

Final Concept Paper
Q5E: Comparability of Biotechnological/Biological Products
Subject to Changes in Their Manufacturing Process
dated 5 February 2002

Endorsed by the Steering Committee on 7 February 2002

Type of Harmonisation Action Proposed

A new tripartite, harmonised guideline is proposed in the Quality topic area on the “Comparability of Biotechnological / Biological Products Subject to Changes in their Drug Substance and /or Drug Product Manufacturing Process”. For establishing these comparisons, it is necessary to address both product and process aspects which, while in some instances region-specific, are uniform in their principles and are necessary to support changes in manufacturing processes yielding products defined within the scope of Q6B. When the Quality aspects have been addressed, experts from the Safety and Efficacy groups will be invited to consider issues in the preclinical and in the clinical areas, as appropriate.

Statement of the Problem

Consistent with modern global manufacturing practices and scientific and economic considerations, changes to the manufacturing process directed toward quality improvement for drug substances and drug products account for a significant proportion of manufacturers’ resources and efforts. These manufacturing process changes may be made both during the development phase and once the product is on the market.

To date, various topics related to the characterisation and quality assessment as well as the manufacturing process for biotechnological/biological products (Q5A, Q5B, Q5C, Q5D, Q6B, and CTD-Q) have been the subject of ICH harmonised guidelines and have proven very useful, in allowing manufacturers to develop a global approach to these issues.

However, there is still a need for further harmonisation as, currently, the technical guidance for establishing the comparability of biotechnological / biological Drug Substances and/or Drug Products, subject to changes in the manufacturing process, varies significantly among the marketing regions represented in the ICH process. As a consequence, manufacturers must meet the individual region-specific requirements in establishing the comparability of a product manufactured by a modified process, prior to implementing changes to the manufacturing process for the product on a global basis. Frequently, this leads to highly dissimilar data collection, reporting requirements, and regional specifications that result in different implementation/distribution schedules for the product. The direct impact of these differing requirements is that:

- industry dedicates significant resources to understand regulatory requirements of individual countries and regions;
- in the different regions, dissimilar data submission packages are necessary to support the comparison of the product from the modified manufacturing process;
- increased inventory of product to prevent shortages is required to meet the needs of different regions;
- delays occur with respect to implementation to satisfy the most stringent documentation requirements;

- economic inefficiency results when multiple sites produce region-specific product due to the difficulty of coordinating the approval of changes in certain regions;
- acceptable product often loses a significant portion of its dating period due to delays in regulatory evaluation;
- patients in some regions need to wait longer for products, which in some cases possess improved quality. Regional specifications and reporting requirements dictate that product may be available in one region and not in another leading to product shortage and patient frustration and misunderstanding.;
- manufacturers are discouraged from implementing improvements to the process.

Proposed Resolution of the Problem

It is proposed that a harmonised guideline be prepared, focused on principles addressing the scientific basis that a manufacturer uses to establish the comparability of “proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.” (same scope as ICH Q6B).

A harmonised guideline will be limited to the scientific approaches to compare products after a change to a production process has been made. The principles for a comparability study would be defined to assess the potential impact of a change on the quality of a given product, as it relates to its safety and efficacy. Where preclinical or clinical data for a drug product derived from previous processes are used to support regulatory submissions for products derived from changed processes, it may be necessary to determine the comparability of drug substance or drug product using the scientific principles established in this document. The guideline should:

- Introduce strategies for establishing the comparability of products, i.e., describe the importance of product attributes, the manufacturing process including evaluation/validation, process controls, and consistency, and the need to consider the entire spectrum of studies (including analytical characterisation, preclinical, and clinical studies) for assessing product comparability and for supporting changes in the manufacturing process for protein therapeutics as defined within the scope of Q6B.
- Define factors which effect the extent and nature of analytical characterisation, preclinical, and clinical comparability studies
- Define the significance of product comparability in terms of the molecular and quality attributes as an essential and critical first step when introducing a change to a manufacturing process, e.g., studies involving analytical characterisation, in-process testing, quality control testing, stability determination.
- Describe analytical techniques available to perform the comparison.
- Describe the value of analytical data in assuring the quality and predicting *in vivo* behaviour of the molecule produced by the changed process.

- Provide a set of criteria to facilitate assessment of data generated from the comparison in order to evaluate the impact of documented differences between the products.

The phase of product development (e.g., early development, marketed product) and the familiarity with the process and product (e.g., change within one site, change in sites) likely dictates the rigor with which the approaches are applied.

Type of Expert Working Group

The EWG should be composed of experts in the Quality field who will develop the guideline. When the Quality aspects have been addressed, experts from the Safety and Efficacy groups will be invited to consider issues in the preclinical and in the clinical areas, as appropriate. This staged approach to guideline development is sensible in view of the nature and complexity of this issue. It is anticipated that:

- the "FDA Guidance Concerning Demonstration Of Comparability Of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April 1996";
- the CPMP, "Note For Guidance On Comparability Of Medicinal Products Containing Biotechnology-Derived Proteins As Drug Substance," CPMP/BWP/3207/00 March 2002;
- the MHLW paper "MHLW's views and scientific approaches for assessing the comparability of biotechnological / biological products, May 2001";
- the ICH guidelines: Q6B, CTD-Q, Q5A, Q5B, Q5C, Q5D, S6; and
- the scientific discussions on comparability obtained at the Biologics 2000 conference sponsored by the IABS/USP/FDA,

can serve as a solid foundation and template, allowing for rapid development of the proposed ICH guideline. Initiation of the work by the EWG should be timely, with consideration given to a gradual phasing in approach, with the expert working group convening first when resources are available.