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

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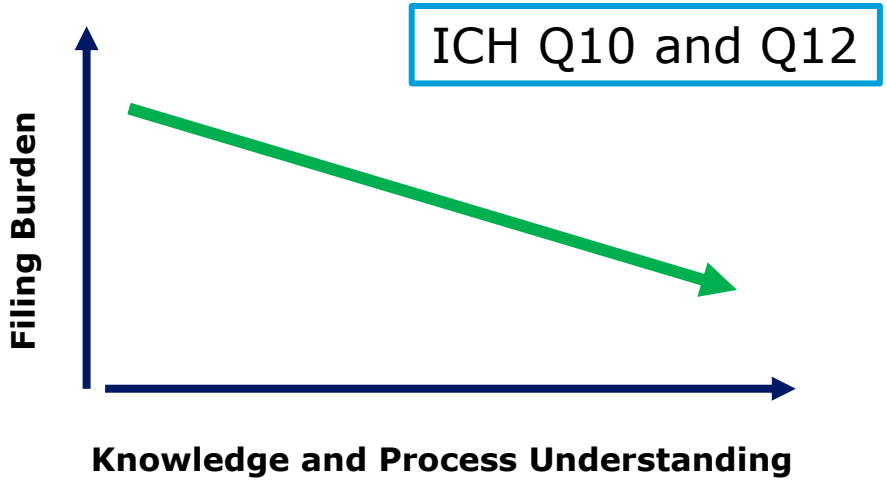
Product and process knowledge – A driver for comparability study



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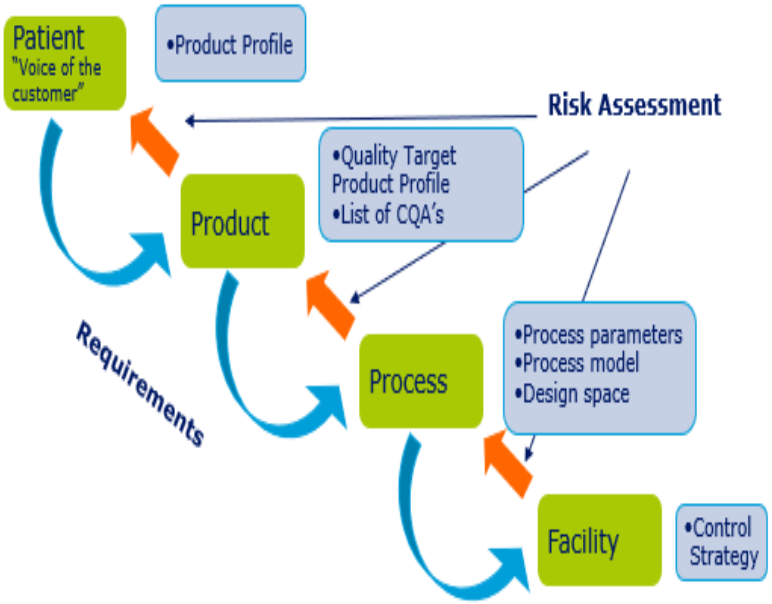
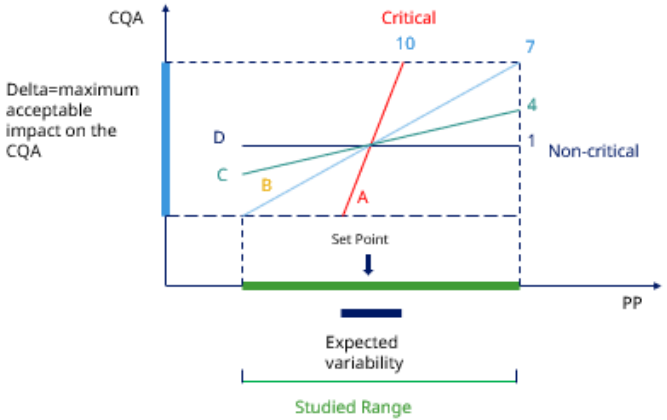
Process development and clinical development are closely linked for innovative product

Quality by Design: Start with the patient's needs in mind

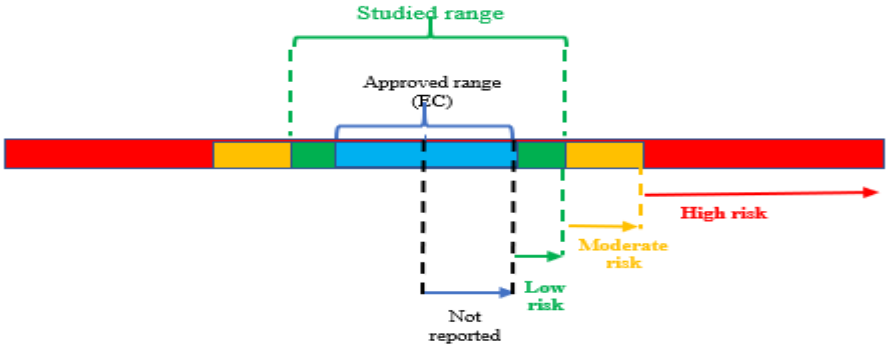


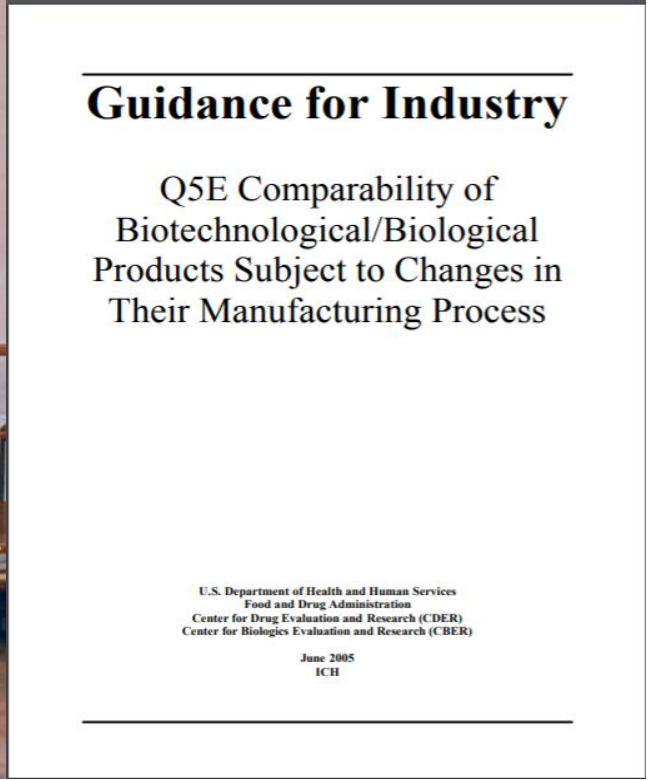
Illustrative example: criticality of process parameters and the risk associated with making changes



Parameter	Severity Score
A	10
B	7
C	4
D	1

- **Risk of making changes on control limit (**Process Parameter C)





Guidance for Industry

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2005
ICH

ICH Q5E Experts Working Group

Comparability Exercise (ICH Q5E): Principles and key to success

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Defining Comparability

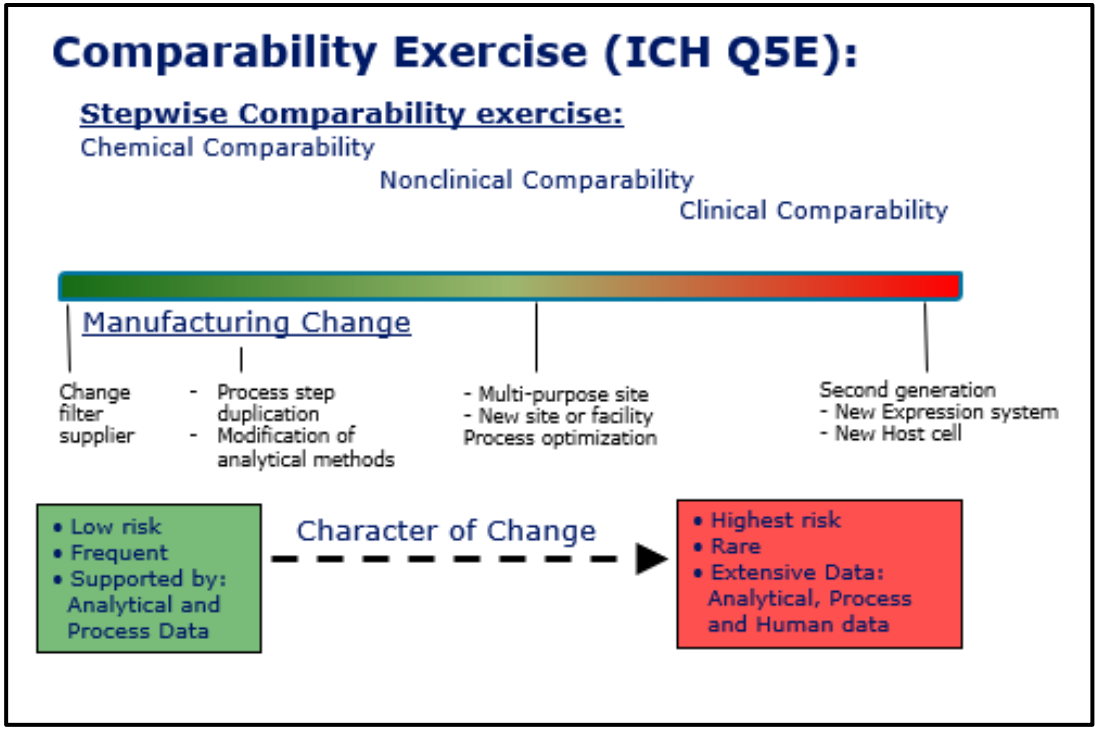
- A determination that a product is “Comparable” indicates that products are highly similar before and after a manufacturing change and that **no adverse impact** on the quality, safety or efficacy of the drug product occurred (ICH Q5E)

  - 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)



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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

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Staying Ahead of the Curve in an Increasingly Complex Regulatory World

A Case Study: Addition of a new drug substance manufacturing site for a licensed recombinant factor VIII product (turoctocog alfa)

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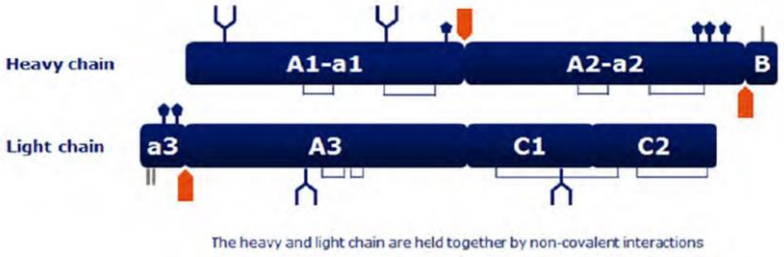
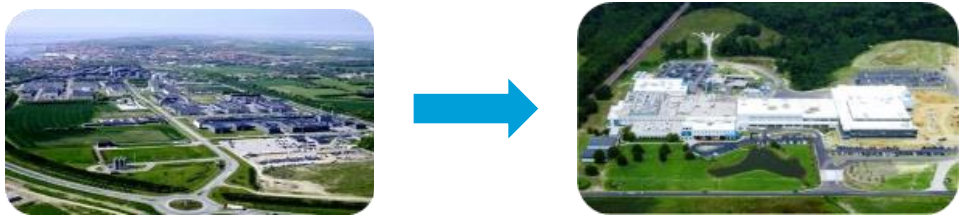
Scope of the Changes



- 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



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Comparability Package Used for US FDA Approval

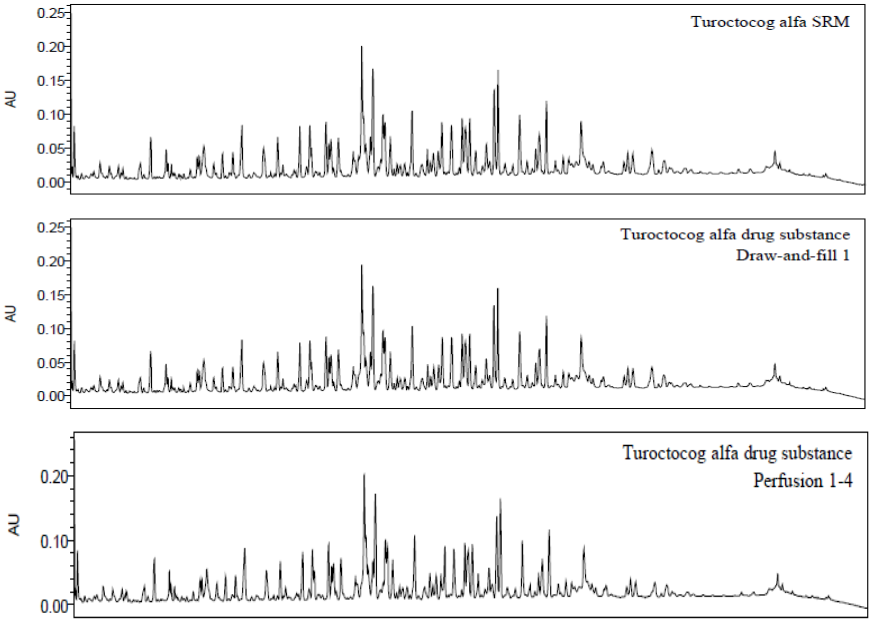
Analytical comparability of the drug substance

- Physico-chemical analysis
- *In-vitro* functionality analysis
- Impurity profiles
- Release specification tests
- Stability

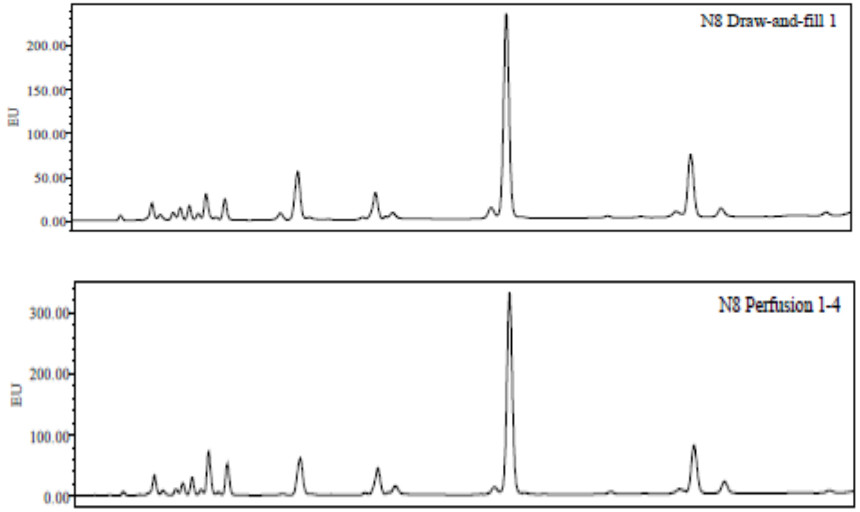
Supportive confirmation data

- 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

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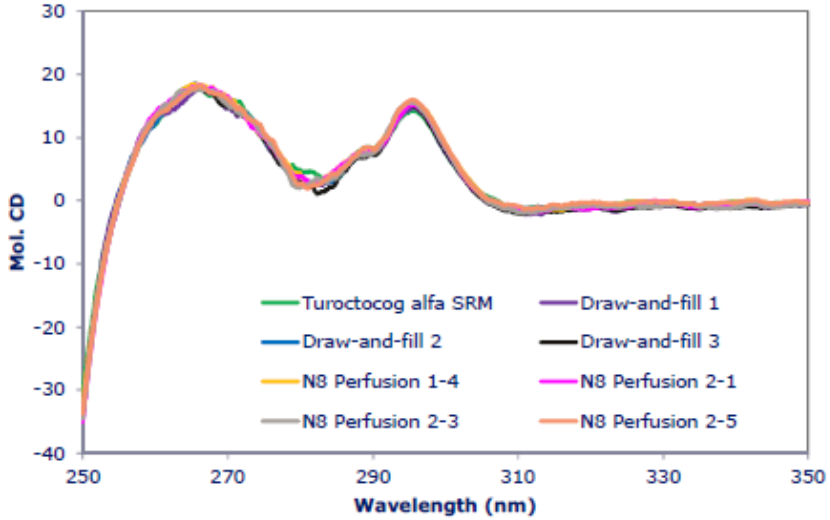
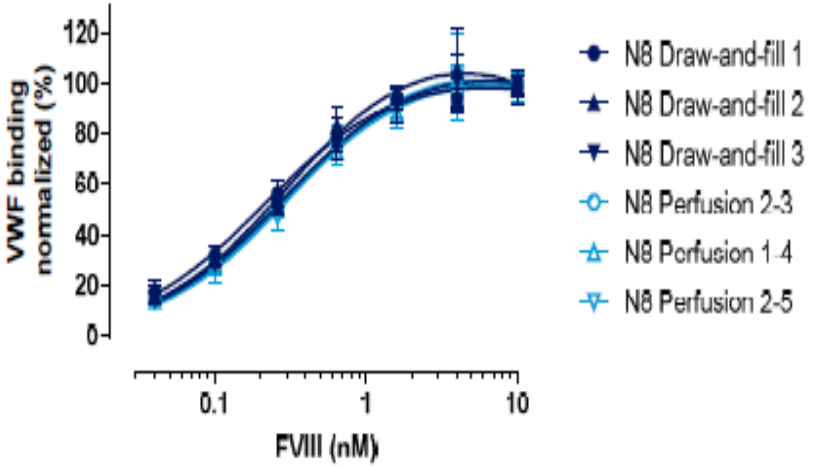
Illustrative Comparability Study Results (2)



Near UV CD spectra



von Willebrand factor bindings

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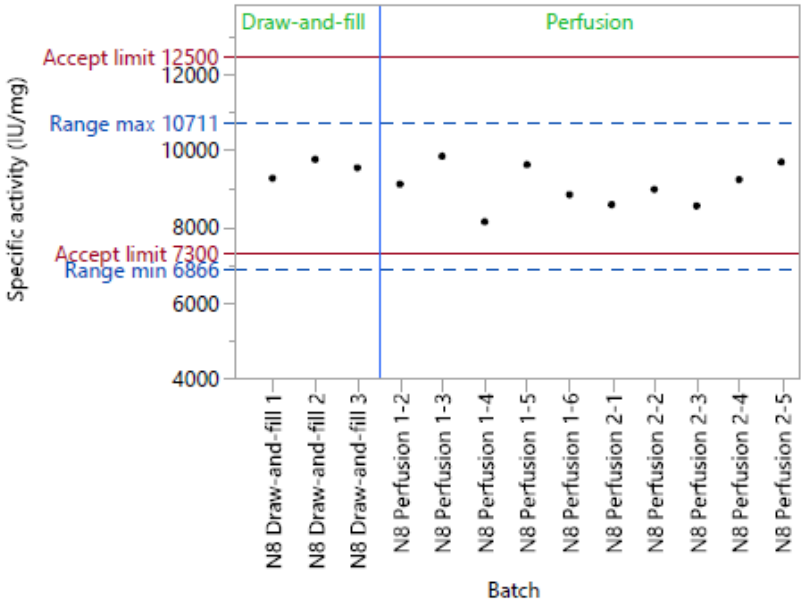
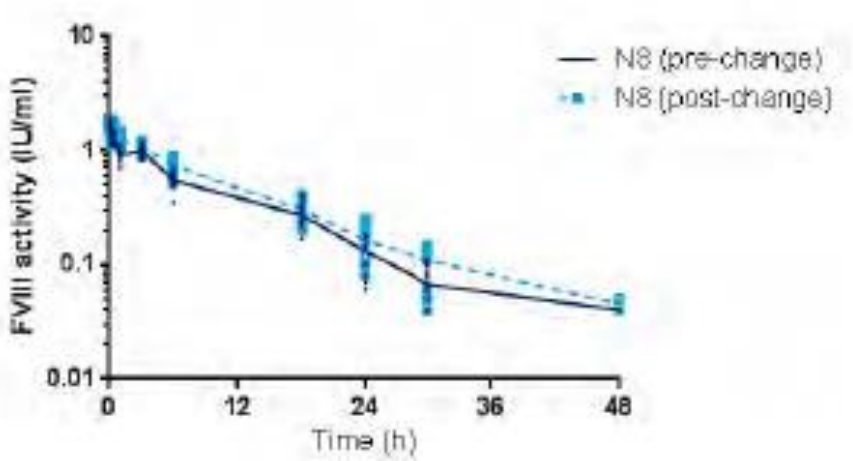
Illustrative Comparability Study Results (3)



Specific activity



Non-clinical *in-vivo* PK studies: Observed FVIII activity versus time after i.v. administration in F8-KO mice

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  - **Wu Zhengyu (Zero),** Director, Regulatory Affairs

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Thank you for your attention