What Are Biologics and Biosimilars?

Regulatory Approval Pathway

Interchangeability and Substitution
Biologics Are More Complex Than Small Molecule Drugs

<table>
<thead>
<tr>
<th>Means of production:</th>
<th>New Chemical Entities and Generics</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small Molecule</td>
<td>Large Glycoprotein (eg, monoclonal antibody)</td>
</tr>
<tr>
<td></td>
<td>Chemical synthesis</td>
<td>Bacteria or yeast</td>
</tr>
</tbody>
</table>

Example¹ (scalea):

<table>
<thead>
<tr>
<th></th>
<th>Acetylsalicylic acid (×1)</th>
<th>Insulin (≈×30)</th>
<th>Adalimumab (≈×800)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2 kDa</td>
<td>≈6 kDa (51 amino acids)</td>
<td>≈144 kDa (1300 amino acids)</td>
</tr>
</tbody>
</table>

¹Molecular weight relative to acetylsalicylic acid.
An Unmet Need Exists for More Affordable Alternatives to Biologic Medicines

- The cost of biologics imposes a strain on the health care system, resulting in limited access and decreased compliance among patients who cannot afford these treatments.

- Biosimilars are alternatives to reference biologics that may decrease health care costs and improve patient access.

What Is a Biosimilar?

FDA Definition

A version of a biologic which is highly similar to a reference product, with no clinically meaningful differences in terms of safety, purity and potency, notwithstanding minor differences in clinically inactive components\(^1,2\)

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2. The Patient Protection and Affordable Care Act, H.R. 3590, 111th Congress (2010).
Shared and Distinct Features Between Biosimilars and Reference Biologics

- **REFERENCE BIOLOGIC**
  - Host cell line
  - Manufacturing processes
  - Protein structure
  - Inactive ingredients
  - Proven efficacy, safety

- **BIOSIMILAR**
  - Host cell line
  - Manufacturing processes
  - Protein structure
  - Inactive ingredients
  - Proven similarity to reference biologic

Amino acid sequence

Mechanism of action

Key Takeaways

• A biosimilar is a version of a biologic that is highly similar to a reference biologic product with regard to safety, purity, and potency.

• Biosimilars are rigorously tested to confirm that no clinically meaningful differences exist in efficacy, safety, purity and potency when compared to the reference product.

• Biosimilars have the potential to increase patient access to treatments by providing lower cost biologics options, thus addressing a crucial unmet need.
Regulatory Approval Pathway in the US
Biosimilarity

• The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was passed as part of health reform (Affordable Care Act) signed into law on 3/23/10.

• BPCI Act created an abbreviated licensure pathway for biological products shown to be *biosimilar to or interchangeable with an FDA-licensed reference product*.

• This licensure pathway permitted a biosimilar biological product to be licensed under section 351(k) of the Public Health Service Act (PHS Act).

• Biosimilarity is based on biosimilar being “highly similar” to the reference product not withstanding minor differences in clinically inactive components...

• ...and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Requirements for FDA Approval Differ Between Biosimilars and New Biologics

- Though the requirements for approval differ between new biologics and biosimilars, the totality-of-the-evidence approach for evaluation of biosimilars ensures that rigorous standards of structure, functionality, efficacy, and safety are upheld.

<table>
<thead>
<tr>
<th></th>
<th>New Biologic</th>
<th>Biosimilar Candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA regulatory pathway</td>
<td>351(a)</td>
<td>351(k)</td>
</tr>
<tr>
<td>Key comparator</td>
<td>Current standard of care</td>
<td>Reference product</td>
</tr>
<tr>
<td>Key comparisons</td>
<td>Safety, purity and potency</td>
<td>Safety, purity, and potency</td>
</tr>
<tr>
<td>Volume of required structural, functional, and animal data*</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Volume of clinical data*</td>
<td>High (phase 1-3)</td>
<td>Lower (mainly phase 1, plus one phase 3)</td>
</tr>
<tr>
<td>Basis of approval for different indications</td>
<td>Phase 2 and 3 studies per indication</td>
<td>One phase 3 study, allowing extrapolation to other indications</td>
</tr>
<tr>
<td>Substitution by other biologic</td>
<td>Not permitted</td>
<td>Substitution possible. Interchangeability requires clinical data</td>
</tr>
</tbody>
</table>

*Comparison of new biologic vs biosimilar candidate

Biosimilar Development Approach

1. **Target definition**
   - Understand originator target molecule variability
   - Map the significant variability and criticality in quality attributes
   - Define biosimilar “goal posts”

2. **Target-directed development**
   - Develop biosimilar to match the reference product across cell line, bioprocess, and drug product development

3. **Characterization of biosimilarity**
   - Establish similarity based on physicochemical, biological, and functional characterization

4. **Regulatory interactions**
   - Interact with regulatory authorities to reach consensus on the appropriate clinical programs required to confirm biosimilarity (innovative trial designs and unique endpoints)

5. **Clinical confirmation**
   - Conduct clinical trial(s) to confirm biosimilarity in the clinical setting
Development of a Biosimilar Required a Paradigm Shift

Comparison with the reference product

**Originator development**
- 351(a) BLA
  - Clinical
  - PK/PD
  - Non-clinical
  - Analytical

**Biosimilar development**
- **Totality of Evidence**
  - 351(k) BLA
    - Clinical
    - PK/PD
    - Non-clinical
    - Analytical

**Confirmatory efficacy, safety, and immunogenicity study in patients**
- Phase 3

**PK bioequivalence studies in healthy volunteers**
- Phase I

**Animal PD, PK, toxicity**

**Structural and functional comparison using state-of-the-art technology**

**Analytical Similarity Assessment**
Demonstrating Similarity to a Reference Product: Totality-of-the-Evidence Approach

### Structural & Physicochemical Characterization
Highly sensitive analytical methods demonstrate high similarity between the reference product and the biosimilar at a molecular level.

### Biologic Characterization
Demonstrate a highly similar functional activity and mode of action in vitro.

### Nonclinical PK and PD
Demonstrate PK/PD bioequivalence and investigate key safety features in animal models.

### Clinical Phase 1 and 3
- **Phase 1:** demonstrate bioequivalence
- **Phase 3:** demonstrate equivalence in efficacy and safety in homogeneous and sensitive population

### Post-approval
Collect additional data across main approved indications (eg, via registries)
Pharmacovigilance across all patients

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Extrapolation of Indications from Reference Product

• Extrapolating from one molecule to the other: safe use of the biosimilar in indications approved for the reference product that share the same MoA.

• The potential exists for a biosimilar product to be approved for one or more conditions of use for which the US-licensed reference product is licensed based on extrapolation of clinical data intended to demonstrate biosimilarity in one condition of use.

• Demonstration of “sameness” of biosimilar to reference product:
  – Extrapolation scientifically justified
  – Extensive data package to address scientific considerations for extrapolation

• Sufficient scientific justification for extrapolating data is necessary.
Key Takeaways

• Biosimilars are approved by the FDA based on the “totality-of-the-evidence” of similarity to a reference product. This evidence includes analytical, preclinical, and clinical development studies that are evaluated based on the same rigorous standards as applied to the reference product.

• In some cases, the FDA may approve a biosimilar for an indication that is approved for the reference product, but that was not directly assessed in biosimilar clinical trials. This is called “extrapolation”.

• Extrapolation to an indication is based on a sufficient scientific justification for the determination of biosimilarity for that indication.
Interchangeability and Substitution
Interchangeability

Interchangeable or Interchangeability means:

• The biological product is biosimilar to the reference product;

• It can be expected to produce the same clinical result as the reference product in any given patient; and

• For a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

Regulatory Requirements for Interchangeability

Preclinical¹

- Demonstrate analytical similarity to the reference product
  - A fingerprint-like characterization of the biosimilar candidate covering multiple product attributes and their combinations, to quantify similarities with or differences to the reference product

Clinical²

- Demonstrate that the risk in terms of safety or diminished efficacy of switching between a biosimilar product and a reference product is not greater than the risk of using the reference product itself
  - Switching study (for products administered more than once)

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**Primary end points:** PK and PD
- $C_{\text{max}}$, $T_{\text{max}}$, $C_{\text{trough}}$, $A\text{UC}_{\text{tau}}$

**Secondary end points:** safety, immunogenicity, efficacy
Key Takeaways

• An interchangeable designation allows a biosimilar product to be substituted for the reference product without the intervention of the provider who prescribed the reference product consistent with state law

• Based on state by state legislation, substitution is a decision at the pharmacy level to switch one product for another without consent of prescribing physician
Biosimilar Development – Preclinical
Biosimilar Development – Clinical
Immunogenicity
Biosimilar Development – Preclinical
Biosimilar Development (1): Producing a Suitable Clone

Characterization of reference product

Cloning of gene of interest and transformation into host cells

Cells produce protein of interest

Suitable cell clone selected, based on characterization of the protein produced

All steps aim to match the reference product in all relevant attributes
Biosimilar Development (2): From Cell Clone to Antibody Manufacturing

Clone selection: Selected clone with “matching” critical quality attributes

Fermentation: Production of antibody on increasingly large scale

Purification: Using centrifugation, chromatography, and filtration

Finished product: Every batch tested according to Good Manufacturing Practice (GMP) before release

Formulation and filling
Key Takeaways

• The totality-of-the-evidence approach is an overall assessment of biosimilarity from multiple comparative evaluations. These evaluations are subjected to the same rigorous standards of structure, functionality, efficacy, and safety as the reference products. Assessments include:
  
  Analytical comparability, in vitro pharmacology, and process science
  Animal studies
  PK/PD bioequivalence
  Clinical studies

• A stepwise approach is required to obtain the data and information required to demonstrate biosimilarity.

• The FDA recommends the product sponsor ranks the quality attributes of a biosimilar candidate based on potential impact on the mechanism of action and function of the product. The scoring of each quality attribute should be proportional to patient risk.
Biosimilar Development – Clinical
Typical Phase I Design for Biosimilars

Objective

• To establish PK bioequivalence of a biosimilar candidate to a reference product
Establishing Bioequivalence Based on AUCs in a Phase I Study

Comparing AUCs Between Biosimilar and Reference Product Arms

AUC = area under the curve.

Conceptual illustration showing hypothetical data.

AUC\(_{0-\infty}\)

Relative exposure (%):

- 60
- 100
- 120
- 140
- 160
- 180

Predefined margin:

- 80
- 125

90% CI for ratio of candidate biosimilar/reference product

Bioequivalence demonstrated

AUC = area under the curve.
Conceptual illustration showing hypothetical data.

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Indication, Patient Population, and Clinical End Points for Phase 3 Biosimilar Candidate Trials

Objective

- To demonstrate biosimilarity, not to independently establish safety and efficacy of the biosimilar candidate

Sensitive indication
- Large effect size
- Easily measurable

Homogenous population

Sensitive end point
- Large effect size
- End point sensitive to drug effect

Minimize variability in patient- and disease-related factors relative to the population studied for licensure of reference product

References:

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Selecting a Sensitive Endpoint for Biosimilars Phase III Trials: An Example From Rheumatoid Arthritis

- Using a sensitive endpoint with a large effect size facilitates detection of possible differences between the biosimilar and reference product (e.g., ACR20, rather than ACR50 or ACR70 for a TNF inhibitor)

ACR = American College of Rheumatology criterion; TNF = tumor necrosis factor; MTX = methotrexate.
Conceptual illustration showing hypothetical data.
Selecting a Sensitive Endpoint for Biosimilars Phase III Trials: An Example From Psoriasis

- Using a sensitive endpoint with a large effect size facilitates detection of any differences between the biosimilar and reference product (eg, PASI75, rather than PASI100 in psoriasis)

PASI = Psoriasis Area and Severity Index.
Conceptual illustration showing hypothetical data.
Key Takeaways

• Rigorous standards of efficacy and safety in clinical trials are required for the approval of both biologics and biosimilars.

• For approval of a biosimilar, the primary goal of the clinical trials is to demonstrate similarity to a reference product, with no clinically meaningful differences in efficacy, safety, purity, and potency.

• Three factors are critical in the design of Phase III clinical trials for biosimilars: a homogeneous patient population, a sensitive disease indication, and a sensitive endpoint measure.

• Previous clinical data of the reference product are useful for identifying the disease indication, endpoint measure, and patient population that is most likely to generate the largest “effect size”.
  - This allows for detecting any meaningful differences that may exist between the biosimilar and the reference product.
Immunogenicity
Immunogenicity of Therapeutic Proteins

- Immunogenicity is the Ability of a Therapeutic Protein to Elicit an Immune Response
  - Just as in reference products, immunogenicity can potentially impact the PK, clinical efficacy, and safety profile of a biosimilar

Clinical consequences that can arise

- Hypersensitivity
- Loss of efficacy

Formation of ADAs is thought to be the main mechanism by which immunogenicity exerts its undesired effects
Detection of Antidrug Antibodies

### Screening assay
- Highly sensitive
- Broad detection of low- and high-affinity ADAs

### Confirmatory assay
- At least as sensitive as screening assay
- High specificity to identify any false-positives

### Titration assay
- Titer is determined from the reciprocal of the highest dilution where the sample gives a signal at or just above assay cut point
- Particularly informative in patients with pre-existing antibodies

### Neutralization assay
- Provides an indication of the potential of the ADA to interfere with the clinical activity of the product
- Assesses neutralizing potential of ADAs based on mechanism of action of the therapeutic protein

Key Takeaways

- Immunogenicity can potentially impact the PK, clinical efficacy and safety profile of biosimilars.
- Evaluation of immunogenicity through detection of ADAs, which can be neutralizing or non-neutralizing, is an important consideration in biosimilar development.
Key Considerations for Biosimilar Manufacturing
Quality Control of Manufacturing Process Is Key for Efficacy and Safety of Therapeutic Proteins

Purity and aggregation\(^1\)

- Cell culture conditions can impact on glycosylation and impurity profiles
- Purification process is designed to purify the target biosimilar while removing process impurities and additives that could potentially be harmful to patients
- Environmental conditions such as temperature can trigger protein aggregation

Batch-to-batch variability

- Variation is a normal feature of biologics—control during production\(^2,3\)
- Process changes—within specifications of critical attributes of product\(^2,3\)
- Thorough comparisons pre- and postchange in a product are required by regulatory authorities for any biologic → no adverse effects on quality, efficacy, and safety\(^2-4\)

Modifications to Manufacturing Processes Are Common

Reasons for changes in process include:\(^1\):

- Moving production site
- Upscaling production
- New technology
- Changes in regulatory requirements

Changes mean that the original version authorized is not identical to currently used version\(^2\)

BUT: efficacy and safety are equivalent to the original version\(^1-3\)

\(^1\)Products listed owned by third party.
Key Takeaways

• Biosimilar manufacturing is a complex process that undergoes a number of quality control measures
• Biosimilars are sensitive to manufacturing conditions, including synthesis, culturing, and purification
• Because it is impossible to precisely replicate manufacturing conditions from product to product and batch to batch, each batch is tested to ensure the quality and activity of the biosimilar