



ICH Q5E Comparability of Biotechnological/ Biological Products

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- **The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.**

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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)

TRANSMISSION TO CHMP	November 2003
TRANSMISSION TO INTERESTED PARTIES	November 2003
DEADLINE FOR COMMENTS	May 2004
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main emphasis of the document is on quality aspects

General Considerations

- Changes to the manufacturing processes of biotechnological/biological products both during development and after approval are normal and expected
- Reasons for changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements.

Applies 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 (same as ICH Q6B, Q5C)
- 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 pre-change and post-change product;
- Products where manufacturing process changes are made in **development** or for which a **marketing authorisation** has been granted.

The process is the product

- **The entire manufacturing process determines the quality of a biotech product**
 - Raw-/Starting Materials
 - Fermentation
 - Purification
 - Formulation
- **Minor process changes can have an impact on the quality**

Quality profile

Release Tests (Specifications)

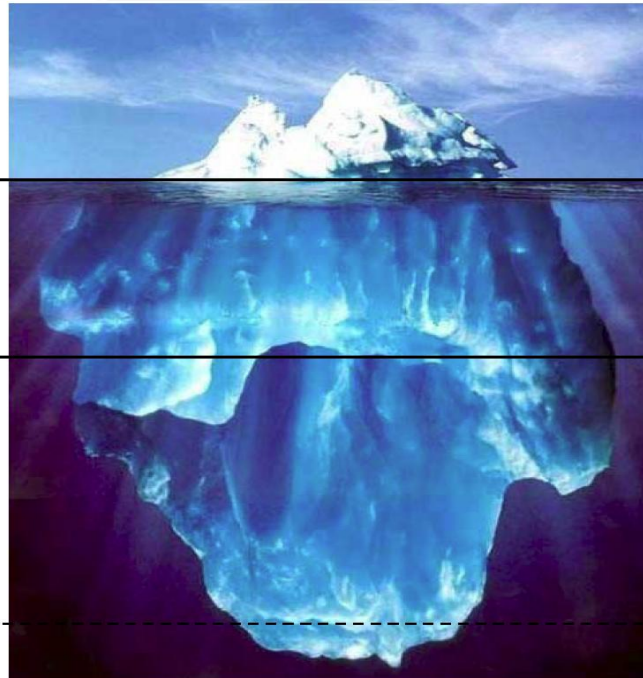
Extended Characterization (Process & Product)

Process Control

- Procedures
 - Materials
 - In-process testing
 - Monitoring
 - Validation
-

Unknown

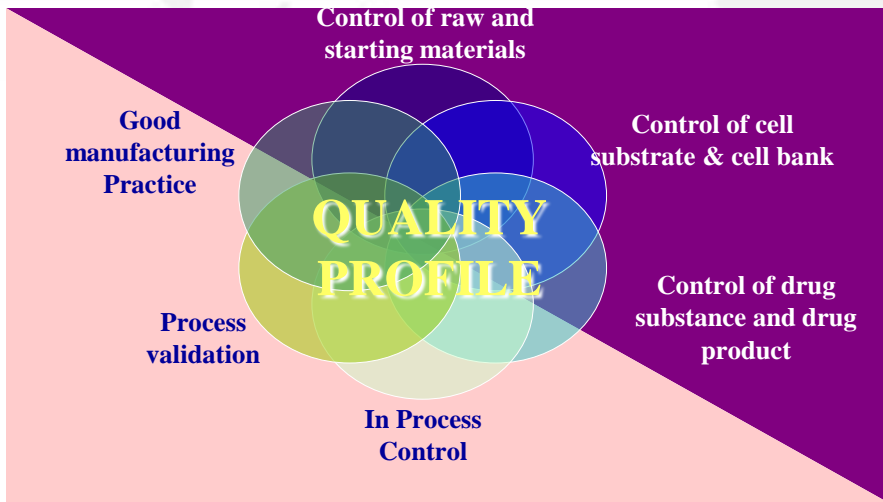
Learned over time –
update control strategy



Classification of changes „major“ or „minor“

- no a priori prediction
- any changes („minor“ or „major“) can have an impact on Q, S, E
- the implication of a change can not be predicted

Product A / Process A

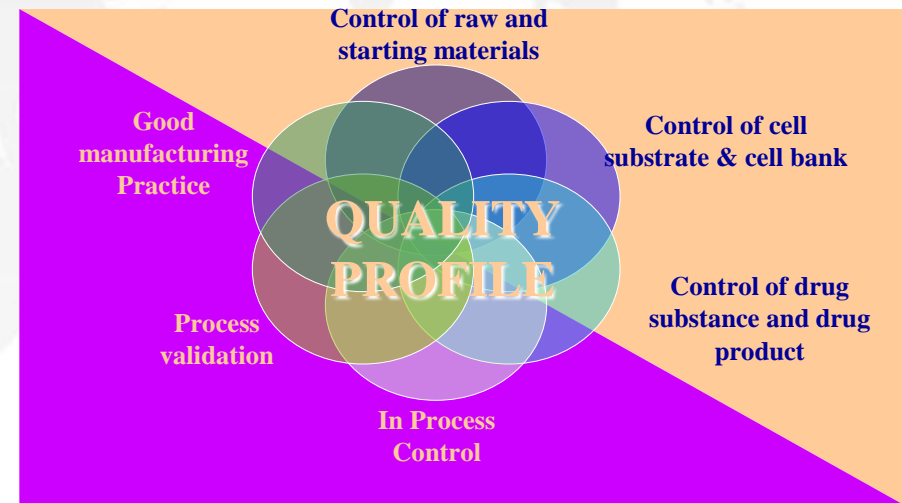
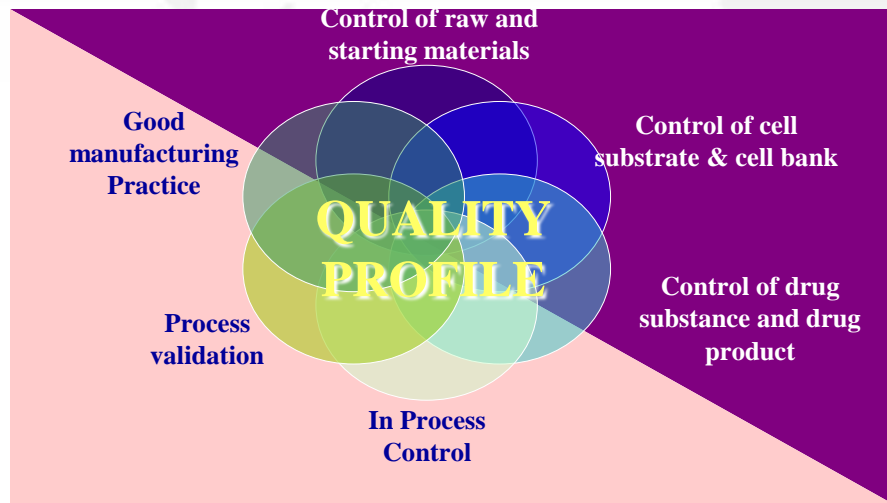


Safety & Efficacy profiles

A

Product A1 / Process A1

Product A2 / Process A2



Safety & Efficacy profiles

A1



Safety & Efficacy profiles

A2

Comparability (ICH Q5E)

- **Comparability exercise:**

- Goal: to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy.
- to collect 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

Comparability (ICH Q5E)

- **Demonstration of comparability:**
 - Does not necessarily mean that the quality attributes of the pre-change and post-change products are identical but highly similar
 - Ensure that differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.
 - Based on combination of analytical testing, biological assays ± nonclinical and clinical data

Comparability (ICH Q5E)

Evaluation of Quality attributes

no difference observed

- Q "highly similar" & no doubt on analytical procedure
- No impact on S/E foreseen

considered comparable

- Q "highly similar" but doubt on analytical procedure

consider non-clinical/
clinical studies

differences observed

- Q "highly similar" but differences observed
- No impact on S/E expected based on experience & relevant data

may be considered comparable

- Q "highly similar" but differences observed
- Impact on S/E cannot be excluded

consider non-clinical/
clinical studies

- Q significant differences

Not comparable /
out of scope

Comparability (ICH Q5E)

- **Comparability exercise: Extent of data depend on:**
 - Step where the change is introduced
 - Potential impact of the change
 - Suitability of analytical techniques
 - Knowledge of the product & relationship between quality attributes and safety and efficacy
- **Determination of comparability**
 - Combination of analytical testing, biological assays, non-clinical and clinical data in some cases
 - Demonstration of highly similar Quality profiles
 - validation batches, recent batches
 - historical results, sample library
 - stability profile
 - Justification of the suitability of the methods
 - appropriately selected to maximize the potential of detecting differences
 - specification: may not be sufficient
 - characterization: may be required

Considerations for the Comparability Exercise

- 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.

Considerations for the Comparability Exercise

Extent of the studies 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;
- The relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience.

Considerations for the Comparability Exercise

- 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 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.

Comparability (ICH Q5E)

- **Manufacturing process considerations**

- Well defined process + controls :
 - Assurance that product is produced in a consistent manner
 - Suitability of controls: confirm that process controls in the modified process provide similar or more effective control of the product quality, compared to the original process

Comparability (ICH Q5E)

- **Manufacturing process considerations**
 - 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 inprocess testing: In-process controls for the post-change process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;

Comparability (ICH Q5E)

- **Manufacturing process considerations**
 - 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,
 - 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
 - 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.
 - Use of prior 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.

Comparability (ICH Q5E)

- **Manufacturing process considerations**
- **Demonstration of state of control with the modified/changed manufacturing process. e.g.**
 - 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 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;
 - Maintenance of the purity level.

Analytical Considerations

- The battery of tests should be selected and optimised to maximise the potential for detecting relevant differences in the quality attributes 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 using methods employing different physicochemical or biological principles
- There might be limitations of the assays (e.g., precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity.
- Do existing tests remain appropriate for their intended use or should be modified?
- Need to add new tests as a result of changes in quality attributes that the existing methods are not capable of measuring ??

Analytical Considerations

Additional characterisation might be indicated in some cases

- For example, 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 (e.g., reference materials, marketed batches), the significance of these alterations should be evaluated.
 - Physicochemical Properties
 - Biological Activity
 - Immunochemical Properties
 - Purity, Impurities, and Contaminants
 - Specifications
 - **Stability**

Analytical Considerations - Stability

- Slight modifications of the production procedures 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.
- **Stability studies** might be able to detect subtle differences that are not readily detectable by the characterisation studies.
 - buffer composition,
 - processing and holding conditions, use
 - organic solvents
 - trace amounts of a protease.
 - Changes of might only be detected by product degradation that occurs over an extended time period;

Analytical Considerations

- Real-time/real temperature stability studies
- Accelerated and stress stability studies to establish degradation profiles and provide a further direct comparison of pre-change and post-change product.
- ICH Q5C and Q1A(R) should be consulted to determine the conditions f

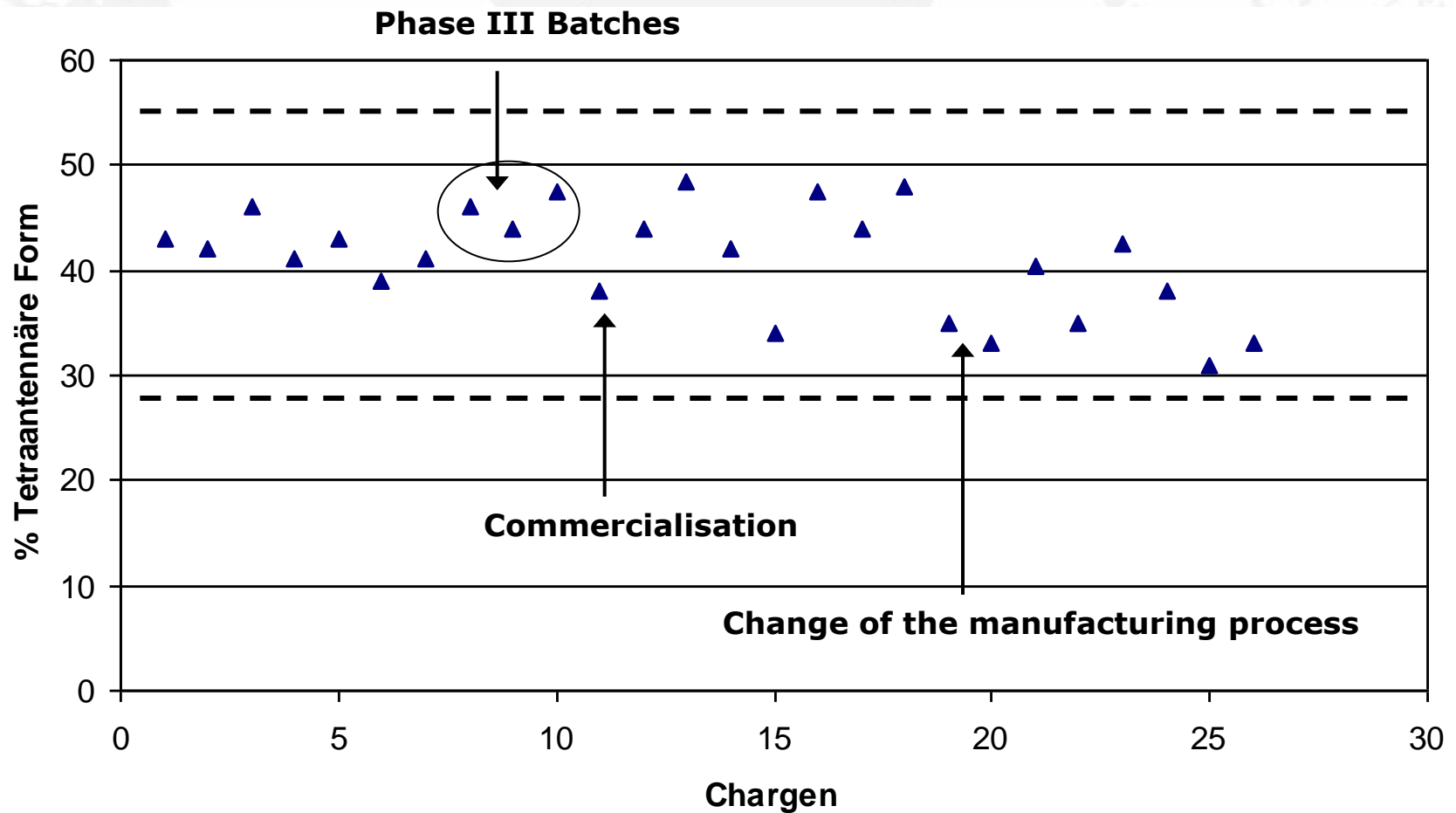
Comparability (ICH Q5E)

- **Comparability exercises during development:**
 - Generally performed to demonstrate that nonclinical / clinical data generated with pre- and post-change products are applicable --- ultimately, to support the marketing authorisation
- **Takes into consideration stage of development, availability of analytical procedures and the available experience**
 - If change introduced before non-clinical studies: generally not an issue
 - If introduced in late stages: may be as comprehensive and thorough as the one conducted for an approved product

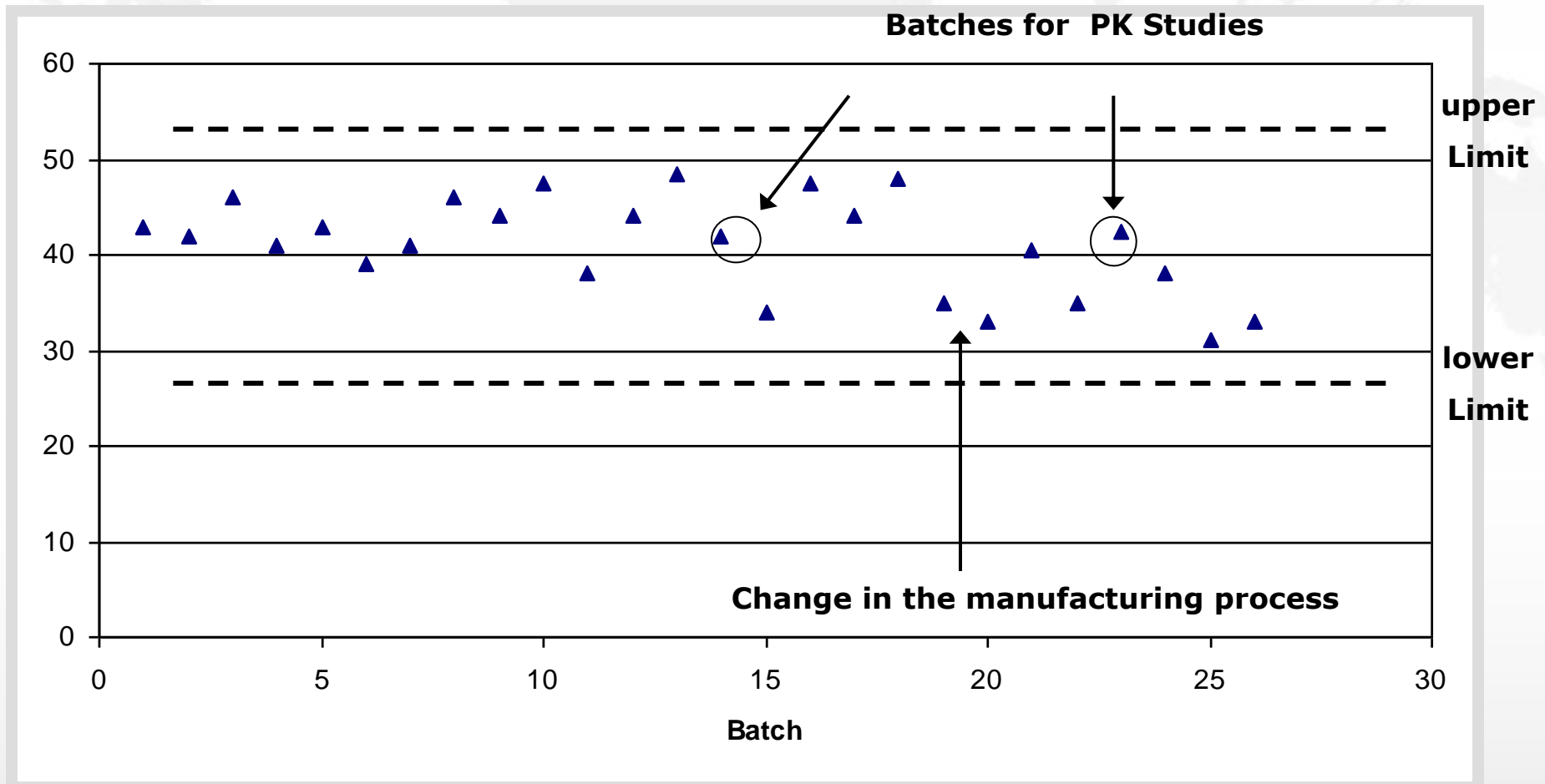
Comparability (ICH Q5E)

- **Comparability exercises during development:**
 - Appropriate assessment tools needed
 - 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, and therefore, bridging non-clinical and/or clinical studies might be needed.

Example “Historical Data”

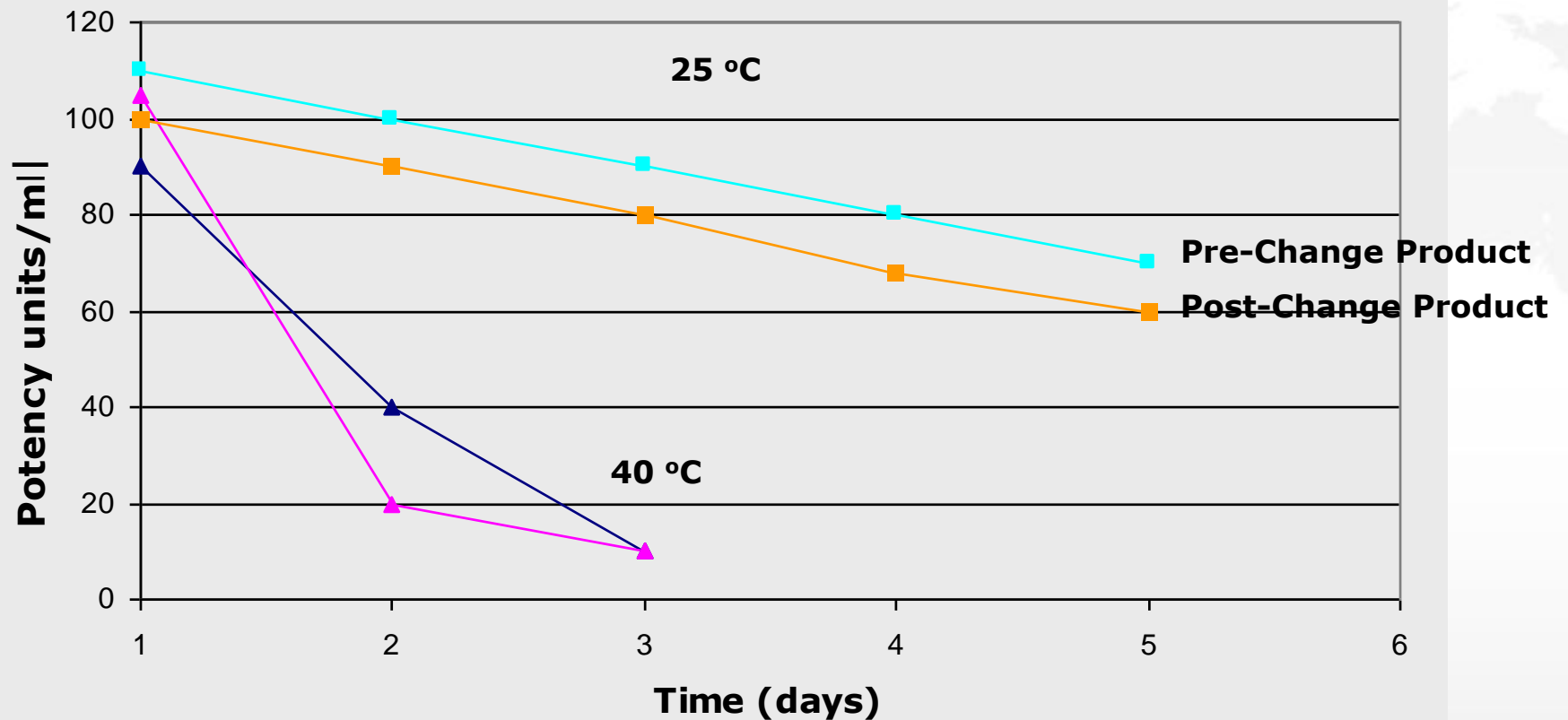


Choosing the „right“ batches



Example for accelerated studies

Storage temperature of the product is 5°C
(Spec for potency 80-120 IU/ml (100 IU/ml))



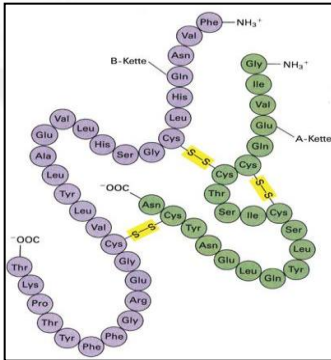
Immunogenicity of Therapeutic Proteins

- **It is impossible to predict**
 - immunogenicity with analytical methods
 - the incidence of unwanted immunogenicity
 - the characteristics of the immune response
 - the clinical consequences & significance of such immunogenicity
- **Immunogenicity to changes that can not be determined by analytical means**
- **Unwanted immunogenicity needs to be investigated in appropriate studies**

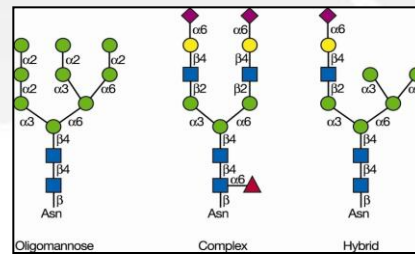
Immunogenicity of Therapeutic Proteins

- Majority of biotherapeutics is immunogenic, both from animal and human origin
 - **immunogenicity no specific problem of biosimilars**
- Currently available biosimilars of first generation biotherapeutics (copies of endogenous GF or hormones)
- Development of Ab
 - Normal reaction to a foreign protein (e.g. protein of animal origin, gene deletion)
 - Breaking the normally existing immune tolerance to self antigens

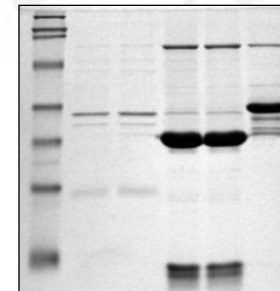
Factors influencing Immunogenicity



Proteinstructure/-size



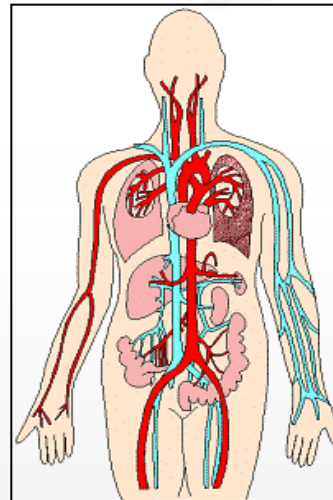
Glyco-structures



Purity Impurity



Formulation,
Stability,
Degradation



Administration, Dose,
Frequency, Co-Medication



MHC, Genotype,
Disease, Age

Factors Causing Immunogenicity

Product-specific causes

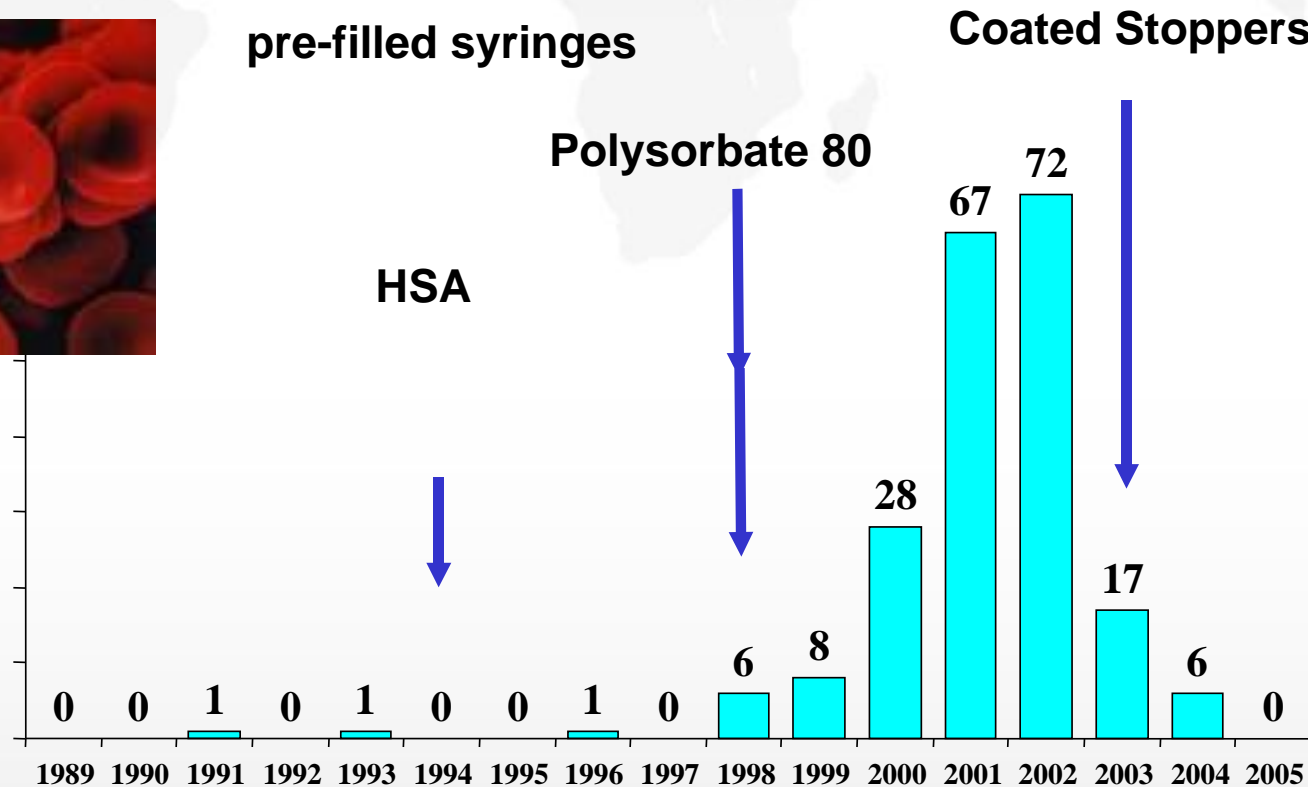
- **Structural differences exogenous/endogenous protein**
- **Structural alterations**
 - Aggregation
 - Degradation – oxidation, deamidation,
 - Conformational changes
- **Storage conditions**
- **Impurities / contaminants**
- **Formulation**

Hierarchy of Risk of Immune Response to Therapeutic Proteins: Product Factors

- **Post-translational Modifications**
 - Aggregation
 - Oxidation
 - Aldehyde Formation
 - Glycosylation (or lack thereof)
 - Truncation
 - Deamidation
 - Citrullination (Deimination)
 - Phosphorylation
 - Arginine methylation
 - Others

as presented by
Dr. A. Rosenberg, FDA, USA

Frequency of PRCA and changes of the formulation for EPREX 1998





Thank You!

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