Comparability Exercise for Biologics: A Case Study

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Agenda

1. Product and process knowledge – A driver for comparability study design

2. Comparability exercise (ICH Q5E): Principles and key to success

3. A Case Study - Addition of a new drug substance manufacturing site for a licensed recombinant factor VIII product
Product and process knowledge – A driver for comparability study

ICH Q10 and Q12
Process development and clinical development are closely linked for innovative product
Quality by Design: Start with the patient’s needs in mind

- **Product Profile**
  - Quality Target
  - Product Profile
  - List of CQA’s

- **Process**
  - Process parameters
  - Process model
  - Design space

- **Facility**
  - Control Strategy

Illustrative example: criticality of process parameters and the risk associated with making changes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severity Score</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>10</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
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- **Risk of making changes on control limit (Process Parameter C)**
Comparability Exercise (ICH Q5E): Principles and key to success
Defining Comparability

- A determination that a product is “Comparable” indicates that products are highly similar before and after a manufacturing change and that no adverse impact on the quality, safety or efficacy of the drug product occurred (ICH Q5E)

- Does not mean pre- and post-change products are physico-chemically or biologically identical

- Existing knowledge is sufficiently predictive to ensure any differences in quality attributes have no adverse impact on safety or efficacy
Comparability May Be Deduced From:

- Quality Studies (Comparative)
  - Physicochemical Tests
  - Functional Assays (Bioassays)
- Nonclinical Studies
- Clinical Studies

In many cases comparability may be deduced from quality studies alone (ICH Q5E)
Comparability: Key to success

- **Product Knowledge**
  - Critical Quality Attributes: what matters and why? Relationship to safety and efficacy?
  - Structure-function understanding: Biological Characterization
  - Product stability/degradation profile: real-time, accelerated, stress
  - Historical ranges: comparability acceptance criteria, clinical experience
  - Extent of difference(s) must be understood: risk-based approach

- **Process Understanding**
  - Potential impact of changes must be evaluated
  - Targeted activities at process, facility, configuration, *etc* to minimize differences as much as possible
  - Link between process parameters and product quality attributes
  - Sources of variability

- And: analytical methods designed and optimised to detect differences
A Case Study: Addition of a new drug substance manufacturing site for a licensed recombinant factor VIII product (turoctocog alfa)
Scope of the Changes

- **Product involved:**
  - Novoeight® (Antihemophilic Factor Recombinant); turoctocog alfa – a 166 KDa glycoprotein

- **Scope of the changes (major post-approval changes):**
  - **Site change** - The manufacturing facility for cell cultivation and purification of the drug substance has been transferred from a Novo Nordisk facility in Denmark to a Novo Nordisk facility in United States
  - **Process Changes** - The cell cultivation process has been improved (*from batch refeed to perfusion methods*) to increase the yield of turoctocog alfa. The purification process has been adapted accordingly
Comparability Package Used for US FDA Approval

Analytical comparability of the drug substance
- Physico-chemical analysis
- *In-vitro* functionality analysis
- Impurity profiles
- Release specification tests
- Stability

Supportive confirmation data
- Drug product specification tests
- Drug product stability
- Non-clinical *in-vivo* comparability studies
Illustrative Comparability Study Results (1)

RP-HPLC profiles of non-reduced tryptic peptides maps

N-linked carbohydrate map
Illustrative Comparability Study Results (2)

Near UV CD spectra

von Willebrand factor bindings
Non-clinical *in-vivo* PK studies: Observed FVIII activity versus time after i.v. administration in F8-KO mice
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Thank you for your attention