ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

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Notice to the Reader: Where reference is made to nonclinical and clinical studies, additional information and modification of these specific items will be provided by ICH Safety and Efficacy Experts.

1.0 Introduction

1.1 Objectives of the Guideline

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. This guideline is intended to assist in the design and conduct of studies used to collect the technical information to establish the comparability of pre-change and post-change products and, thereby, confirm that the manufacturing process changes did not have an adverse impact on the quality, safety and efficacy of the drug product.

1.2 Background

Manufacturers[1] of biotechnological/biological products frequently make changes to manufacturing processes[2] of products[3] both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate.

While ICH documents have not specifically addressed considerations for demonstrating comparability between pre-change and post-change products, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes (see References). This document builds upon the previous ICH guidelines and provides additional direction regarding approaches to:

- Compare post-change product to pre-change product following manufacturing process changes and
- Assess the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy.

[1] For convenience, when the term “manufacturer” is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).
[2] For convenience, when the term “manufacturing process(es)” is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.
[3] For convenience, when the term “product” is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.

1.3 Scope

The principles adopted and explained in this document apply to:

- Proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures;
- Products where changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of pre-change and post-change products; and
- Products where process changes are made in development or for which a marketing authorisation has been granted.

The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. Manufacturers are advised to consult with the appropriate regional Regulatory Authority to determine applicability.

1.4 General Principles

The goal of the comparability exercise is to ensure the quality, safety and efficacy of the drug product produced by a changed manufacturing process through collection and evaluation of the relevant data to determine whether there is any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change products are identical; but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product might not be warranted. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and post-change products are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

To identify the impact of a manufacturing process change, a careful evaluation of all potential consequences on the product, not just the obvious, should be performed. Based on this evaluation, acceptance criteria to define highly similar post-change product can be established. Quality data on the pre- and post-change products are generated, and a comparison is performed that integrates and evaluates all data available, e.g., characterisation, routine batch analyses, stability, in-process control, and process validation/evaluation data. The comparison of the results to the predefined acceptance criteria allows an objective assessment of whether or not the pre- and post-change products are comparable.

Following the evaluation of the quality attributes the manufacturer could be faced with one of several outcomes including:

- Based on appropriate comparison of relevant quality attributes, pre- and post-change products are highly similar and considered comparable, i.e. no adverse impact on safety or efficacy profiles is foreseen.

- Although the products appear highly similar, there is doubt concerning the capability of the analytical procedures to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider performing additional nonclinical and/or clinical studies.
- Some differences have been observed in the quality attributes of the pre-change and post-change products, but it can be justified that no adverse consequence on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and post-change products can be considered comparable.
- Although the pre- and post-change products are similar, some differences have been identified in the comparison of quality attributes and possible adverse consequences on safety and efficacy profiles cannot be excluded. In such situations, the generation and analysis of additional data on quality attributes is unlikely to be sufficient to determine if pre- and post-change products are comparable. The manufacturer should consider performing nonclinical and/or clinical studies to reach a definitive conclusion, taking into account characteristics of the drug product such as therapeutic window, clinical usage (acute vs. chronic administration), dosing characteristics, and potential for immunogenic responses.
- Differences are so significant that it is determined that quality attributes for products are not comparable (i.e., they are not highly similar). This outcome is not within the scope of this document and is not discussed further.

2.0 Guidelines

2.1 Considerations for the Comparability Exercise

The goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy. Therefore, it might be appropriate to collect data on the drug product to support the determination of comparability even though all process changes occurred in the manufacture of the drug substance. Comparability can be deduced from quality studies (partial or comprehensive), but might sometimes need to be supported by comparability bridging studies. The extent of the studies that demonstrate comparability will depend on:

- The production step where the changes are introduced;
- The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, related substances);
- The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and
- The relationship between quality attributes and safety and efficacy, based on the overall nonclinical and clinical experience.

When considering the comparability of products, the manufacturer should evaluate, for example:

- Relevant physicochemical and biological characterisation data regarding quality attributes;
- Results from analysis of relevant samples from the appropriate stages of the manufacturing process (e.g., intermediate, drug substance, and drug product);

- The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the protein and, hence, potential product-related substances and product-related impurities;
- Batches used for demonstration of manufacturing consistency;
- Historical batch data that provide insight into potential "drift" of quality attributes with respect to safety and efficacy, following either a single or a series of manufacturing process changes. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.

In addition to evaluating the data, manufacturers should also consider:

- Critical control points in the manufacturing process that affect product characteristics, e.g., the ability of downstream steps to accommodate material from a changed cell culture process, as well as the impact of the process change on the quality of downstream product;
- Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the post-change process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
- Nonclinical or clinical characteristics of the drug product: Clinical characteristics, such as therapeutic index, clinical use (e.g., acute vs. chronic administration), dosing, route of administration, and potential for immunogenic response, of the drug product can be important in planning the comparability exercise; and
- Each indication for a multi-indication product: The structure-activity relationships, mechanism of action, safety profile, and toxicities of the same product can vary with each clinical indication and, if so, should be addressed for each clinical indication.

2.2 Quality Considerations

2.2.1. Analytical Techniques

The battery of tests for the comparability exercise should be carefully selected and optimised to the product to maximise the potential of detecting differences in the quality attributes that might result from the proposed manufacturing process change. To address the full range of physicochemical properties or biological activities, it might be appropriate to apply more than one analytical procedure to evaluate the same quality attribute (e.g., molecular weight, impurities, secondary/tertiary structures). In such cases, each method should employ different physicochemical or biological principles to collect data for the same parameter to maximise the possibility that differences in the product caused by a change in the manufacturing process might be detected.

It can be difficult to ensure that the chosen set of analytical procedures for the pre-change product will be able to detect modifications of the product due to the limitations of the assays (e.g., precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity. Consequently, the manufacturer should determine:

- Whether or not existing tests remain valid for their intended use or should be modified. For example, when the manufacturing process change gives rise to a different impurity profile in the host cell proteins, manufacturers should confirm

that the test used to quantitate these impurities is still suitable for its intended purpose. It might be appropriate to modify the existing test to detect the new impurities;

- The need to add new tests as a direct result of changes in quality attributes that the existing methods are not capable of measuring. That is, when specific changes occur in quality attributes as a result of process change (e.g., following addition of a new raw material or modification of a chromatographic purification step), it might be appropriate to develop new analytical procedures, i.e., to employ additional analytical techniques above and beyond those used previously for characterisation or to establish routine specifications.

The measurement of quality attributes does not necessarily entail the use of validated assays but the assays should be scientifically sound and provide results that are reliable. Those methods used for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

2.2.2 Characterisation

Characterisation of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.

When a manufacturing process change has been made that has the potential to have an impact on quality attributes, a complete or limited (but rationalised) repetition of the characterisation activity conducted for the market application is generally warranted to directly compare the pre-change and post-change products. However, additional characterisation might be indicated in some cases. When process changes result in a product characterisation profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials, the significance of these alterations should be evaluated.

Each of the following criteria should be considered as a key point in the conduct of the comparability exercise.

Physiochemical Properties

The manufacturer should address the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be addressed. Following a manufacturing process change, manufacturers should attempt to determine that higher order structure (secondary, tertiary, and quaternary structure) is maintained in the product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay (see biological activity below) could indicate a correct conformational structure.

Biological Activity

Biological assay results serve multiple purposes in the confirmation of product quality attributes that are useful for characterisation and batch analysis, and, in some cases, serve as a link to clinical activity. The manufacturer should recognise the limitations of biological assays, such as high variability, that might prevent detection of differences that occur as a result of a manufacturing process change.

In cases where the biological assay also serves as a complement to physicochemical analysis, e.g., as a surrogate assay for higher order structure, the use of a relevant biological assay with appropriate precision and accuracy might provide a suitable approach to confirm that change in specific higher order structure has not occurred following manufacturing process changes. Where physicochemical or biological assays are not considered adequate to confirm that the higher order structure is maintained, it might be appropriate to conduct a nonclinical or clinical study.

When changes are made to a product with multiple biological activities, manufacturers should consider performing a set of relevant functional assays designed to evaluate the range of activities. For example, certain proteins possess multiple functional domains that express enzymatic and receptor mediated activities. In such situations, manufacturers should consider evaluating all relevant functional activities.

Where one or more of the multiple activities are not completely correlated with clinical safety or efficacy or if the mechanism of action is not understood, the manufacturer should confirm that nonclinical or clinical activity is not compromised in the post-change product.

Immunochemical Properties:

When immunochemical properties are part of the characterisation (e.g., for antibodies or antibody-based products), the manufacturer should confirm that post-change product is comparable in terms of the specific properties.

Purity, Impurities, and Contaminants:

The combination of analytical procedures selected should provide data to evaluate the change in purity profile in terms of the desired product.

If differences are observed in the purity and impurity profiles of the post-change product relative to the pre-change product, the differences should be evaluated to determine their impact on safety and efficacy. Where the change results in the appearance of new impurities, it might be appropriate to characterise the new impurities, and in some cases, to conduct appropriate nonclinical or clinical studies to confirm that there is no adverse impact on safety or efficacy of the drug product.

Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product.

2.2.3 Specifications

The tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterise it. The manufacturer should confirm that the specifications after the process change are appropriate to ensure product quality. Results within the established acceptance criteria, but outside historical manufacturing control trends, might suggest product differences that warrant additional study or analysis. Modification, elimination, or addition of a test (i.e., in the specification) might be indicated where data suggest that the previous test is no longer relevant for routine batch analysis of the post-change product. For example, the elimination of bovine serum from the cell culture process would remove the need for related analyses. However, a widening of the acceptance criteria is generally not considered appropriate and should be justified. In

some cases, additional tests and acceptance criteria on the relative abundance of specific new impurities might be appropriate if the impurity profile is different following the manufacturing process changes. When evaluating both the test methods and acceptance criteria for the post-change product, it is important to consider the general principles for setting specifications as defined in Q6B, i.e., the impact of the changes on the validated manufacturing process, characterisation studies, batch analysis data, stability data, and nonclinical and clinical experience.

2.2.4 Stability

For many manufacturing process changes even slight modifications of the production procedures, including those made early in the manufacturing process for the drug substance, might cause changes in the stability of the post-change product. Any change with the potential to alter protein structure or purity and impurity profiles should be evaluated for its impact on stability, since proteins are frequently sensitive to changes, such as those to buffer composition, processing and holding conditions, and use of organic solvents. Furthermore, stability studies might be able to detect subtle differences that are not readily detectable by the characterisation studies. For example, the presence of trace amounts of a protease might only be detected by product degradation that occurs over an extended time period; and, in some cases, divalent ions leached from container closure might change the stability profile because of the activation of trace proteases not detected in stability studies of the pre-change product. Generally, therefore, real-time concurrent stability studies on the product potentially affected by the change should be conducted, as appropriate.

Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of pre-change and post-change products. The results thus obtained might show product differences that warrant additional evaluation and also identify conditions indicating that additional controls should be employed in the manufacturing process and during storage to eliminate these unexpected differences. Appropriate studies should be considered to confirm that suitable storage conditions and controls are selected.

ICH Q5C and Q1A(R) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.

2.3 Manufacturing Process Considerations

A well-defined manufacturing process with its associated process controls is necessary to assure that acceptable product is produced on a consistent basis. Approaches to determining the impact of any process change will vary with respect to the specific process, the product, the extent of the manufacturer's knowledge of and experience with the process, and development data generated. The manufacturer should confirm that the process controls in the modified process provide similar or more effective control of the product quality, compared to those of the original process.

A careful consideration of potential effects of the planned change on steps downstream and quality parameters related to these steps is extremely important (e.g., for acceptance criteria, in-process specification, in-process tests, operating limits, and validation/evaluation, if appropriate). This analysis will help identify which tests should be performed during the comparability exercise, which in-process or batch release acceptance criteria or analytical procedures should be re-evaluated and which steps will not need to be considered. For example, analysis of process intermediates might suggest potential differences that should be evaluated to determine the suitability of existing tests to detect these differences in the product. The rationale for excluding parts of the process from this consideration should be justified.

While the process will change and the associated controls might be redefined, the manufacturer should confirm that pre-change and post-change products are comparable. To support the comparison it is often useful to demonstrate, for example, that specific intermediates are comparable or that the modified process has the capability to provide appropriate levels of removal for process- and product-related impurities, including those newly introduced by the process change. To support process changes for approved products, data from commercial-scale batches are generally indicated.

The process assessment should consider such factors as the criticality of the process step and proposed change, the location of the change and potential for effects on other process steps, and the type and extent of change. Information that can aid this assessment is generally available from several sources. The sources can include knowledge from process development studies, small scale evaluation/validation studies, experience with earlier process changes, experience with equipment in similar operations, changes in similar manufacturing processes with similar products, and literature. Although information from external sources is useful to some extent, it is within the context of the specific manufacturing process and specific product that the change should be assessed.

When changes are made to a process, the manufacturer should demonstrate that the associated process controls, including any new ones, provide assurance that the modified process will also be capable of providing comparable product. The modified process steps should be re-evaluated and/or re-validated, as appropriate. The in-process controls, including critical control points and in-process testing, should ensure that the post-change process is well controlled and maintains the quality of the product. Typically, re-evaluation/re-validation activities for a simple change might be limited to the affected process step, if there is no evidence to indicate that there is impact on the performance of subsequent (downstream) process steps, or on the quality of the intermediates resulting from the subsequent steps. When the change considered affects more than a single step, more extensive analysis of the change and resultant validation might be appropriate.

Demonstration of state of control with the modified/changed manufacturing process might include, but is not limited to, such items as:

- Establishment of modified specifications for raw, source and starting materials, and reagents;
- Appropriate bioburden and/or viral safety testing of the post-change cell banks and end-of-production cells;
- Adventitious agent clearance;
- Removal of product- or process-related impurities, such as residual host cell DNA and proteins; and
- Maintenance of the purity level.

For approved products, an appropriate number of post-change batches should be analysed to demonstrate consistent performance of the process.

To support the analysis of the changes and the control strategy, the manufacturer should prepare a description of the change that summarises the manufacturing process of the pre-change process and the post-change process and that clearly highlights modifications of the process and changes in controls in a side-by-side format.

2.4 Demonstration of Comparability during Development

During product development, it is expected that multiple changes in the manufacturing process will occur that could impact drug product quality, safety, and efficacy.

Comparability exercises are generally performed to bridge nonclinical and clinical data generated with pre-change to post-change product in order to facilitate further development and, ultimately, to support the marketing authorisation. Comparability studies conducted for products in development are influenced by factors such as the stage of product development, the availability of validated analytical procedures, and the extent of product and process knowledge, which are limited at times due to the available experience that the manufacturer has with the process.

Where changes are introduced in development before nonclinical studies, the issue of assessing comparability is not generally raised because the manufacturer subsequently conducts nonclinical and clinical studies using the post-change product as part of the development process. During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulates, and the analytical tools develop, the comparability exercise should utilise available information and will generally become more comprehensive. Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorisation, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product. Some outcomes of the comparability studies on quality attributes can lead to additional nonclinical or clinical studies.

In order for a comparability exercise to occur during development, appropriate assessment tools should be used. It should be recognised that during development, analytical procedures might not be validated, but should always be scientifically sound and provide results that are reliable and reproducible. Due to the limitations of the analytical tools in early development, physicochemical and biological tests alone might be considered inadequate to determine comparability, and therefore, repeating elements of the nonclinical or clinical studies already performed would be considered appropriate.

3.0 Nonclinical and Clinical Considerations

Notice to the Reader: Where reference is made to nonclinical and clinical studies, additional information and modification of these specific items will be provided by ICH Safety and Efficacy Experts.

Determinations of product comparability can be based solely on quality considerations (see section 2.2) if the manufacturer can provide assurance of comparability through analytical studies as outlined in this document. Additional evidence from nonclinical or clinical studies is appropriate when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies should be determined on a case-by-case basis in consideration of various factors, which include:

- Quality findings, e.g.,
  - The type, nature, and extent of differences between the post-change product and the pre-change product with respect to quality attributes including product-related substances and the impurity profile;
  - The results of the evaluation/validation studies on the new process including the results of relevant in-process tests; and
  - The capabilities and limitations of tests used for any comparability studies.
- The nature of the product, e.g., product complexity, therapeutic class;
- Dosing regimen;
- Route of administration;
- The therapeutic window based upon dose ranging studies;

- Chronic vs. acute use;
- Extent of knowledge regarding structure-activity relationships;
- Previous experience with immunogenic events or responses in patients;
- Mechanism of action;
- Patient population;
- Availability of existing nonclinical and clinical data; and
- Knowledge of how a difference in quality attributes might impact on safety and efficacy.

4.0 Glossary

Comparability Bridging Study:
A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process.

Comparable:
A conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety, or efficacy of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might be indicated.

Comparability Exercise:
The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.

Quality Attribute:
A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define the adventitious agent safety, purity, potency, identity, and stability of the product. Specifications measure a selected subset of the quality attributes.

5.0 References

Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (Q5A)

Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (Q5B),

Stability Testing of Biotechnological/Biological Products (Q5C)

Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (Q5D)

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B)

Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (Q7A)

Text on Validation of Analytical Procedures (Q2A)

Validation of Analytical Procedures: Methodology (Q2B)

The Common Technical Document (M4Q)

Stability Testing of New Drug Substances and Products Q1A(R)