The Impact of Biosimilars on Patients and the Global Biotech Industry

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Biosimilars are not Generics

• Biosimilars (or follow-on-biologics) are fundamentally different from generic chemical drugs:
  – Size and complexity of the active substance
  – Nature of the manufacturing process
  – Route of administration

• Unlikely a biosimilar product could be demonstrated to be identical to an innovator product
  – Quality and nature of source products in manufacturing process
  – Process used to extract and purify the product
  – Natural variability of protein molecules
  – Current limitations of analytical methods

• Biogen Idec experience suggests that we cannot measure everything

• Therefore, biosimilars require a unique pathway to bring them to market to protect the interests of patients
Biogen Idec Experience

• **Amevive®**
  – LFA3-Fc fusion protein to treat mod/sev psoriasis
  – Cell line change in Phase II
  – Change in pharmacodynamics (reduced potency)
  – *Only detected in toxicology and clinical trials*

• **Avonex®**
  – Protein cytokine, interferon beta to treat MS
  – Cell line change post Phase III
  – Change in immunogenicity profile (25% NAB+ decreased to <5%)
  – *Only detected in clinical trials*
Impact on Patients and Industry Depends on Regulatory Pathway

There are three key issues that will determine the impact of biosimilars on patients and industry

<table>
<thead>
<tr>
<th>Level of Scientific Evidence</th>
<th>Patient Safety</th>
<th>Incentives for Innovation</th>
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<tbody>
<tr>
<td>• Level of analytical characterization</td>
<td>• Relationship between physicians and patients</td>
<td>• Non-patent Data Exclusivity / Regulatory Exclusivity</td>
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<td>• Amount of pre-clinical testing</td>
<td>• Similar post-marketing surveillance and/or post-marketing clinical studies similar to innovators</td>
<td>• Patent dispute resolution system</td>
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<td>• Clinical testing hurdle</td>
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<td>• Immunogenicity</td>
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<td>• Manufacturing</td>
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Today, clinical testing remains the only valid assessment of a product's safety, efficacy, and immunogenicity profile.

Given that biosimilars cannot be shown to be identical to innovator products, physicians need to be aware of which products their patients are taking.

Incentives to continue to research, develop and manufacture innovative breakthrough therapies must be maintained.
Impact to Patients
*Immunogenicity Is Key*

- If the human body reacts to a biosimilar protein as foreign by generating *increased antibodies vs. the innovator protein*, then the body is telling you that *there is something different*.

- If antibodies are neutralizing (NAB+), then this impacts the long-term efficacy for patients:

![Graph showing Relapse Rate (mo.19-36) and MRI (yr 2-3) for Pivotal trial of Betaseron RRMS]
Biosimilar Competitors Likely to Need More Capabilities than Small Molecule Generics

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<thead>
<tr>
<th>R&amp;D</th>
<th>Reg./Legal</th>
<th>Sales/Mktg</th>
<th>Mfg/Dist</th>
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<tr>
<td>• No true research capability, only demonstrate bioequivalence</td>
<td>• Standardized approach to dossier preparation</td>
<td>• Pure push model; effort on distribution channel; payors, wholesalers &amp; pharmacies</td>
<td>• Efficient low-cost mfg and sourcing</td>
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<td>• Robust generic pipeline focused on first to market</td>
<td>• Strong patent litigation capability</td>
<td>• Efficient global distribution system</td>
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Small Molecule Generics Success Factors

Major Differences for Biosimilars

- Substantial R&D investments anticipated for cell-line, clinical trials, process development & scale-up
- Regulatory requirements may vary by molecule
- IP significantly more complex
- Both push and pull efforts critical
  - Field force to detail MDs
- A&P spend to compete against innovators
- Mfg process more complex – purification; fill/finish
- Distribution able to accommodate biologics

Price Decreases on Entry of Biosimilars Not Expected to be as Severe as Small Molecule Generics

Source: McKinsey / Biogen-Idec analysis