UNDERSTANDING THE SIMILARITIES AND DIFFERENCES BETWEEN THE INNOVATOR AND BIOSIMILAR COMPARABILITY EXERCISE

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Innovator Manufacturing Change vs. Biosimilar Product Development

Innovator Manufacturing Change

Optimizing an approved process for a product that has undergone significant R&D and a full pre-clinical and clinical regulatory approval process.

Biosimilar Product Development

Attempting to reverse engineer or recreate the innovator’s product starting from published information and the product on the market.

* While the technological processes for comparing products may be similar, a biosimilar manufacturer and innovator have very different knowledge and tools available to them.
Clarifying Terminology:
Comparability is Often Used in Different Ways and for Different Purposes

Innovator Comparability

Innovator comparability testing measures quality attributes of a single product after a manufacturing process change

Also referred to as:
• Innovator product manufacturing change
• Manufacturing change comparability
• Manufacturing comparability

Biosimilar Comparability

Biosimilar testing involves the analytical, pre-clinical, and clinical comparison between two different, but related products

Also referred to as:
• Biosimilarity Exercise
• Comparability Exercise
• Biosimilarity Comparison
• Biosimilar Reference Product Comparison

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Post Manufacturing Change Assessment vs. Biosimilar Development

Key Considerations:

• ‘Similar’ does not equal ‘same’

• Small alterations can make a BIG difference

• US FDA and EMA clearly distinguish the requirements for manufacturing comparability vs. biosimilarity

• Knowledge produces consistency and confidence
‘Similar’ Does Not Equal ‘Same’
Biosimilars and Twins: Identical DNA, Minor differences in Features

- The active ingredient of a biosimilar can at best only resemble that of the innovator product.
- How an innovator makes its biologic can never be duplicated down to the last detail; a biosimilar is made using cells, materials and processes that differ from the innovator product.
- This is true even if a biologic and its biosimilar start from the same genetic blueprint, in much the same way as identical twins, despite the same genes, have different fingerprints.
Two Different Processes Create Two Non-Identical Biologic Products

START
Both may use the same gene sequence

Different vectors to insert the gene

Different host cells to grow the protein

Different fermentation/culture conditions

Different downstream processing

Different biophysical characteristics in final product

END
Biologics Manufacturing Control at Every Step

For comparability, the innovator has a rich testing database from every in process step of every batch, the biosimilar only has access to the final product.

Cell Culture
- Cell Bank
- Bioreactor
- Harvest

Purification
- Chromatography 1, 2, 3

Final Dosage Form
- Virus Filter
- Concentration
- Bottling

In Process Testing Data From Every Process Step

Final Tests
### Accumulated Experience and Knowledge Generates Sustainable Quality and Predictability

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<tbody>
<tr>
<td><strong>Innovator Development</strong></td>
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<td>Discovery and Target Validation</td>
<td>Cell Line, Process Development</td>
<td>Process Characterization, Validation</td>
<td>Process monitoring, Scale and Site changes, Comparability Protocols, Process consistency Assurance</td>
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<td>Non-clinical Studies</td>
<td>Characterization of Molecule, Structure Function Studies, Justify and Establish Specifications</td>
<td>Deep understanding of Product Properties, Comparability Protocols to assure consistent product</td>
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### Biosimilar Development

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<td><strong>Biosimilar Development</strong></td>
<td>Cell Line, Process Development, Characterization</td>
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<td>Analytical Characterization, Establish Specifications</td>
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## CASE STUDIES:
### EMA Biosimilar Applications Rejections and Withdrawals

<table>
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<tr>
<th>Biosimilar vs. Innovator</th>
<th>Year</th>
<th>Differences</th>
<th>Consequence</th>
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| Alpheon *(interferon alpha 2a)* vs. Roferon-A® | 2006 | - Differences identified between the two medicines (such as impurities)  
- Non-validated finished product evaluation process  
- Lack of stability data  
- Rates of return of disease after treatment discontinuation, and more side effects\(^1\) | - CHMP recommended that Alpheon be refused marketing authorization  
- No new trials being conducted for Alpheon |
| Human Rapid Marvel, Human Long Marvel and Human 30/70 Insulins vs. Humulin® S, I and M3 Insulins, respectively | Feb 2008 | - Clinical differences in rates of lowering blood sugar levels\(^2\)  
  - “Trend in favor of Humulin”  
- Inadequate submission of active or finished product process  
- Non-validated manufacturing process | - Marvel withdrew its applications for marketing authorizations |
| Solumarv, Isomarv and Combimarv vs. Humulin® S | Nov 2012 | - New bioequivalence data needed to be in line with new requirements in the EMA biosimilar insulin guideline (currently being revised)  
- Questions raised on clinical study size and patient population as well as the sensitivity of the clamp study | - Marvel withdrew its applications for marketing authorization  
- Intends to repeat and submit new bioequivalence on each PK/PD data clamp study |

Humulin and Referon-A are trademarks of Eli Lilly, and Roche respectively.

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Biosimilars: ‘Similar But Not the Same’

- Biosimilars manufactured by different manufacturers will differ from the innovative product and from each other
  - They are **not** generic biologics
  - They use a **different ‘host cell’** to develop the biosimilar product
  - The active ingredient of a biosimilar can at best only resemble that of the original biologic

- How an innovator makes its biologic can never be copied down to the last detail; a biosimilar is made using different cells and different processes

- This is recognised in the Regulatory guidance: EMA Guideline On Similar Biological Medicinal Products *CHMP/437/04* (Effective Oct 2005)
  - “Due to the complexity of biological/biotechnology-derived products **the generic approach is scientifically not appropriate** for these products”
Small Alterations Can Make a BIG Difference
How Well Do We Understand Our Biologic?

**GOAL:**
Consistent manufacturing yielding consistent product therefore producing consistent SAFETY + EFFICACY

**Release Tests**
- Certificate of Analysis

**Characterization Tests**
- Process characterization
- Extended product characterization and comparability

**Process Control**
- Process and product impurities
- Raw materials
- Process monitoring and in-process testing
- Controls, setpoints, ranges, hold times
- Process validation

6,440 Carbon Atoms Are a Lot to Track

- Few intact antibody structures have been solved
- Rarely is detailed structural information available to help guide process development
- Differences frequently occur in a subpopulation of molecules further complicating analytical studies

Molecular Weight: 148,683.5 [g/mol] Molecular Formula: C₆,₄₄₀ H₉,₉₂₈ N₁,₇₀₄ O₂,₀₁₁ S₅₆ (Anti-canine lymphoma monoclonal antibody “MAb 231”)

What is important functionally?

Which Changes Matter? Which Don’t?

We don’t know unless identified and clinically tested!

A single additional H-bond increases thermodynamic stability and could change the aggregation.

Molecular Weight: 148,683.5 [g/mol] Molecular Formula: C6,440 H9,928 N1,704 O2,011 S56

Does this impact safety/efficacy?
Case Studies: “Not so Comparable” Manufacturing Changes

Innovator process changes resulting in significant clinical impact

<table>
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<tr>
<th>Product</th>
<th>Change</th>
<th>Impact</th>
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<tbody>
<tr>
<td>Myozyme/Lumizyme(^1) (glucosidase alpha)</td>
<td>160 to 2,000 liter scale produced glycosylation differences</td>
<td>New clinical trial, biologics regulatory submission, and name change from myozyme to lumizyme</td>
</tr>
<tr>
<td>Eprex (epoetin alpha)(^2)-(^4)</td>
<td>Replaced HSA with sorbitol-80 stabilizer using un-coated stoppers in PFS</td>
<td>Increased incidence of neutralizing antibodies and PRCA</td>
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PRCA: pure red cell aplasia. HSA: human serum albumin. PFS: pre-filled syringe

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US FDA and EMA Clearly Distinguish the Requirements for Manufacturing Comparability vs. Biosimilarity
Regulatory Perspective of Manufacturing “Comparability”

• Manufacturers make changes when:
  – Maintaining state of the art manufacturing process
  – Increasing scale
  – Improving product stability
  – Complying with changes in regulatory requirements

• Relevant quality attributes are evaluated
  – Manufacturers evaluate potential impact of process modifications on clinical safety and efficacy of the drug

• Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate\(^1\)
  – This is known as the comparability exercise

• How does this differ from the development of a biosimilar?

1. ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.
“Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer.”

“This is because a manufacturer who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters.”

Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (i.e., changes during development and post-authorization), as addressed by ICH Q5E.

"The comparability exercise for a similar biological medicinal product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier and should be dealt with separately when presenting the data."

Why Manufacturing Comparability is Not Biosimilarity

The manufacturer of a proposed product will likely have a different manufacturing process e.g., different:

- Cell line
- Raw materials
- Equipment
- Processes
- Process controls
- Acceptance criteria

From that of the reference product and no direct knowledge of the manufacturing process for the reference product

“Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer’s post-manufacturing change product is comparable to the pre-manufacturing change product.”


Knowledge Produces Consistency and Confidence
Experience Brings Confidence

Innovator Biologic
Justification for Changes

- Deep understanding of innovator molecule, process and product
- 15 years of development experience
- 10+ years of on-market experience
- 10,000s of patients treated
- 100s of batches produced
- Process, site, scale changes reviewed and approved globally

Biosimilar Biologic
Basis for Approval

- Understanding of biosimilar molecule, process, and product
- 5 years of development
- 0 years of on-market experience
- 10s to 100s of patients treated
- 10+ product batches produced
- Process, site, scale approval status

The numbers and years shown for innovators and biosimilars are estimates, based upon time of biosimilar approval, and may differ in some cases.
HUMIRA as an Example:
Innovators Have Singular Knowledge of Their Controls, Compound, Process, and Product

Incremental Capacity added to Assure Supply while maintaining high quality

- 16 years of approved scale, equipment, yield, raw material changes
- Tight trends controlled through process knowledge, controls and specifications
- >500 batches of interchangeable product
- Patient confidence continuously assured
- Over 23,000 Patients Enrolled in HUMIRA Randomized Clinical Trials

|------|------|------|------|------|------|------|------|------|

Developed and launched at one site with multiple scales

Scale-up

Scale-up

Scale-up
What About Drift?
Drift ≠ Manufacturing Change

Drift is **unintended** change over time in some characteristic(s) of bioengineered products if not controlled within regulatory limits

- All biologics, whether innovator products or biosimilars, can drift if not adequately controlled
- Regulators require and manufacturers need to apply appropriate quality controls and specifications to control against the potential for drift
- Products not meeting these requirements will not be released for use by patients.

Manufacturing Change and Drift are Very Different Concepts
Conclusions

1. Demonstrating biosimilarity to a reference product differs from assessing the manufacturing comparability of a product before and after manufacturing changes made by the same manufacturer\textsuperscript{1-3}

2. EMA/FDA recognize differences between manufacturing comparability vs establishing biosimilarity because:
   - Similar does not equal same
   - Small alterations can make a BIG difference
   - Innovator’s exclusive knowledge produces consistency and confidence following a manufacturing change
   - Drift is not the same as a manufacturing change

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3. ICH Q5E Comparability of biotechnological/biological products subject to changes in their manufacturing process.
“The only source of knowledge is experience.”

- Albert Einstein