Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH

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I. INTRODUCTION (1) [2]

A. Objectives of the Guidance (1.1)

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. Therefore, this guidance is intended to assist manufacturers of biotechnological/biological products in the collection of relevant technical information that serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety, and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical, or clinical strategy. The main emphasis of the document is on quality aspects.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2004.

B. Background (1.2)

Manufacturers[3] of biotechnological/biological products frequently make changes to manufacturing processes[4] of products[5] 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 relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact[6] 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 prechange and postchange product, 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 section IV (4.0) References). This document builds upon the previous ICH guidances and provides additional direction regarding approaches to:

- Comparing postchange product to prechange product following manufacturing process changes; and
- Assessing 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 of the product.

C. Scope (1.3)

The principles adopted and explained in this document[7] 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

[3] 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).

[4] 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.

[5] For convenience, when the term *product* is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.

[6] Improvement of product quality is always desirable and encouraged. If the results of the comparability exercise indicate an improved quality suggesting a significant benefit in efficacy and/or safety, the pre- and postchange product may not be comparable. However, this result could be considered acceptable. The manufacturer is advised to consult the appropriate regional regulatory authority.

[7] This document applies to situations in which all three of the bulleted conditions are present.

highly purified and characterized using an appropriate set of analytical procedures;

- Products where manufacturing process changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of prechange and postchange product; and
- Products where manufacturing process changes are made in development or for which a marketing authorization 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.

D. General Principles (1.4)

The goal of the comparability exercise is to ensure the quality, safety, and efficacy of drug product produced by a changed manufacturing process through collection and evaluation of the relevant data to determine whether there might be 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 prechange and postchange product 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 postchange product are not 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 postchange product 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 foreseeable consequences for the product should be performed. In consideration of this evaluation, appropriate criteria to define highly similar postchange product can be established. Generally, quality data on the pre- and postchange product are generated, and a comparison is performed that integrates and evaluates all data collected, e.g., routine batch analyses, in-process control, process validation and/or evaluation data, characterization and stability, if appropriate. The comparison of the results to the predefined criteria should allow an objective assessment of whether or not the pre- and postchange product 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 postchange product are highly similar and considered comparable, i.e., no adverse impact on safety or efficacy profiles is foreseen.

- Although the pre- and postchange product appear highly similar, the analytical procedures used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider employing additional testing (e.g., further characterization) or nonclinical and/or clinical studies to reach a definitive conclusion.
- Although the pre- and postchange product appear highly similar, some differences have been observed in the quality attributes of the prechange and postchange product; but it can be justified that no adverse impact on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and postchange product can be considered comparable.
- Although the pre- and postchange product appear highly similar, some differences have been identified in the comparison of quality attributes and a possible adverse impact on safety and efficacy profiles cannot be excluded. In such situations, the generation and analysis of additional data on quality attributes are unlikely to assist in determining whether pre- and postchange product are comparable. The manufacturer should consider performing nonclinical and/or clinical studies.
- Differences in the quality attributes are so significant that it is determined that the products are not highly similar and are therefore not comparable. This outcome is not within the scope of this document and is not discussed further.

II. GUIDANCE (2)

A. Considerations for the Comparability Exercise (2.1)

The goal of the comparability exercise is to ascertain that pre- and postchange drug product are comparable in terms of quality, safety, and efficacy. To meet this goal, the product should be evaluated at the process step most appropriate to detect a change in the quality attributes. This may entail evaluating the product at multiple stages of manufacture. For example, even though all process changes occurred in the manufacture of the drug substance, in cases where the drug product could be impacted by the change, it might be appropriate to collect data on both the drug substance and the drug product to support the determination of comparability. Comparability can often be deduced from quality studies alone (limited or comprehensive analysis, as appropriate), but might sometimes need to be supported by comparability bridging studies. The extent of the studies necessary to 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, product-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 overall nonclinical and clinical experience.

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

- Relevant physicochemical and biological characterization 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 product and, hence, potential differences in product-related substances and product-related impurities;
- Batches used for demonstration of manufacturing consistency;
- Historical 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 impact of the process change on the quality of in-process materials, as well as the ability of downstream steps to accommodate material from a changed cell culture process;
- Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the postchange process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
- Nonclinical or clinical characteristics of the drug product and its therapeutic indications (see section II.E (2.5) of this guidance.

B. Quality Considerations (2.2)

1. Analytical Techniques (2.2.1)

The battery of tests for the comparability exercise should be carefully selected and optimized to maximize the potential for detecting relevant differences in the quality attributes of the product 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 maximize 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 prechange product will be able to detect modifications of the product due to (1) the limitations of the assays (e.g., precision, specificity, and detection limit) and (2) the complexity of some products due to molecular heterogeneity. Consequently, the manufacturer should determine:

- Whether or not existing tests remain appropriate 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 result of changes in quality attributes that the existing methods are not capable of measuring. That is, when specific changes in quality attributes are expected as a result of a 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 characterization or routine testing.

The measurement of quality attributes in characterization studies 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 to measure quality attributes for batch release should be validated in accordance with ICH guidances (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

2. Characterization (2.2.2)

Characterization 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 rationalized) repetition of the characterization activity conducted for the market application is generally warranted to directly compare the prechange and postchange product. However, additional characterization might be indicated in some cases. For example, when process changes result in a product characterization profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials (e.g., reference materials, marketed batches), the significance of these alterations should be evaluated. Results of comprehensive characterization of the material used in pivotal clinical trials could provide a useful point of reference for subsequent comparability exercises.

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

- **Physicochemical Properties**

The manufacturer should consider 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 considered. 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 can serve multiple purposes in the confirmation of product quality attributes that are useful for characterization and batch analysis, and, in some cases, could serve as a link to clinical activity. The manufacturer should consider 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 sufficiently correlated with clinical safety or efficacy or if the mechanism of action is not understood, the manufacturer should justify that nonclinical or clinical activity is not compromised in the postchange product.

- **Immunochemical Properties**

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

- **Purity, Impurities, and Contaminants**

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

If differences are observed in the purity and impurity profiles of the postchange product relative to the prechange product, the differences should be evaluated to assess their potential impact on safety and efficacy. Where the change results in the appearance of new impurities, the new impurities should be identified and characterized when possible. Depending on the impurity type and amount, it might be appropriate to conduct 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. New contaminants should be evaluated to assess their potential impact on the quality, safety and efficacy of the product.

3. Specifications (2.2.3)

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 characterize 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 postchange 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 unless justified. In some cases, additional tests and acceptance criteria on the relative amount 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 postchange 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, characterization studies, batch analysis data, stability data, and nonclinical and clinical experience.

4. Stability (2.2.4)

For certain manufacturing process changes, even slight modifications of the production procedures might cause changes in the stability of the postchange 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 made to buffer composition, processing and holding conditions, and the use of organic solvents. Furthermore, stability studies might be able to detect subtle differences that are not readily

detectable by the characterization 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; or, in some cases, divalent ions leached from the container closure system might change the stability profile because of the activation of trace proteases not detected in stability studies of the prechange product. Therefore, real-time/real temperature stability studies on the product potentially affected by the change should be initiated, as appropriate.

Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of prechange and postchange product. 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.

C. Manufacturing Process Considerations (2.3)

A well-defined manufacturing process with its associated process controls ensures 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 at least 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, in-process hold times, 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 reevaluated, and which steps should not be impacted by the proposed change. For example, analysis of 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 prechange and postchange product 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 reevaluated and/or revalidated, as appropriate. The in-process controls, including critical control points and in-process testing, should ensure that the postchange process is well controlled and maintains the quality of the product. Typically, reevaluation/revalidation activities for a simple change might be limited to the affected process step if there is no evidence to indicate that there is an 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 postchange cell banks and cells at the limit of in vitro cell age for production;
- 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 postchange batches should be analyzed 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 summarizes the prechange and the postchange manufacturing process and that clearly highlights modifications of the process and changes in controls in a side-by-side format.

D. Demonstration of Comparability During Development (2.4)

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 demonstrate that nonclinical and clinical data generated with prechange product are applicable to postchange product in order to facilitate further development and, ultimately, to support the marketing authorization. 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 postchange 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 accumulate, and the analytical tools develop, the comparability exercise should utilize 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 authorization, 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. Analytical procedures used during development 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 clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability; therefore, bridging nonclinical and/or clinical studies, as appropriate, might be needed.

E. Nonclinical and Clinical Considerations (2.5)

1. Factors To Be Considered in Planning Nonclinical and Clinical Studies (2.5.1)

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 suggested in this document. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis in consideration of various factors, which include among others:

Quality findings

- Drug product — The type, nature, and extent of differences between the postchange product and the prechange product with respect to quality attributes including product-related substances, the impurity profile, stability, and excipients.
  For example, new impurities could warrant toxicological studies for qualification;
- Results of the evaluation/validation studies on the new process including the results of relevant in-process tests;
- Availability, capabilities, and limitations of tests used for any comparability studies.

The nature and the level of knowledge of the product

- Product complexity, including heterogeneity and higher order structure — Physicochemical and in vitro biological assays might not be able to detect all differences in structure and/or function;
- Structure-activity relationship and strength of the association of quality attributes with safety and efficacy;
- Relationship between the therapeutic protein and endogenous proteins and the consequences for immunogenicity;
- Mode(s) of action (unknown vs. known, single vs. multiple active sites).

Existing nonclinical and clinical data relevant to the product, aspects of product use, and product class

- Therapeutic indications/target patient groups — The impact of possible differences can vary between patient groups, e.g., risk for unintended immunogenicity. It may be appropriate to consider the consequences separately for each indication;
- Posology, e.g., dosing regimen, route of administration — The risk of certain possible consequences of a difference, such as immunogenicity, could be higher with chronic administration as compared to short-term administration; subcutaneous administration might induce immunogenicity more often than intravenous administration;
- The therapeutic window/dose-response curve — The impact of a certain change could be different for products that have a wide therapeutic window as compared to those with a more narrow window. The safety or efficacy of products with a steep or a bell-shaped dose-response curve can be affected by minor changes in pharmacokinetics or receptor-binding;
- Previous experience, e.g., immunogenicity, safety — The experience with the original product or with other products in the same class can be relevant, especially with regard to rare adverse effects, e.g., knowledge about the consequences of immunogenicity;
- Pharmacokinetic (PK)/pharmacodynamic (PD) relation, distribution, clearance.

2. Type of Studies (2.5.2)

The nonclinical and clinical studies referred to in this document might include, depending on the situation, PK studies, PD studies, PK/PD studies, clinical efficacy studies, specific safety studies, immunogenicity studies, and pharmacovigilance studies. The purpose of these studies is to enable comparison of pre- and postchange product. Where appropriate, these studies should be direct comparative studies.

GLOSSARY (3)

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 have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, 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 contribute to the conclusion.

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 identity, purity, potency, and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes.

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