Biosimilars, Regulatory Framework and Outcome So Far

Dedicated to your information and advancement.

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Manufacturing of biologics is complex – and each process is unique

- DNA Vector
- Cloning into DNA Vector
- Same AA - maybe the same genetic sequence
- Different purification protocol
- Downstream
- Different in-process controls
- Maybe a different formulation
- Large-Scale Fermentation
- Formulation
- Different recombinant cell system
  - e.g., bacterial or mammalian cell

Biological Products are complex, and the manufacturing process impacts product quality

- The expression system leaves “imprint” on the product
  - *S. cerevisiae, E. coli*, Mammalian cell lines
- The primary structure of the protein has intrinsic properties: same chemical environment leads to structurally same derivatives
  - De-amidated forms, oxidised forms, aggregates etc.
- Each manufacturing process has a unique combination of
  - Solvents, enzymes, column materials, pH, buffers etc.
  - Results in individual “fingerprint” of impurities
- Analytical methods must be developed to capture all relevant impurities
- Purification methods must be tailored to the host cell and manufacturing methodology applied
Comparability exercises:
Process changes versus biosimilar product

Stepwise Comparability exercise:
- Clinical Comparability
- Nonclinical Comparability
- Chemical Comparability

Complete Comparability exercise:
- Clinical Comparability
- Nonclinical Comparability
- Chemical Comparability

Biosimilars
- New:
  - DNA?
  - Cell line
  - Process Technology?
  - Fermentation process
  - Purification process
  - Analytics
  - Facilities
  - Formulation?
  - And - no history

Character of Change
- Low risk
- Frequent
- Supported by: Analytical and Process Data

- Highest risk
- Rare
- Extensive Data: Analytical, Process and Human data

Regulatory Frameworks
In Europe, the scientific complexity sets the requirements for documentation

- Simple
  - Chemicals
  - Recombinant DNA technology
  - General
  - Blood-derived incl. rec. FVIII and FIX

- Complex
  - Immunologicals (vaccines and allergens)
  - Advanced therapy (gene and cell therapy)

Biosimilars

Generic (essentially similar) Full Dossier

Europe has implemented science-based comparability approach encompassing both Quality, Non-clinical and Clinical Investigations

<table>
<thead>
<tr>
<th>TITLE</th>
<th>MAIN MESSAGES</th>
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<tbody>
<tr>
<td>Guideline on Similar Biological Medicinal Products</td>
<td>- Unlike generics, biosimilars cannot be demonstrated to be “the same”</td>
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<tr>
<td>Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues</td>
<td>- Minor differences acceptable, but must be justified</td>
</tr>
<tr>
<td>Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical &amp; Clinical Issues</td>
<td>- Direct comparisons limited to drug product</td>
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<td>- Greater differences require more clinical data</td>
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<td>- Head to head comparison to show</td>
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<td>- Similar efficacy and efficacy</td>
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<td>- Similar immunogenic characteristics</td>
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<td>- Risk Management Program required</td>
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<td>- Class-specific nonclinical and clinical requirements</td>
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<td>- Study designs, post-marketing commitments etc.</td>
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</table>

Coagulation factors (FVIII and FIX) excluded from current guidelines
Clinical endpoints for comparative trials

- Clinical endpoints are linked to disease/mode of action
  - Insulin lowers blood glucose – measured directly in blood
  - hGH stimulates growth – measured when children grow
- One guidance document – hard to cover variety of diseases
  - Class specific guidance recommended (EMEA example)

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues

Biosimilar Approvals In Europe to Date:
For “6” biologics approved; 2 rejected; 3 withdrawn

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Common Name International Nonproprietary Name</th>
<th>Biosimilar Sponsor(s)</th>
<th>Reference Product</th>
<th>Decision</th>
<th>Decision Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnitrone®</td>
<td>somatropin</td>
<td>Sandoz</td>
<td>Genotropin®</td>
<td>Approved</td>
<td>April 12, 2006</td>
</tr>
<tr>
<td>Valtropin®</td>
<td>somatropin</td>
<td>BioPartners</td>
<td>Humatrope®</td>
<td>Approved</td>
<td>April 24, 2006</td>
</tr>
<tr>
<td>Alphesin®</td>
<td>Interferon alfa-2a</td>
<td>BioPartners</td>
<td>Roferon-A®</td>
<td>Negative Opin.</td>
<td>June 28, 2006</td>
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<tr>
<td>Abseamed®</td>
<td>Epoetin alfa</td>
<td>Hexal Medice</td>
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<tr>
<td>Retacrit®</td>
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<tr>
<td>&quot;Hospira EPO&quot;</td>
<td>Epoetin zeta</td>
<td>Hospira Stada</td>
<td>Eprex®</td>
<td>Approved</td>
<td>Dec. 18, 2007</td>
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<td>Silapor®</td>
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<tr>
<td>&quot;Teva G-CSF&quot;</td>
<td>Filgrastim</td>
<td>Teva Ratiopharm CT</td>
<td>Neupogen®</td>
<td>Approved</td>
<td>Sept. 15, 2008</td>
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</tbody>
</table>
US regulatory pathways..

- **Food Drug & Cosmetic (FD&C) Act**
  - NDA (incl. insulin and growth hormone)
- **Public Health Service (PHS) Act**
  - BLA (MAB’s, EPO, vaccines etc.)

- **505(j)**
  - Could be open to approval of similar versions of proteins approved under an NDA such as insulin and growth hormone

- **505(b) 2**
  - Rely on reference product data

- **No provisions for approval of similar versions of proteins approved under an BLA**

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No framework for approval of bio-similar products in the US yet

- **Drugs**
  - No general pathway for follow-on biotech drugs established
  - Omnitrope (biosimilar hGH) approved under 505(b)(2) in 2006
  - Insulins – could be approved in similar manner

- **Biologics**
  - No provisions for approval of similar versions of proteins approved under an BLA
  - So far, no conclusion despite legislative activities in 2007

- **Main issues under discussion**
  - Clinical trials and comparability studies
  - Exclusivity
  - Interchangeability/automatic substitution

- **Latest development**
  - Jan 2009: New administration followed by
    - Eshoo-Barton Amendment (House)
    - Hagan-Enzi-Hatch Amendment (Senate)

Drugs: Chemical Entities and e.g. Insulin, hGH and Heparins
Biologics: e.g. EPO, Monoclonal Antibodies, Coagulation Factors
Rest of the world

- Australia: Adopted the EU guidelines 2006
- Malaysia: Guidance finalised August 2008
- Turkey: Guidance finalised August 2008
- Taiwan: Guidance finalised November 2008
- Japan: Guidance finalised March 2009
- Israel: Regulation published March 2009
- Canada: Second draft guidance March 2009
- Korea: Draft guidance published June 2009
- Singapore: Draft guidance published June 2009
- WHO: 3rd draft guidance discussed July 2009
- And more ....
- All are based on the comparability principles established by EMEA for biosimilars

Biosimilar lessons learned
Early version of Omnitrope® (somatropin)
Reference product: Genotropin (Pfizer)

- Early version of the product: 57% of patients developed antibodies against Omnitrope
  - Problem was residual host-cell protein
- Re-developed purification process
- Conducted a second phase 3 study
- Antibody levels reduced (comparable)
- Approved by EMEA, FDA, TGA – and recently by Health Canada and PMDA in Japan

Link between quality parameter (HCP) and clinical safety (immunogenicity) found in clinical studies

* Source: European Public Assessment Report

Alpheon (alpha interferon)
Reference product: Roferon (Roche)

- Differences in impurity profile were observed

  Key Clinical Data
  - PK (3 studies):
    supra-bioavailability (early study); comparable; inconclusive
  - PD (2 studies): PD equivalence/no PD equivalence
  - Safety&Efficacy:
    - Clinically and statistically significant difference in virological relapse rate found: more patients on Alpheon had relapse
    - Different rate of adverse events and laboratory-related events judged as clinically relevant

Clinical studies evaluating efficacy and safety demonstrated clinically meaningful differences leading to Rejection by EMEA

* Source: European Public Assessment Report
Marvel Insulins: Human Long, Rapid and Mix

- Not possible to conclude that purity is comparable to reference product
- Clinical (PK/PD) data: Significant differences in bioavailability compared to reference products
- File withdrawn from EMEA

PD studies demonstrated clinically meaningful differences
Clinical safety and efficacy study confirmed difference

* Source: European Public Assessment Report

Somatropin: New Thioether Variant Identified

- Thioether variant found in some hGH products (up to ~30%)
  - Hormotrop®, Yelit®, Cryotropin®
- Thioether variant not identified in
  - Saizen®
  - International standards: NIBSC 98/574 (r), NIBSC 80/505 (p), EP r-hGH CRS
- Thioether variant:
  - Not detected by compendial and other existing chromatographic methods – new methods required
  - Generated by high pH at elevated temperature (40 deg C)
  - Significantly reduced biopotency in rat model
- Analytical methods must be “tailor made”

New impurity identified with reduced biopotency
Change in Clinical efficacy & safety cannot be excluded

Because no two Biotech Products can be “the Same”

- **Approval standards necessary to protect patient safety**
  - Full comparability exercise needed (Quality, Nonclinical and Clinical)
  - Extrapolation to other indications needs to be scientifically justified and if necessary supported by clinical data
- **All protein drugs should be prescribed and given to patient using a unique name and be clearly identifiable.**
  - Product tracing and adverse event reporting
- **Pharmacovigilance**
  - Risk Management Plans and post-approval safety commitments equally relevant for innovator and biosimilar products
- **Label/Package Insert must be transparent and clear**
  - Provide overview of clinical data acquired with biosimilar vs reference
  - Clear guidance on interchangeability/substitutability based on data
- **Automatic substitution raises strong concerns**
  - No data to support repeated switches in “standard” comparability exercise
  - Fifteen countries across Europe have brought in new rules to prevent automatic substitution of biological medicines by biosimilars (Source: APM Health Europe, 21 February 2008).