Regulatory and Scientific Issues of Biosimilars

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Executive Director, PharmaNet
Member, FDA Alumni Association

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May 16-18, 2011
I am currently an employee of PharmaNet Development Group. I am Executive Director, Consulting Division.

I worked at the U.S. Food and Drug Administration (FDA) in 1991-2004. I was Deputy Director, New Drug Chemistry Division II, Office of New Drug Chemistry, CDER.

The following are my views and not necessarily the views of the Food and Drug Administration Alumni Association (FDAAA), or FDA, or PharmaNet.

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Agenda

- Definition and Products of Biosimilars
- Regulatory Update in US
- Comparability Concept and Biosimilar
- CMC Issues and Biosimilars
- Conclusion
Definition of Follow-On Biologics/Biosimilars

BIOSIMILAR BIOLOGICAL PRODUCT means a biological product approved under an abbreviated application for a license of a biological product that relies in part on data or information in an application for another biological product licensed under section 351 of the Public Health Service Act. (Biologics Price Competition and Innovation Act of 2009)

….. to be “similar” to an approved reference medicinal product, marketed by an independent applicant and is subject to all applicable data protection periods and/or intellectual property rights for the originator product. The requirements for the Marketing Authorization Applications for biosimilars are based on the demonstration of the similar nature of the two biological medicinal products (biosimilar versus reference biologic product) and require comparative quality, non-clinical, and clinical studies to demonstrate safety and efficacy. (EU Biosimilar definition)
Candidates for Biosimilars/Follow-on Biologics

- A **well-characterized** biological product similar to an approved reference product with patents and exclusivity expired.
- A product meeting quality standards including GMP.
- Same indication(s) and mechanism of actions.
- Comparability established by quality, pre-clinical and clinical testing.
- Approval by regulatory agencies based on existing knowledge and abbreviated data as permitted by law or regulations.
- Pharmacovigilance program for post-approval monitoring.
# Classes of Biologics/Biological Products

<table>
<thead>
<tr>
<th>Poorly characterized</th>
<th>Well-characterized*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional vaccines</td>
<td>Natural proteins</td>
</tr>
<tr>
<td>Whole blood</td>
<td>rDNA-derived proteins</td>
</tr>
<tr>
<td>Blood derivatives</td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>Blood components</td>
<td>rDNA-derived vaccines</td>
</tr>
<tr>
<td>Allergenic extracts</td>
<td></td>
</tr>
<tr>
<td>Stem cells</td>
<td></td>
</tr>
<tr>
<td>Somatic cell and gene therapeutics</td>
<td></td>
</tr>
<tr>
<td>Toxins</td>
<td></td>
</tr>
</tbody>
</table>
Specified Biological Products Approved in US

NDAs (FD&C Act)
- Insulin
- Growth Hormone
- FSH, LH, hCG, TSH
- Calcitonin
- Parathyroid Hormone
- Aprotinin
- Imiglucerase (Cerezyme)
- Hyaluronidase

BLAs (PHS Act)
- Interferons
- G-CSF
- Erythropoeitin
- Cytokines
- t-PA
- Enzymes
- Monoclonal antibodies
- rDNA blood products

NDA: New Drug Application
Food, Drug & Cosmetic Act

BLA: Biologic License Application
Public Health Service Act
Biologics Price Competition and Innovation Act

- Under Patient Protection and Affordable Care Act 2010
- Licensures of biosimilars for products regulated under PHS Act
- Two classes of products—biosimilar and interchangeable
- 12 years of exclusivity for new biological products and 1 year for the first interchangeable.
- Comparability in quality, safety, efficacy, and immunogenicity to a reference product (FDA may waive any of these studies).
- FDA is required to issue guidance, but should not preclude reviews of, or actions on applications, even without guidance.
- Complicate process of “confidential access” to biosimilar applications for patent assessment by the “representatives” of innovators.
- Revised definition of all proteins as biological products under PHS Act
- Phase out of approval of protein product approval under FD&C Act in 10 years.
Two Classes of Biosimilar Products in US

- **General requirements**
  - A highly similar protein molecule to reference product
  - Same mechanism of action(s)
  - Same strength, dosage form and route of administration

- **Biosimilar biological products**
  - No clinically meaningful differences
  - To be considered as a new active ingredients
  - Not interchangeable

- **Interchangeable biological products**
  - Risk of safety or diminishing efficacy of alternation and switching is not greater than the risk of continued use of reference product.
  - Substitution with the innovator's products permitted
Confidential Access and Exchanges of Patent List

- Biosimilar applicant must provide application within 20 days of FDA acceptance for determination of infringement claims by
  - Outside counsel and one in-house counsel
  - Representative of third-party patent owner

- Reference product sponsor must provide within 60 days of receiving confidential information to biosimilar applicant:
  - A list of patents for which RP sponsor believes claim of infringement could be “reasonably be asserted”

- The reference product sponsor can offer the biosimilar applicants to license specific patents

- Interactions on the patent claims between two parties within certain time limit.
# Data Requirements For Biosimilar Products

<table>
<thead>
<tr>
<th></th>
<th>Insulin, GH</th>
<th>EPO, IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application</strong></td>
<td>NDA</td>
<td>BLA</td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>CMC</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>PK &amp; PD</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Bioequivalence</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>Labeling</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**NDA**: New Drug Application  
**ANDA**: Abbreviated New Drug Application  
**BLA**: Biologics License Application  
**FD&C 505(b)(1)**: Data requirement  
**FD&C 505(b)(2)**: Data requirement  
**FD&C 505(j)**: Data requirement  
**PHS (Biosimilar)**: Data requirement  

* Abbreviated Comparative studies
Comparability Exercises

Innovator Products
Step-wise testing based on:
- Molecular complexity
- Manufacturing process
- Degree of characterization
- Clinical indications
- Production history
- Availability of safety and clinical data

- Quality Studies
  - Physicochemical tests
  - Bioactivity/Potency assays
  - Stability
- Non-clinical Studies
  - PK/PD studies
  - Toxicology
- Clinical Studies
  - Efficacy
  - Immunogenicity

ICH Q5E: Quality attributes are highly similar (not necessary identical).

Biosimilar Products
Comprehensive studies due to:
- Different cell line and production process
- Different characterization and release tests
- Short production history
- Extensive safety and clinical data not available
Comparability Exercise

Innovator Products
Step-wise testing based on:
- Molecular complexity
- Manufacturing process
- Degree of characterization
- Clinical indications
- Production history
- Availability of safety and clinical data

Quality Studies
- Physicochemical tests
- Bioactivity/Potency assays
- Stability

Non-clinical Studies
- PK/PD studies
- Toxicology

Clinical Studies
- Efficacy
- Immunogenicity

Biosimilar Products
Comprehensive studies due to:
- Complex structure
- Different cell line and production process
- Different characterization and release tests
- Extensive safety and clinical data not available

ICH Q5E: Quality attributes are highly similar (not necessary identical).
Comparability Concept for Biosimilars

Quality comparability data

- New Drugs
- Biosimilars

<table>
<thead>
<tr>
<th>% Relative data</th>
<th>Quality</th>
<th>Pharm/Tox</th>
<th>Non-clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>160</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Non-clinical</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Clinical</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Goals of Quality, Non-clinical, and Clinical Studies

- **Quality**
  - To demonstrate of comparability of the product to a reference product—
    the most critical step.

- **Pre-clinical toxicology**
  - To confirm therapeutic index and safety profile.
  - To qualify impurities by short-term animal studies.
  - Full animal toxicity studies are not necessary.

- **Non-clinical PK/PD studies**
  - To confirm dosing regimen by PK profiles.
  - To confirm the mechanism of actions by biomarkers (PD).

- **Clinical safety**
  - To compare immunogenicity and/or hypersensitivity with the reference products.

- **Efficacy**
  - To conduct confirmatory trials or other clinical trials for interchangeability.
  - Use of complementary biomarkers, or surrogate endpoints in some cases.
Perfect Candidates-Growth Hormone and Insulin

- First two rDNA proteins approved in 80s with extensive human data available from multiple manufacturers.
- Known mechanism of action and validated biomarkers.
- Small, simple, non-glycosylated and highly purified protein with proven structures and known impurities.
- Physico-chemical tests and public reference standard (WHO and EP) available.
- Clinically relevant bioassays.
## Follow-on GH Approved By FDA

<table>
<thead>
<tr>
<th>Data</th>
<th>Requirements</th>
<th>Omnitrope data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td>Comparative analysis</td>
<td>Highly similar active ingredient to Genotropin, WHO and EP reference standard</td>
</tr>
<tr>
<td><strong>Bioassay</strong></td>
<td>Comparative bioassay</td>
<td>Bioassays (rat weight gain)</td>
</tr>
<tr>
<td><strong>Pharm/tox</strong></td>
<td>May be waived</td>
<td>14-day rat and local tolerance</td>
</tr>
<tr>
<td><strong>PK/PD</strong></td>
<td>Comparative PK/PD</td>
<td>IGF-1 response (PD marker)</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Comparative data</td>
<td>Low immunogenicity (15 months)</td>
</tr>
<tr>
<td><strong>Efficacy (Clinical Trials)</strong></td>
<td>Efficacy and immunogenicity data</td>
<td>3 sequential multi-center trials (134 subjects) vs. ~253 for Genotropin</td>
</tr>
</tbody>
</table>
## Immunogenicity for GH

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Cell Line</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humatrope</td>
<td><em>E. coli</em></td>
<td>481 patients, 2% with Ab &gt; 2mg/L</td>
</tr>
<tr>
<td>Nutropin</td>
<td><em>E. coli</em></td>
<td>0/232 with Ab &gt; 2mg/L</td>
</tr>
<tr>
<td>Protropin</td>
<td><em>E. coli</em></td>
<td>26,000 treated, 0.4% with Ab &gt; 2mg/L,</td>
</tr>
<tr>
<td>Norditropin</td>
<td><em>E. coli</em></td>
<td>0/358 with Ab &gt; 2mg/L, 12 months</td>
</tr>
<tr>
<td>Saizen</td>
<td>Mouse cells</td>
<td>1/280 with Ab &gt; 2mg/L</td>
</tr>
<tr>
<td>Genotropin*</td>
<td><em>E. coli</em></td>
<td>419, 1.9% with Ab; 0 &gt; 2mg/L</td>
</tr>
<tr>
<td>Omnitrope</td>
<td><em>E. coli</em></td>
<td>134, 1% with no effect on efficacy</td>
</tr>
<tr>
<td>Valtropin</td>
<td>Yeast</td>
<td>98, 3% with no effect on efficacy</td>
</tr>
</tbody>
</table>
### Other Approved Biosimilars/Follow-ons

<table>
<thead>
<tr>
<th>Type</th>
<th>Product</th>
<th>Company</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin</td>
<td>Omnitrope, Valtropin</td>
<td>Sandoz, BioPartner</td>
<td>US, EU, Japan, Australia, Canada</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Biocrite, Abseamed Hexal</td>
<td>Sandoz, MAP Hexal Biotech (same CMC infor.)</td>
<td>US, EU</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>Retacrit, Silapo</td>
<td>Stada, Hospira</td>
<td>EU</td>
</tr>
<tr>
<td>(Minor differences in quality)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoetin kappa</td>
<td>JR-013</td>
<td>JCR</td>
<td>Japan</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Biograstim, Teva-Grastim, Rtiograstim Filgrastim</td>
<td>CT Arznemittel Ratioparma, Teva Sandoz/Ratiopharm</td>
<td>EU</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Hydase/Vtrase/Hylenes</td>
<td>PrimaPharm, ISTA, Baxter</td>
<td>US (DESI)</td>
</tr>
</tbody>
</table>
## Rejected or Withdrawn Biosimilar Submissions

<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>Company</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpheon</td>
<td>Interferon $\alpha$-2A</td>
<td>BioPartner</td>
<td>Rejected by EU</td>
</tr>
<tr>
<td>Insulin Marvel</td>
<td>Insulin</td>
<td>Marvel Life Science</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Short</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Marvel</td>
<td>Insulin</td>
<td>Marvel Life Science</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30/70 Mix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Marvel</td>
<td>Insulin</td>
<td>Marvel Life Science</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Long</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Why Was Alpheon Biosimilar Rejected by EMEA?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Guidance</th>
<th>Actual studies/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC</td>
<td>CMC and comparative data to Roferon- A</td>
<td>Deficiencies on impurity, stability data and process validation</td>
</tr>
<tr>
<td>Efficacy</td>
<td>A randomized, parallel group comparison against the reference product, 48 weeks</td>
<td>455 Hepatitis C patients: More return of disease, More side effects</td>
</tr>
<tr>
<td>Safety</td>
<td>Immunogenicity Assay, 48 weeks</td>
<td>Immunogenicity assay not validated</td>
</tr>
</tbody>
</table>

*Failure to comparability - quality and clinical comparative testing*
Why Were Marvel Insulin Biosimilars Withdrawn?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Guidance</th>
<th>Actual studies/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMC</td>
<td>CMC and comparative data to reference product (Lilly Humulin)</td>
<td>1. Inadequate CMC information, e.g. specification, impurities…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Quality comparability not established.</td>
</tr>
<tr>
<td>Animal studies</td>
<td>4-week repeat dose tox in rats, and local tolerance</td>
<td>Comparability not established</td>
</tr>
<tr>
<td>Human PK/PD</td>
<td>PK (single dose cross-over): Insulin and IGF binding; PD( double-blind, cross-over): glucose level</td>
<td>Comparative PK/PD not performed</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Not required</td>
<td>Clinical studies were performed, but considered irrelevant</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>SC 12 months</td>
<td>Immunogenicity not properly tested</td>
</tr>
</tbody>
</table>

*EMEA concluded that Marvel insulins were not comparable to Humulin*
Quality Issues of Biosimilars

- Quality comparability critical to successful product development
- Conformance to all quality standards for new products

- **Shorter timeline for more comprehensive quality information**
  - Traditional phase I, II, III etc. do not apply
- **Process development to produce comparable product**
  - Cell line, culture conditions, and purification process
- **Source of reference product for comparability studies**
  - Approved for marketing in US

- Adequate characterization tests and acceptance criteria for detection of subtle differences
- Relevance of bioassay for comparability testing
- Assessment of risk of different impurities profiles
- Dosage form and formulation
- Comparable stability
Pre-clinical and Non-clinical Issues

- Animal pharmacology and toxicology
  - Failure to meet quality comparability as a pre-condition for studies with one species
  - Lack of relevant animal model for mechanism of actions and toxicology profiles
  - Interference by antibody against products
  - New study approaches that are different from innovator’s

- Human PK/PD studies
  - Lack of validated, biomarkers, and PD markers
  - Challenges in bioanalytical methods
  - Choices between normal subjects and patients
  - Availability of study drugs
Clinical Issues of Biosimilars

- Low sensitivity of comparative clinical studies to detect subtle differences
  - Statistical consideration and trial size and duration
- Higher requirements for interchangeable biological products
  - Multiple cross-over trial design may be necessary
- Lack of surrogate biomarkers and endpoints
- Product-specific protocol design
- New Safety concerns
  - Immunogenicity
- Extrapolation of multiple indications?
Carbohydrate Profiles and Comparability

*Nature Biotechnology* 26, 592 (2008)

**FDA balks at Myozyme scale-up** by George Mack

“Genzyme ran into a snag in April when the US Food and Drug Administration (FDA) rejected its application to produce Myozyme (alglucosidase alfa, rhGAA) in its 2,000-liter-scale facility under the same approval authorization given for its 160-liter-scale plant. The FDA says the carbohydrate structure of the products manufactured at each scale differs and thus the 2,000-liter product requires a new biologic license application”

*Genzyme has been acquired by Sanofi-Aventis.*
Epoeitin Alfa

- 30.4 Kda
- 2 disulfide linkages
- 165 amino acids
- 4 glycosylation sites

Monoclonal Antibodies

- 150 kda
- Pyro-Glu
- Methionine oxidation
- deamidation
- High mannose,
  - G0, G1, G1, G2
- Sialylation

Erstellt von Jamiri

S. Kozlowski, OBP, CDER
Glycoform Profiles and Comparability Testing

(H. S. has contributed to meetings and publications sponsored by Amgen, Roche, Johnson & Johnson and Shire.)

(Dr. Stephan Fischer, Roche)
A Case of MAb Biosimilar or Not?

- Reditux by Dr. Reddy’s approved in India in 2007
- Analysis by Genentech:
  - Identical amino acid sequence and molecular weight
  - Glycoforms not comparable
  - Charge distribution not comparable
  - Aggregate content not comparable
  - Effector function not comparable
  - Higher host cell protein content
  - Clinical data with Reditux in NHL comprised 17 patients only

Reed Harris, Genentech, Presentations at FABIAN 2008 “Biopharma, Biosimilar, Biogenerics? Bioanalysis”, Groningen, the Netherland, 2008 and “Biogenerics 2008”.
Conclusion

- US biosimilar law provides opportunities and challenges.
- Understand quality comparability is the most critical and challenging step for biosimilar development.
- Develop manufacturing process for production of similar drug substance and product consistency early.
- Secure the source of reference product for comparability testing.
- Establish tests and acceptance criteria for comparability to the reference product.
- Complete extensive comparative product characterization.
- Establishment of quality comparability should be completed prior to the start of non-clinical and clinical studies.
- Without published product-specific guidance, prior interactions with FDA are important for development.
Thank You!

谢谢

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