PD or together with PK/PD studies although the high similarity of quality attributes has been demonstrated by the comparability exercise in terms of quality attributes, clinical studies should be required to confirm the comparability of the efficacy for the intended indication between a FOBMP and its RBP.

A comparative study should be adequately designed and validated before the comparability of efficacy is evaluated between a FOBMP and its RBP. In other words, the required and appropriate number of subjects should be set with the clinically established endpoints and the acceptable range of the comparability (comparability margins) should be also established before the study. When an adequate surrogate endpoint can be used, the true endpoint is not necessarily used. However, the surrogate endpoint should be validated based on supportive data and literatures.

When the efficacy for a certain indication is comparable between a FOBMP and its RBP and the pharmacological action for other indications is also expected to be similar to that of the RBP if it has multiple indications, its other indications that have already been licensed can be sometimes extrapolated to a FOBMP. In such a case, only indications of the RBP used as a reference can be extrapolated, but the indications of other recombinant therapeutic proteins with the same category that have already been licensed cannot be extrapolated.

When the mechanism of action is different among the indications or has not been demonstrated, the comparability of efficacy should be shown for each indication.

### **8.3 Confirmation of clinical safety**

Safety profile of a FOBMP is likely different from that of the RBP even after the comparability of efficacy has been demonstrated. The implementation of clinical safety studies including evaluation of immunogenicity should be considered as needed, even when clinical studies on efficacy are not required because the comparability has been demonstrated by PK, PD or PK/PD studies.

When a clinical study is conducted to compare the efficacy, the study can be designed to assess the safety (the kind and the frequency of adverse events) concurrently.

Particularly, when safety concerns were raised from the analytical results for impurity profiles, the

number of cases should be adequately set for thorough analyses.

With respect to a medicinal product for long-term administration, the implementation of a repeated dose study should be considered.

In addition, a study, by which the appearance of antibody and the other immunogenicity can be scientifically evaluated, should be conducted at an adequate stage of clinical development. When the appearance of an antibody is observed, its analysis should be conducted to elucidate whether or not the antibody is neutralizing and demonstrate its class, affinity and specificity. In addition, the impact of the antibody on the efficacy and the safety should be also evaluated. The formation of antibodies to impurities and the reactivity to a specific carbohydrate antigen should be fully considered.

### **9. Post-marketing surveillance**

Safety profiles etc. should be continuously investigated after marketing because only limited information are usually obtained from clinical studies and there are some factors such as immunogenicity in the FOBMP that are different from those in generic products. Probable risks that have not been sufficiently evaluated in the comparability exercise during the development process are assumed to exist and on such assumption a post-marketing surveillance should be designed adequately. Manufacturers are advised to consult with the Regulatory Authority to determine the detailed methods and plans for the post-marketing surveillance and the risk control and to submit them at the time of application for approval. Results of the post-marketing surveillance should be reported to the Regulatory Authority by an adequate time after licensing of the FOBMP.

During the relevant surveillance period, it is important to secure traceability concerning adverse events, and it should basically avoid mixed or alternate use of the FOBMP with the RBP or a product with the same category/indication.

### **ICH Guidelines to be used as references**

1. ICH Q2A guideline “Validation of Analytical Procedures: Text (Items)”
2. ICH Q2B guideline “Validation of Analytical Procedures: Text (Methodology)”
3. ICH Q5A guideline “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin”
4. ICH Q5B guideline “Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products”
5. ICH Q5C guideline “Stability Testing of Biotechnological/Biological Products”
6. ICH Q5D guideline “Derivation and Characterisation 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 “Safety Assessment of Biotechnological Products in Preclinical Studies”

## **Glossary and Definition**

### **1. Quality Attribute :**

Quality Attribute defines the potency, biological activity and physicochemical property of the intended active ingredient in the product as well as the kinds and the contents of the product-related substance, product-related impurity and process-related impurity.

### **2. Product-related substance**

Product variants that are formed during the manufacturing process or the storage period, have biological activities and have no adverse impact on the safety and efficacy of the product. These variants have characteristics comparable to the product and are not considered as impurities.

### **3. Impurity :**

The component contained in the active ingredient or the drug product, other than the product, product-related substances and excipients. There are process-related impurities and product-related impurities.

### **4. Product-related impurity :**

Product variants (for example, precursors, decomposed matters and variants obtained during the manufacturing process or the storage period) other than the product-related substances

### **5. Process-related impurity:**

Impurities derived from the manufacturing process. There are impurities derived from cell substrates and cell culture solutions as well as those derived from the manufacturing processes including extraction, separation, processing and purification of the product (for example, reagents/test solutions used after the cell culture process, and leakage from a carrier for chromatography).

### **6. (Official) Reference standards :**

These are international reference standards and domestic reference standards. There are the international reference standards distributed by NIBSC and the official reference standards distributed by the Society of Japanese Pharmacopoeia, used for measurement of potency and for chromatography, (calibration),etc. The application of these standards to tests other than the intended purposes is inadequate.

### **7. Acceptable range (Comparability margin):**

In a comparative study between a follow-on or subsequent-entry biological medicinal product and the reference biological product for the purpose of demonstrating the comparability between these

products, the confidence interval is shown for comparison of the primary endpoint between these products. The acceptable range is established based on the relationship between the pre-specified acceptable level and the confidence interval.

**End of Text**

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**JGA Comments on the translation and use of some words:**

**Comparability:**

Sometimes it is difficult to have exactly corresponding words between two languages. In this translation, this is used in the same meaning of this word used in the text of Q5E of ICH. This could be replaced by “equivalence” in many places, that is to say, “equivalence” in terms of quality, efficacy and safety.

**Follow-on biological medicinal product (FOBMP):**

FOB was borrowed from U.S. regulatory draft’s text as the author of the guideline coined a new word in Japanese for a new class which is not “generic”, though close in meaning and apparently following US, WHO(Subsequent-entry) or EU (Biosimilar)idea.

**Re-examination Period:**

After the marketing approval or licensing of a new or patent-protected drug, it usually lasts 6 to 8 years with the marketing right protection with obligatory post-marketing surveillance which is required for the MAH (marketing authorization holder) or marketer-manufacturer.

**Marketer-manufacturer:**

- One of the pharmaceutical business license categories which is required for manufacturing and marketing of pharmaceuticals and issued by the local governor.
- Licenses for manufacturing and licenses for marketing separately exist for different purposes and controlled by the local governor.
- A biopharmaceutical manufacturing license is controlled by Minister of Health, Labour and Welfare, (the central government)

End