Development of Biosimilar Drugs, Opportunities and Challenges

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About Biosimilar Drugs

- A “copy” of the patent expired biological drug (protein/ppt/mAb)
- Different from the generic small molecule drugs – much more complicated, never truly be “IDENTICAL”
  - Big size, post-translational modification
  - Heterogeneous isoforms
  - Immunogenicity
  - Complicated manufacture process
  - Injected proscription drug
- Need special regulatory process & guidelines
  - Efficacy & safety – in vitro/in vivo tests
  - Immunogenicity test
  - Post-market surveillance
- Need special legislation
  - Years of exclusivity
  - Interchangeability/automatic substitution

Higher success rate, lower development cost
Core Competencies for Biosimilar Developers

Biosimilars World

- Marketing
- Biological manufacture
- Pharmacovigilance
- Clinical trial design

Traditional Generic World
- Patent
- Regulatory Manufacture

Biological manufacture
Biologics Market Growing Faster than Small Molecule Drugs

Market Size By Drug Type

Worldwide Market size (€B)

- Large Molecule Drugs: CAGR 18%
- Small Molecule Drugs: CAGR 9%

Biologics Market By Segment

Worldwide Market size (€B)

- Biosimilars: CAGR 103%
- Antibodies: CAGR 27%
- Recombinant Proteins: CAGR 10%

1. 2007 to 2010 based on forecasts
Note: Biologicals from players in emerging markets, non-protein antinfectives, vaccines, pregnancy hormones and non-protein hormones are excluded from the current analyses
Source: Datamonitor; BCG
Biosimilars Key Drivers

- In 2010, global pharma market reached $830 B. Biological drugs market exceeded $116 B (14%). Biosimilar drug sales $380M
- Large number of biological drug patents expire soon (>60B by 2015)
- Increasing market demand
  - Aging population
  - Health awareness
  - Affordability and insurance coverage
- Increasing healthcare cost
- Increasing innovative drug R&D cost

affordable, safe, and efficacious biological drugs

Biosimilars would free up healthcare funds for new innovative drugs

Higher success rate, lower development cost
Slower and Costly


2-3 years 1 year 2-3 years 1 year

Innovative Biologics ~ $1B

Generics

Biosimilars $30-100M

$3-8 M
EU
- EU Commission: legislative framework in 2004
- EMEA: general guidelines in 2005
- Over 10 products marketed since 2006 (hGH, EPO, GCSF, Insulin and IFN)

Australia
- Guideline established in fall 2006
- Several biosimilar products approved

USA
- Congress passed the new legislation in March 2010 (12 years data exclusivity)
- FDA working on new regulatory guidelines

Japan
- Guideline established in fall 2008
- The first biosimilar drug approved

India: active

China: No clear guidelines available, active discussions
Criteria for Biosimilar Products

Key: comparable **quality**, **safety**, and **efficacy** to the reference medicine

- **Non-clinical studies**
  - Analytical studies: biochemical/biophysical, cellular activities and characteristics, MOA
  - Animal studies: pharmaco-toxicological assessment, clinically relevant activity

- **Clinical studies**
  - Comparative PK, PD
  - Efficacy (> one surrogate marker)
  - Safety
  - Immunogenicity
  - Route of administration, dosage form, strength

- **Clinical safety and pharmacovigilance**
  - Post-market monitoring
  - Risk management plan

- **Manufacturing – Quality, safety, efficacy**
Immunogenicity – clinically relevant anti-drug antibody

- Causes of immunogenicity - complicated
  - Product related
    - structure, stability, etc.
    - Product and process-related impurity, post-translational modification
    - Route of administration, dosing regimen and schedule
  - Patient related
    - Genetic or acquired, age
    - Underlying disease and treatment
  - Ab classes, affinity, specificity

- Safety impact of immunogenicity
  - Varies from indication
  - Therapeutically irrelevant or
  - Life-threatening
    - Reduce efficacy
    - Cross-reactivity to endogenous protein
    - Serious general immune effects
  - Alters PK, PD and activity in patients
Immunogenicity – clinically relevant anti-drug antibody

How to reduce immunogenicity
- In-silico modeling to identify T-cell epitopes
- In-vitro cell-based assays to confirm/identify T-cell epitope
- Maintain human sequence and post-translational modification
- Reduce the impurity to the minimum level

How to test immunogenicity
- Develop appropriate strategy in clinical study design
- State of art and validated screening and confirmatory assay with appropriate specificity and sensitivity
- Sufficient patient numbers and data points
- Justified timing of sampling
- Consider interference from impurity and circulating antigen
Biosimilars vs Innovators

Process = product

- Production cell line
- Formulation
- Manufacture
- Route of administration
Hurdles:
- Manufacture process is complex and expensive to achieve “similar” quality, safety, and efficacy profile
- Uncertainty of regulatory pathway in US, China, and many other countries
- Non-interchangeable
- Conflicting interests among regulators, original biologics makers, insurance payers, practitioners, and patients

Don’ts:
- Don’t change primary sequence
- Don’t change major process and formulation
- Don’t change the route of delivery, dose regime and schedule
- Don’t aim at “better”, aim at “same” or “as similar as possible”
SFDA Regulatory Requirements

- Marketed product outside of China
  - Comparable manufacture process and QA/QC standards
  - Comparable biological activity in vitro and in vivo
  - 1 month tox on 1 species*
  - 1-2 efficacy models
  - Full clinical trial

- Marketed product in China
  - Comparable manufacture process and QA/QC standards
  - Comparable biological activity
  - 1 month tox on 1 species*
  - 1-2 efficacy models
  - Phase III trial

* Based on the comparability to the known drug, the pharmacology and toxicology study can be reduced or eliminated
Biological Drugs on the Market in China

- New generation of biological drugs
  - EPO, TPO, 3SBio + many developers
  - GCSF, many developers
  - Enbrel (益赛普), CITIC, Celgen

- “Legacy” biological drugs
  - Interferon
  - hGH
  - Insulin
  - Interleukins
Case Study: human erythropoietin

Biochemical Assessment of Erythropoietin Products From Asia Versus US Epoetin alfa Manufactured by Amgen

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4Amgen Inc., Department of Quality Assurance, Thousand Oaks, California 91320
# Recombinant Human Erythropoietin (rHuEPO) Sample List from Asia

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<th>Marketed Country</th>
<th>Trade Name</th>
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EPO China Market Growth

Chinese Total EPO Market in Volume and Sales (1999-2010)

Source: IMS Health
Chinese EPO Market Volume and Value (1999-2010)

Chinese EPO Market is Crowded

Source: IMS Health
Iso-electro-focus (IEF) Gel

(A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).
SDS–PAGE with Western Blot Analysis for Aggregation
Relative Denaturation - 9G8A antibody assay to detect unfolding structure

Samples from China, Korea and India were compared to Amgen Epogen. A value of 1 indicates no difference in folding between the sample and the EPO standard.
Concentration

Striped bars represent the labeled concentration and solid bars represent the concentration measured by ELISA.
rHuEPO from Korea, China, and India were compared with the innovator product, Epoetin alfa, in vitro for molecular integrity, glycoforms, and ELISA.

Some rHuEPO from Korea, India, and China contained more glyco-forms and other impurities.

These data emphasize potential biochemical discrepancies resulting from different cell lines, manufacturing processes, and quality control.

These data formed the basis for a strong argument in favor of establishing high standards of quality control in product manufacturing and processing.
Challenges for Biosimilars Development

- Competition
- Regulation
- Innovator
- IP
Opportunities and Challenges

**Opportunities**
- Large market needs and growing affordability
- Existing manufacturing technology
- Growing understanding to biological drugs
- Competitive pricing advantage on global market
- Low risk low cost

**Challenges**
- Lack of clear regulatory guidance in many countries (US, China)
- Balanced legislation which protect and promote innovative drugs
- Complicated analytical techniques
- Development of manufacturing capability
- Enter the market at risk (against innovative drug and other competitors)
- No interchangeability, brand marketing required