EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Sundhedsstyrelsen
Danish Health and Medicines Authority

Manufacturing process changes, biologic product comparability and post approval changes

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EU Definition (Directive 2001/83/EC, Annex I (= Directive 2003/63/EC)) of a biological medicinal product

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

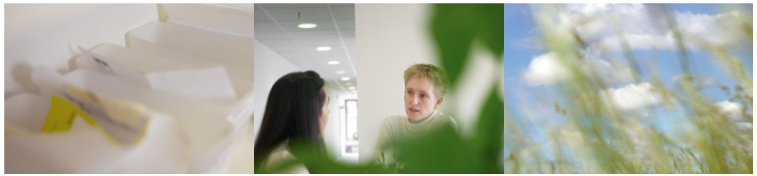
Step 5

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.**



Background ICH Q5E

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.**

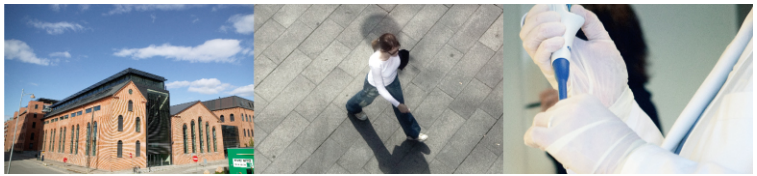
It is important to note that from a regulatory perspective changes to the manufacturing process or product is evaluated by to ”sets of eyes”

Changes before applying for a Marketing Authorisation

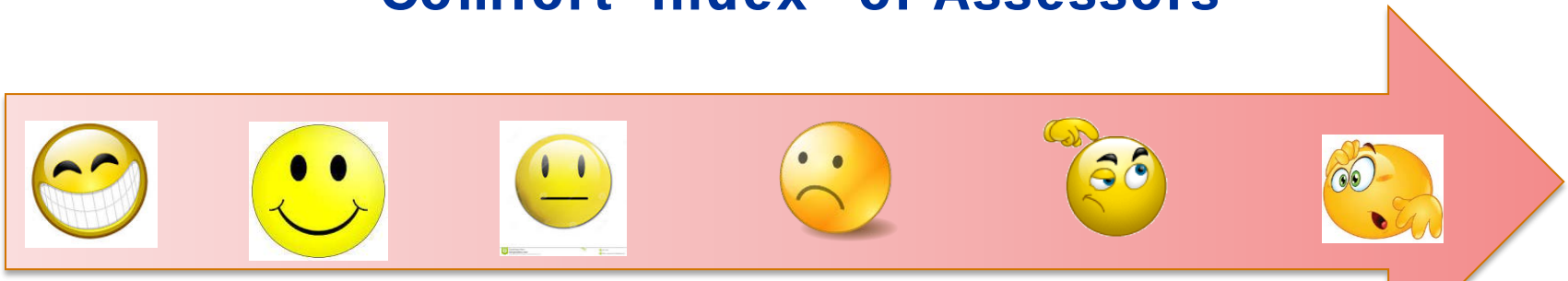
- Changes to the manufacturing process are expected
- Product quality is expected to improve e.g higher purity (lower levels of aggregates)
- Main purpose of the comparability study is to confirm/support that the pre- and post-change product are not so different that the non-clinical and clinical studies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

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

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

- 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/ore new drug product manufacture

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
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- Purification, - order of purification steps, replacement and/or removal of purification steps
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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.

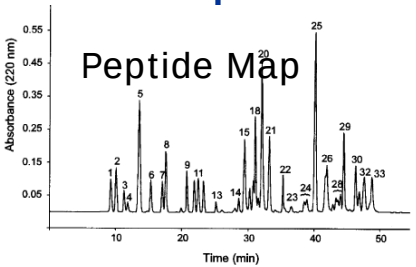
ICH Q5E – Think smart

The extent of the studies necessary to demonstrate comparability will depend on:

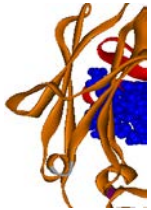
- The production step where the changes are introduced;
- The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product related substances);
- 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.

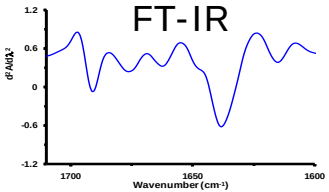
Proteins are complex molecules that form multiple levels of structure

1° Structure
Amino acid sequence

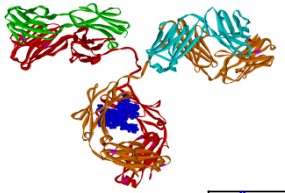


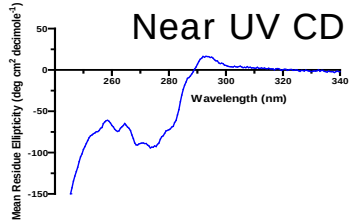
2° Structure
Sub-structure
(a-helix, b-sheet, etc.)



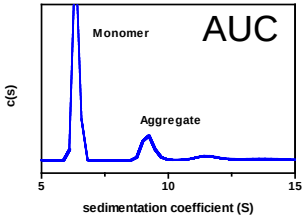


3° Structure
Three dimensional structure

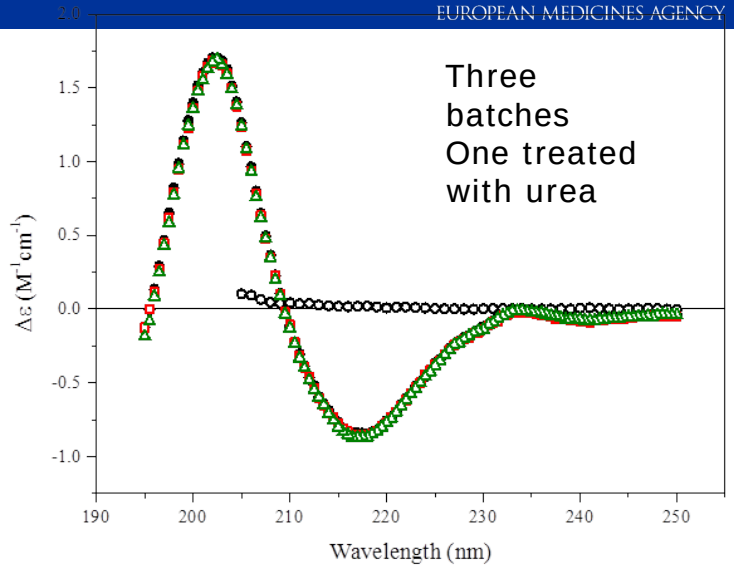




4° Structure
Self-associated structure
(aggregation)



Characterisation Principles



Orthogonal methods should be used to analyse:

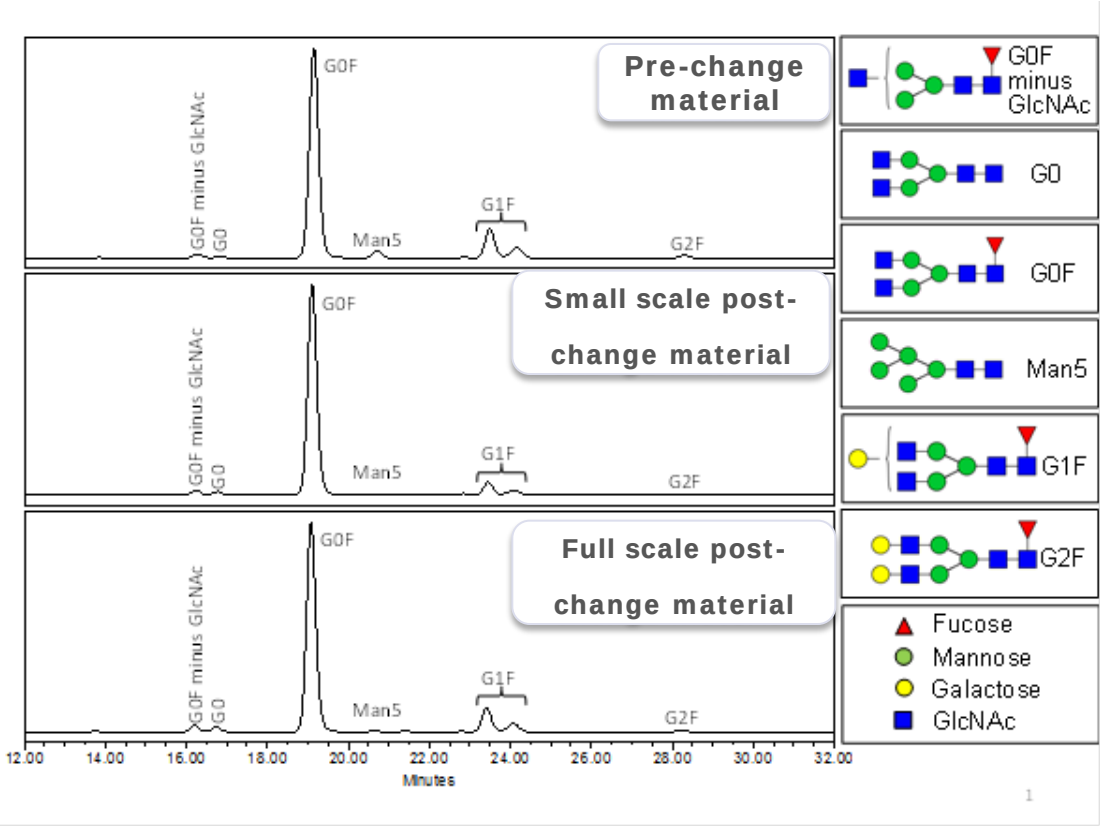
- Primary structure and Molecular Mass
  - Edman Degradation, Peptide mapping, Sulfhydryl Analysis for disulphide bonds…..
- Secondary – and higher order structure
  - Near and Far-UV CD Spectra, FTIR

Characterisation
Principles

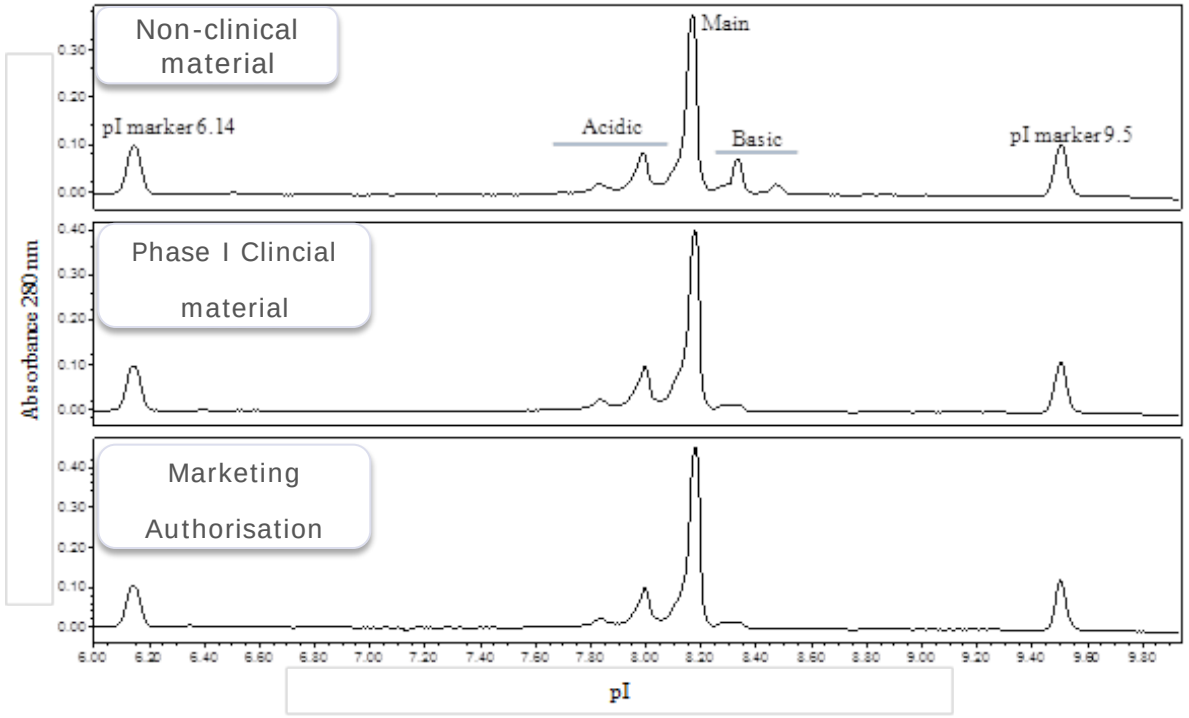
Orthogonal methods should be used to analyse:

- Purity and Heterogeneity/isoforms including post-translational modifications:
  - Size
  - Charge
  - Glycosylation

N-Linked Oligosaccharide Profiles



Imaged capillary electrophoresis

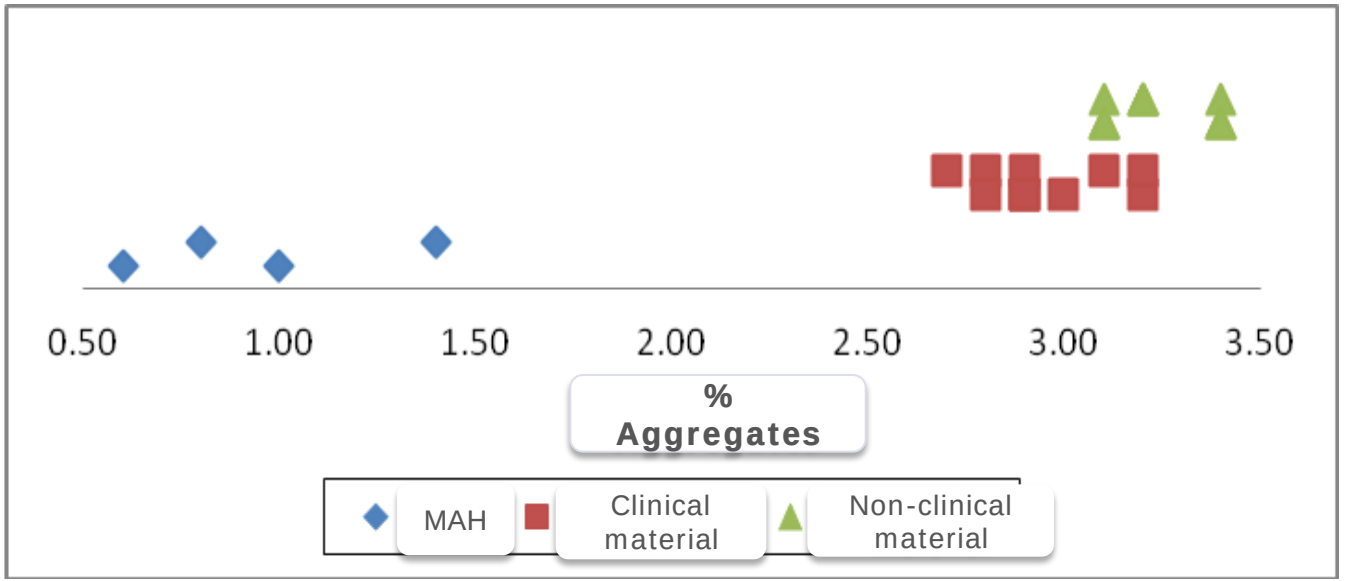


Characterisation Principles

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

SE-HPLC Analysis - Aggregates



Parameter	Method	
Structural characterisation		
Primary structure	RP-HPLC-UV based peptide mapping	
	LC/MS based peptide mapping	
	LC/ESI-MS/MS based sequencing	
	Amino acid analysis	
Secondary structure	CD spectroscopy	
Tertiary structure	FL spectroscopy	
	NMR spectroscopy	
Disulphide bridges	LC/ESI-HRMS	
Free thiol groups	Colorimetric assay (FL)	
Intact molecular weight	LC/ESI-HRMS	
Glycosylation site mapping	LC/ESI-MS/MS	
Glycosylation pattern	HILIC-UHPLC-FL	
Monosaccharide composition analysis	RP-HPLC-FL	
Thermodynamic stability	DSC	
Identification tests for active substance		
Determination based on hydrophobicity	RP-HPLC UV detection	
Determination based on size	Reducing/non-reducing chip-electrophoresis	
Determination based on charge	Capillary isoelectric focusing	
Purity		
Variants and impurities with different molecular weight	SEC-HPLC	
	Reducing/non-reducing chip-electrophoresis	
Aggregation	Dynamic light scattering	
Variants with different charge	IEX-HPLC	
Fab/Fc-related purity	IEX-HPLC	
Assays		
Active substance content	RP-HPLC UV detection	
Sialic acid content	RP-HPLC-FL	

	Parameter to be tested	In vitro assay (Method)
Binding to target antigen	Binding to CD20	CD20 binding assay (SPR)
Binding to representative isoforms of FcγR, FcRn and complement	Binding to all Fcγ receptors	CD16a binding assay (SPR)
	Binding to all Fcγ receptors	CD32a binding assay (SPR)
	Binding to all Fcγ receptors	CD64 binding assay (SPR)
	Binding to FcRn receptors	FcRn binding assay (SPR)
Fab-associated functions	Receptor activation	Apoptosis inducing property on CD20 expressing cells (Cytotoxicity assay)
Fc-associated functions	ADCC	ADCC effector assay on CD20 expressing cells (Calcein release assay)
	CDC	Complement-dependent cytotoxicity measurement (Viability assay)
	Complement activation	Complement activation assay (ELISA)

	Parameter to be tested	In vitro assay
Binding to representative isoforms of FcγR, FcRn and complement	Binding to all Fcγ receptors	Binding to FcγRIIb (CD32b) (SPR)
	Binding to all Fcγ receptors	Binding to FcγRIIIa (CD16a) high affinity (SPR)
	Binding to all Fcγ receptors	Binding to FcγRIIIb (CD16b) (SPR)
	Binding to complement[(a)]	C1q binding assay (ELISA)
Fab-associated functions	Receptor activation	Inhibition of cell proliferation through CD20 receptor (Viability assay)
Other	Cytokine release[(a)]	Release of IL-6, IL-8, IFNγ, TNF (Whole Blood Assay)

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)

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