Manufacturing process changes, biologic product comparability and post approval changes

Nanna Aaby Kruse, Senior Biological Assessor at Danish Health and Medicines Authority

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A biological medicinal product is a product, the active substance of which is a biological substance.

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control.

The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93 (products produced by use of recombinant DNA technology); advanced therapy medicinal products as defined in Part IV of this Annex.
ICH Q5E

European Medicines Agency

June 2005
CPMP/ICH/5721/03

ICH Topic Q 5 E
Comparability of Biotechnological/Biological Products

Step 5

NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (CPMP/ICH/5721/03)
Objectives of the Guideline ICH Q5

- 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.

- Collection of relevant technical information which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product.
Manufacturers of biotechnological/biological products frequently make changes to manufacturing processes of products 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.
Identical or comparable..??
Some general principles of ICH Q5E

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change 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 post-change product are not warranted.
It is important to note that from a regulatory perspective changes to the manufacturing process or product is evaluated by to “sets of eyes”

Changes before applying for a Marketing Authorisation

• Changes to the manufacturing process are expected
• Product quality is expected to improve e.g. higher purity (lower levels of aggregates)
• Main purpose of the comparability study is to confirm/support that the pre- and post-change product are not so different that the non-clinical and clinical studies already conducted is still valid

Changes after a Marketing Authorisation is granted

• NO changes to the product are expected
Medicinal Drug Product development changes

**vs.**

"Comfort index" of Assessors

Very early development before non-clinical studies

Early development non-clinical studies conducted

Early development phase I/II clinical studies conducted

Late development phase III pivotal clinical studies conducted

Marketing Authorisation

Post Approval

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Changes seen **during development** of a Medicinal Product

- Change in the genetic construct of the cell line and/or change in the cell line
- Change in the fermentation process. – The process itself, the scale, the mode of running (perfusion, fed-batch, single-equipment etc.), raw materials used during fermentation
- Harvest process
- Order of purification steps, replacement and/or removal of purification steps
- Formulation of drug product and manufacture of drug product
- New drug substance and/or new drug product manufacture

Each of these changes can potentially change the quality of the product.

Changes to quality are acceptable, if justified to be without effect on safety and efficacy and do not “in-validate” former studies.
Changes seen after a Marketing Approval of a Medicinal Product

- Change in the genetic construct of the cell line and/or change in the cell line
- Change in the fermentation process. – the scale, the mode of running (perfusion, fed-batch, single-equipment etc.), raw materials used during fermentation
- Harvest process
- Purification, - order of purification steps, replacement and/or removal of purification steps
- Formulation of drug product and manufacture of drug product
- New drug substance and/or new drug product manufacture

At this stage product is NOT expected to be changed and any change that may be seen needs carefully investigation and justified in relation to safety and efficacy of the product
Some general principles of ICH Q5E

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 post-change product can be established.

Generally, quality data on the pre- and post-change 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/evaluation data, characterisation 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 post-change product are comparable.
ICH Q5E – Think smart

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.
Proteins are complex molecules that form multiple levels of structure

1° Structure
Amino acid sequence

2° Structure
Sub-structure
(a-helix, β-sheet, etc.)

3° Structure
Three dimensional structure

4° Structure
Self-associated structure
(aggregation)
Characterisation Principles

Orthogonal methods should be used to analyse:

• Primary structure and Molecular Mass
  • Edman Degradation, Peptide mapping, Sulfhydryl Analysis for disulphide bonds…..
• Secondary – and higher order structure
  • Near and Far-UV CD Spectra, FTIR

Three batches
One treated with urea

22 April, 2015
Characterisation

Principles

Orthogonal methods should be used to analyse:

- Purity and Heterogeneity/isoforms including post-translational modifications:
  - Size
  - Charge
  - Glycosylation
N-Linked Oligosaccharide Profiles

Pre-change material

Small scale post-change material

Full scale post-change material

- Fucose
- Mannose
- Galactose
- GlcNAc
Imaged capillary electrophoresis

Non-clinical material

Phase I Clinical material

Marketing Authorisation
Characterisation Principles

Orthogonal methods should be used to analyse:

• Impurities of the product: Aggregates, Deamidation and Oxidation
• Impurities of the process: Host cell protein, resin leachables
• Biological activity: Mode of action, binding to receptors, receptor binding effect
• Forced degradation studies
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
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<tbody>
<tr>
<td><strong>Structural characterisation</strong></td>
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<td>LC/MS based peptide mapping</td>
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<td>LC/ESI-MS/MS based sequencing</td>
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<td>Amino acid analysis</td>
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<td>Secondary structure</td>
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<td>Disulphide bridges</td>
<td>LC/ESI-HRMS</td>
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<td>Free thiol groups</td>
<td>Colorimetric assay (FL)</td>
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<td>Intact molecular weight</td>
<td>LC/ESI-HRMS</td>
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<td>Glycosylation site mapping</td>
<td>LC/ESI-MS/MS</td>
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<td>Glycosylation pattern</td>
<td>HILIC-UHPLC-FL</td>
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<td>Monosaccharide composition</td>
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<td>analysis</td>
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<td>Thermodynamic stability</td>
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<td><strong>Identification tests for active substance</strong></td>
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<td>Determination based on hydrophobicity</td>
<td>RP-HPLC UV detection</td>
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<td>Determination based on size</td>
<td>Reducing/non-reducing chip-electrophoresis</td>
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<td>Determination based on charge</td>
<td>Capillary isoelectric focusing</td>
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<td><strong>Purity</strong></td>
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<td>Variants and impurities with different molecular weight</td>
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<td>Variants with different charge</td>
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<td>Fab/Fc-related purity</td>
<td>IEX-HPLC</td>
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<td><strong>Assays</strong></td>
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<td>Active substance content</td>
<td>RP-HPLC UV detection</td>
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<td>Sialic acid content</td>
<td>RP-HPLC-FL</td>
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<td>Parameter to be tested</td>
<td>In vitro assay (Method)</td>
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<tr>
<td><strong>Binding to target antigen</strong></td>
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<td>Binding to CD20</td>
<td>CD20 binding assay (SPR)</td>
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<td>Binding to all Fcγ receptors</td>
<td>CD16a binding assay (SPR)</td>
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<td>CD32a binding assay (SPR)</td>
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<tr>
<td>Binding to all Fcγ receptors</td>
<td>CD64 binding assay (SPR)</td>
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<tr>
<td>Binding to FcRn receptors</td>
<td>FcRn binding assay (SPR)</td>
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<td>Fab-associated functions</td>
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<tr>
<td>Receptor activation</td>
<td>Apoptosis inducing property on CD20 expressing cells (Cytotoxicity assay)</td>
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<tr>
<td>Other</td>
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<td>Fc-associated functions</td>
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<td>ADCC effector assay on CD20 expressing cells (Calcein release assay)</td>
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<td><strong>Binding to representative isoforms of FcγR, FcRn and complement</strong></td>
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<td>Binding to all Fcγ receptors</td>
<td>Binding to FcγRIIb (CD32b) (SPR)</td>
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<td>Binding to FcγRIIa (CD16a) high affinity (SPR)</td>
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<tr>
<td>Binding to FcγRIIib (CD16b) (SPR)</td>
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<tr>
<td>Binding to complement</td>
<td>C1q binding assay (ELISA)</td>
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<tr>
<td><strong>Fab-associated functions</strong></td>
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<tr>
<td>Receptor activation</td>
<td>Inhibition of cell proliferation through CD20 receptor (Viability assay)</td>
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<td><strong>Other</strong></td>
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<tr>
<td>Cytokine release</td>
<td>Release of IL-6, IL-8, IFNγ, TNF (Whole Blood Assay)</td>
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How much comparability do we need?

How much do we need to know?

C. Schneider, Chair of biosimilar working party
How much comparability do we need?

How much do we need to know?

C. Schneider, Chair of biosimilar working party
Thank you for your attention

Further information

ICH Topic Q 5 E Comparability of Biotechnological / Biological Products. Note for Guidance on Biotechnological / Biological Products Subject to Changes in their Manufacturing Process (CHMP/ICH/5721/03)

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
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