Challenges of Biosimilars
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November 2014
Future of Biosimilars
Drug Complexity

<table>
<thead>
<tr>
<th>Small Molecule Drug</th>
<th>Large Molecule Drug</th>
<th>Large Molecule Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong> 21 Atoms</td>
<td><strong>HGH</strong> 3,000 Atoms</td>
<td><strong>IgG Antibody</strong> 25,000 Atoms</td>
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<tr>
<td><strong>Bike</strong> 20 lbs</td>
<td><strong>Car</strong> 3,000 lbs</td>
<td><strong>Business Jet</strong> 30,000 lbs Ø fuel</td>
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</table>
Future of Biosimilars

What is a Biosimilar?

“A biosimilar is a biological product that is highly similar to a reference biological product notwithstanding minor differences in clinically inactive components, and for which 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.”

From FDA DRAFT Guidance: “Quality Considerations in Demonstrating Biosimilarity to a Reference Product.” Feb 2012.
**Future of Biosimilars**

**Drug Complexity**

<table>
<thead>
<tr>
<th>Innovator/Originator Pharmaceutical Drug</th>
<th>Timeline</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecule</td>
<td>&gt;10 years</td>
<td>$500 million</td>
</tr>
<tr>
<td>Large Molecule</td>
<td>&gt;10 years</td>
<td>$&gt;800 million</td>
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</table>

<table>
<thead>
<tr>
<th>Follow Up Drug (Generic &amp; Biosimilar)</th>
<th>Timeline</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Generic</td>
<td>2 years</td>
<td>$2 million</td>
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<tr>
<td>Biosimilar</td>
<td>8 years</td>
<td>$250 million</td>
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Biosimilars will not deliver the same cost savings as generic drugs and supposedly not even gain a strong foothold in the biologics market until 2019 according to Global data.
Future of Biosimilars
Biosimilars Global Forecast

• **The biosimilar market is projected to be a multi-billion dollar industry in the next few years**

• **Analysts agree that biosimilar market size will be fairly significant in the next few years, ranging between $2-3 billion by 2015**

Forces driving the rapid expansion of the biosimilar industry are an ever-increasing pressure to reduce healthcare costs, expectations for booming market growth due to patent expiry of high-value innovator biologics, and better-defined regulatory pathways.
Future of Biosimilars
Risks and Requirements

• Biosimilar development strategies must adapt to evolving regulatory requirements
  • *New regulations in Europe and USA*

• Clinical development strategies must focus on patient selection and appropriate clinical endpoints
  • Maximizing patient recruitment and choosing the most sensitive patient population
  • How similar is similar?

• Commercial strategies must optimize market uptake of biosimilars market
  • Size, product price, reimbursement policies, healthcare policies, competing products and barriers for uptake
Future of Biosimilars
Development Requirements

STRUCTURAL CHARACTERIZATION OF BIOSIMILAR PRODUCTS

1. Amino acid sequence
2. Amino acid composition
3. Terminal amino acid sequence
4. Peptide map
5. Sulfhydryl group(s) and disulfide bridges
6. Carbohydrate structure
Future of Biosimilars

Development Requirements

PHYSICO-CHEMICAL PROPERTIES OF BIOSIMILAR PRODUCTS

1. Molecular weight or size
2. Isoform pattern
3. Extinction coefficient
4. Electrophoretic pattern
5. Liquid Chromatographic pattern
6. Spectroscopic profiles
Future of Biosimilars
Manufacture and Formulation Requirements

Structural and Functional Characterization

- Primary Structures  ➔  Identical Amino Acid Sequence
- Higher Order Structures  ➔  Secondary, tertiary, quarternary and aggregation
- Enzymatic PTM  ➔  Glycosylation, phosphorylation, g-Carboxylation, b-hydroxylation
- Other protein variants  ➔  Amidation/deamidation, oxidation, disulfide bonds

Identify Post-Translational Modifications (PTM) and assess impact
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Manufacture and Formulation Requirements

Purity & Comparability

- In vitro receptor-binding or cell-based assays
- Biosimilarity testing
- Levels of product related impurities (aggregates, oxidized forms, deamidated forms)
- Process related impurities and contaminants (host cell proteins, residual genomic DNA, reagents, downstream impurities)
Future of Biosimilars
Preclinical and Clinical Studies

Non-Clinical Studies
- Comparative studies, single dose
- Assess Toxicity, additional support for biosimilarity, and contribute to the immunogenicity assessment

Comparative Clinical PK and PD
- Including immunogenicity

Comparative Clinical Safety and Effectiveness Data
## Future of Biosimilars

### Patents expiration

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<tbody>
<tr>
<td>Avastin (bevacizumab)</td>
<td>12 Jan 2005</td>
<td>26 Feb 2004</td>
<td>4 Jul 2019</td>
<td>21 Jan 2022</td>
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<td>Humira (adalimumab)</td>
<td>0 Sep 2003</td>
<td>31 Dec 2002</td>
<td>31 Dec 2016</td>
<td>16 Apr 2018</td>
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<td>Ananep (darbepoetin alfa)</td>
<td>6 Aug 2001</td>
<td>17 Sep 2001</td>
<td>6 Jul 2016</td>
<td>15 May 2024</td>
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<tr>
<td>Entere (etanercept)</td>
<td>3 Feb 2000</td>
<td>2 Nov 1998</td>
<td>1 Feb 2015</td>
<td>22 Nov 2018</td>
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<td>EpoGen/Eprex (epoetin alfa)</td>
<td>1 Jun 1989</td>
<td>20 Aug 2013</td>
<td>Expired</td>
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<tr>
<td>Lupron (leuprolide acetate)</td>
<td>20 Feb 1991</td>
<td>2012</td>
<td>Expired</td>
<td>3 Dec 2013</td>
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*EU providers 10 years of data exclusivity. US EPA: Act provides 12 years exclusivity. **In the UK, Other major EU markets follow on 28 August 2015.

Source: GABI/Online (www.gabineten.org); Shippard et al. [1], Bernstein Research [2]

Notes: 1. Data updated on 17 January 2014. 2. Patent expiry dates are subject to change.

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future of biosimilars

Twelve biological products with global sales of more than US$67 billion will be exposed to biosimilar competition by 2020, with Enbrel (etanercept) whose US patent has been extended until 2028, scoring global sales of US$7.3 billion; coming in second after Humira (adalimumab) with global sales of US$7.9 billion.
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Case Studies

Recommendations/Requirements for Bioanalytical Testing Used in Comparability Studies for Biosimilar Drug Development

AAPS Biosimilar Focus Group
Future of Biosimilars
Bioanalytical Testing

The final goal of this exercise is to provide:

A meaningful interpretation of comparability study data for biosimilar drug development not only to ensure safety and efficacy but also allow for drug substitution and exchangeability.
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Bioanalytical Testing

It is critical to demonstrate the comparability of the Biosimilar to their Originator product.
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Bioanalytical PK

Scenario 1: One assay can quantify both Reference and Biosimilar

Validate one assay

Scenario 2: One assay for Reference, One assay for Biosimilar

Validate two assays

Investigation – could mean Biosimilar is not Biosimilar
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Bioanalytical PK

Development Phase
- Confirms similarity of standard curves
- Ensures Innovator biotherapeutic and Biosimilar calibrator curves are parallel
- Recommends a statistically based approach for comparing curves
- Software availability (ALLFIT)

Pre-Validation Phase
- Confirmatory evaluation of parameters established in Development prior to Validation

Validation Phase
- Confirms comparable reactivity of Biosimilar & Innovator in common LBA
- Systematic comparison of QC results
  - Phase 1: Intra-batch evaluation
  - Phase 2: Inter-batch evaluation
- Direct comparison of Biosimilar against Innovator
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Bioanalytical PK

- Phase 1: intra-batch evaluation for each QC concentration
- Lab system suitability requirements for pre-validation
- Phase 2: inter-batch evaluation, Biosimilar and Innovator
  - Inter-batch mean bias (%RE) ±20% (25% ULOQ, LLOQ)
  - Inter-batch %CV ≤20% (25% ULOQ, LLOQ)
  - Inter-batch %TE ≤30% (37.5% ULOQ, LLOQ)
- Phase 3: inter-batch comparison between Biosimilar and Innovator
  - Absolute value of Biosimilar and Innovator inter-batch %RE ≤20% (25% ULOQ, LLOQ)
  - 90% confidence interval for this difference ±30% (±37.5% ULOQ, LLOQ)
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Bioanalytical PK

A single LBA should be used to support PK assessments

**Development phase:** standard curve generated using Biosimilar drug should be demonstrated to be parallel to a Originator drug standard curve

**Validation phase:** Biosimilar drug QC samples should be demonstrated to be bioanalytically similar to Originator drug QC samples

Successful completion enables a laboratory to use one assay to support a Biosimilar drug development program
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Immunogenicity Regulatory

**FDA:** “The goal of the immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses....Thus, establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key element in the demonstration of biosimilarity.”

**EMA:** “Immunogenicity testing of the biosimilar and the reference products should be conducted within the comparability exercise by using the same assay format and sampling schedule. Assays should be performed with both the reference and biosimilar molecule in parallel (in a blinded fashion) to measure the immune response against the product that was received by each patient.”
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Immunogenicity Testing

Meaningful interpretation of comparability study data:

- Incidence (% of the patient with a positive immune response)
- Titer (low, mid or high titer)
- Neutralization ADA %
- Clinical relevance of ADA
Future of Biosimilars
Immunogenicity Testing

Scenario 1: One assay can detect Anti Drug Antibodies (ADA) to both Reference and Biosimilar products

Validate one assay using the Biosimilar product

Scenario 2: One assay to detect ADA for Reference, One assay to detect ADA for Biosimilar

Validate two assays
## Future of Biosimilars
### Immunogenicity Testing

<table>
<thead>
<tr>
<th>1 Assay</th>
<th>2 Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>• Cost, Analysis of Blinded studies, Less inter-assay variation, comparability easier to perform</td>
<td>• ADA against unique structure of the innovator drug may not be detected</td>
</tr>
<tr>
<td>• Biosimilars can artifactually have higher immunogenicity incidence</td>
<td>• Difficulty to compare 2 qualitative assays results</td>
</tr>
</tbody>
</table>
Future of Biosimilars

Conclusions

• Biosimilar development strategies must adapt to evolving regulatory requirements
  • New regulations in Europe and USA
  • AAPS Biosimilar Focus group

• Clinical development strategies
  • How similar is similar?
  • Choose the right assay

• Commercial strategies must optimize market uptake of biosimilars market
  • Size, product price, reimbursement policies, healthcare policies, competing products and barriers for uptake
Questions?
Future of Biosimilars

Publications

“Systematic Verification of Immunogenicity between a **Biosimilar** and a Reference Biotherapeutic: Committee Recommendations for the Development and Validation of a Single Anti-Drug Antibody assay to Support Immunogenicity Assessments”

“Systematic Verification of Bioanalytical Similarity between a **Biosimilar** and a Reference Biotherapeutic: Committee Recommendations for the Development and Validation of a Single Ligand Binding Assay to Support Pharmacokinetic Assessments”

“**Biosimilar**”
*Cai XY*, (Press publication in October 2014). Dominique Gouty.

FBB Focus On: Challenges Associated With Biosimilars (October 23, San Diego, CA)
"Challenges Associated by **Biosimilars**" by Dominique Gouty