Observation on Follow-on Biologics / Biosimilars

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Forward Looking Statements

This presentation may include forward looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.
Contents

1. Features of FOBs/biosimilars

2. Guidelines on FOBs/biosimilars

3. Next steps of FOBs/biosimilars

4. FOBs/biosimilars of antibody drugs
Follow-on Biologics (FOBs)/Biosimilars

- Biological products made by manufacturers other than the originator and developed as similar products referring to the original product after its patent expiration.

- From a scientific view, FOBs/biosimilars are not “identical” or “same” with the original product, therefore different processes and requirements compared to general generic drug development are required.

- Two processes for development are possible:
  - New drug application with a full data package as same as the original bio-product. (The Japanese guideline does not define this case as a FOB)
  - Application with comparable data to the original product in quality, safety and efficacy based on comparative studies. (Expectation of reduction of development costs and time)
Complexity of Drugs by Molecular Size

How many/much checks/times/labors are needed to keep the functions?
Definition of Wording

**FOBs are different substances from the original product!**

Generics

- **Biosimilars**: Similar Biological Medical Products
- **FOBs**: Follow-on biologics
- **SBPs**: Similar biotherapeutic products
- **SEBs**: Subsequent entry biologics

Sameness [identical] => Not applied for biosimilars

Similarity => Applicable for evaluation of biosimilars

Comparability => ICH-Q5E (minor process change by the same manufacturer,
(The Japanese guideline is on extension of this concept)
Hurdles for ‘Biosimilars’

- Production capabilities including facilities, technology and human resources
- Complicated and unclear patent situation; expensive royalties
- Difficulties in assessment and proof of comparability, including safety
- Unforeseeable direction of regulatory authorities

- Complex nature of materials (heterogeneity, impurities, high-ordered structure, etc.)
- Insufficient scientific methodology for assessment of chemical/biological comparability
  - Many parts of the methodology rely on product-by-product experience
  - Proof of comparability requires an enormous amount of data (manufacturing process/site change by original manufacturer)
  - Generic manufacturers do not have access to full data of brand products
- Impossible to predict safety (especially immunogenicity)

Abbreviated approval process does not have sufficient scientific support in the case of ‘FOBs’
Independent process for ‘FOBs’
Grounds for Comparability of Biologics

“Comparability”

Substance

Similarity

Reference

Product Qualities
- Physicochemical
- Biological
- Surrogate Markers
- Pharmacokinetics
- Pharmacodynamics

Manufacturing Process
- Cell line
- Fermentation
- Harvesting
- Isolation/Purification
- Scale
- Facility

Experiences
- Manufacturing
- Analytical
- Biological
- Clinical

Clinical Outcomes
- Efficacy
- Safety
- Immunogenicity

Only part of “Properties” available to FOB/biosimilar makers
Heterogeneities of Bioproducts (EPO)

- Process conditions and in-process controls will determine the product composition

(Dr. Stephan Fischer, Roche Penzberg)
Comparability of the Product Batches

From an established process
(part of “comparability” data)

Comparability of batches upon process changes monitored by IEF

G025-G029: 5 fermentation runs (basic process)
G030: reference standard
G039: variation, optimized RP-HPLC
G044: variation, sterile filtration
G061: variation, fermentation media constituent
G003: variation, produced in new building

Source: H: Haug, V. Pfeifer, Roche Penzberg
Difference of Product Profile

Product from different manufacturers

Figure 1. Iso-electro-focus (IEF) Gel with Western blots for isoform detection: (A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).


Note: Products above are not approved according guidelines of EU/Japan
Microheterogeneity Affects to Bioactivity

IEF patterns

Sialic acid (mol/mol)
- huEPO-(1): 14.0
- huEPO-(2): 14.2

HPLC pattern

in vivo activity (U/mg)
- huEPO-(1): 226,000
- huEPO-(2): 400,000

Available assays are insufficient to prove identity. Microheterogeneity changes biological activity of the product.

(Dr. Stephan Fischer, Roche Penzberg)
Even in the case of site-change by the same manufacturer according the regulations, an unexpected event happened.
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Guidelines of Biosimilars in EU

Current

Overarching guideline
“Guideline on Similar Biological Medicinal products”

Guideline on quality issues
Guideline on non-clinical/clinical issues

Product-class Specific Annexes (non-clinical/clinical)

Insulin  hGH  G-CSF  EPO  in preparation

IFN-a
LMWH

Next issues

Pharmacovigilance, Revision of EPO guideline
Immunogenicity, Biosimilars of antibody drugs
### Approved Biosimilars in EU

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Company</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnitrope®</td>
<td>Somatropin</td>
<td>Sandoz</td>
<td>Apr, 2006</td>
</tr>
<tr>
<td>Valtropin®</td>
<td>Somatropin</td>
<td>BioPartners</td>
<td>Apr, 2006</td>
</tr>
<tr>
<td>Binocrit®</td>
<td>epoetin alfa</td>
<td>Sandoz</td>
<td>Aug, 2007</td>
</tr>
<tr>
<td>Epoietin alfa-Hexal®</td>
<td>epoetin alfa</td>
<td>Hexal</td>
<td>Aug, 2007</td>
</tr>
<tr>
<td>Absamead®</td>
<td>epoetin alfa</td>
<td>Medice Arzneimettel</td>
<td>Aug, 2007</td>
</tr>
<tr>
<td>Silapo®</td>
<td>epoetin zeta</td>
<td>Stada Arzneimettel</td>
<td>Dec, 2007</td>
</tr>
<tr>
<td>Retacrit®</td>
<td>epoetin zeta</td>
<td>Hospira Enterprises</td>
<td>Dec, 2007</td>
</tr>
<tr>
<td>Tevagratstim®</td>
<td>filgrastim</td>
<td>Teva Generics</td>
<td>Sep, 2008</td>
</tr>
<tr>
<td>Ratiogratstim®</td>
<td>filgrastim</td>
<td>Ratiopharm</td>
<td>Sep, 2008</td>
</tr>
<tr>
<td>Biogratstim®</td>
<td>filgrastim</td>
<td>CT Arzneimettel</td>
<td>Sep, 2008</td>
</tr>
<tr>
<td>Filgrastim ratiopham®</td>
<td>filgrastim</td>
<td>Ratiopharm</td>
<td>Sep, 2008</td>
</tr>
<tr>
<td>Filgrastim Hecal®</td>
<td>filgrastim</td>
<td>Hexal</td>
<td>Feb, 2009</td>
</tr>
<tr>
<td>Zarzio®</td>
<td>filgrastim</td>
<td>Sandoz</td>
<td>Feb, 2009</td>
</tr>
</tbody>
</table>

(Insulin Marvel: withdrawal, Alpheon (IFN-α): rejection)
Guideline on FOBs in Japan

March 4, 2009

◆ Guideline to secure quality, safety and efficacy of follow-on biologics

◆ Generic and brand names of follow-on biologics

◆ Application for approval of follow-on biologics

◆ MHLW’s comments for the public opinions on the guideline draft

July 21, 2009

◆ Questions and Answers regarding the guideline
## Major Features of Japanese/EU GL

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Framework</strong></td>
<td>Single guideline covering all protein drugs (insulin to Mab)</td>
<td>An overarching GL and sub-GLs by product</td>
</tr>
<tr>
<td><strong>Basic concept</strong></td>
<td>Evaluation by comparability studies on quality (ICH Q5E) and PK/PD profiles, together with clinical data complementing the data (case-by-case and step-by-step approach)</td>
<td>Proof of “similarity” in combination of quality, non-clinical and clinical study data based on comparative studies</td>
</tr>
<tr>
<td><strong>Post approval</strong></td>
<td>Plans for post-marketing surveillance study and risk management required at submission of application</td>
<td></td>
</tr>
<tr>
<td><strong>Naming</strong></td>
<td>Nonproprietary and brand names for FOBs should be distinguished from the comparator or other FOBs</td>
<td>INN: same as the comparator</td>
</tr>
</tbody>
</table>
Image of Data Requirements

- Comparability to the comparator
  - Data required by ICH Q5E

- Manufacturing process
  - Quality attributes of FOB (full data)

- Case-by-case Step-by-step
  - Depends on data until then

- Clinical
  - Efficacy
  - Safety
  - Post-marketing

- Comparative
  - Independent
Price Competition of FOBs

Brand price

Competing power of FOBs

Taking brand shares
Reduction of brand prices

Competing power of Generics (share vs. price)

FOB prices “case-by-case”

Manufacturing costs (initial investment, technologies)
Approval requirements
pre-clinical (P2,P3)
Post-authorization (PMS, resources)

Generic price

(Biosimilar prices are 10~40% off to brand prices in EU)
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Situation in the USA (1)

Review for drug approval in the USA

**Food Drug and Cosmetic Act**
- Traditional chemicals, Hormones (Insulin, hGH, etc.)
  - =>NDA 505 (b) 1  New drugs (full data)
  - =>NDA 505 (b) 2  New drugs (published data usable)*
  - =>ANDA 505 (j)  Generic drugs (abbreviated review)

**Public Health Service Act**
- Biological products (cytokines, antibodies, and others)
  - =>BLA  New drugs (full data)

Need of a new law for abbreviated review process of FOBs

(*Omnitrope was approved but FDA does not recognize it as a FOB)
## Situation in the USA (2)

<table>
<thead>
<tr>
<th>Legislative stage</th>
<th>Scientific stage =&gt; Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interchangeability</strong></td>
<td><strong>Biosimilar exclusivity</strong></td>
</tr>
<tr>
<td>Access to Life Saving Medicines Act (Feb 07)</td>
<td>yes</td>
</tr>
<tr>
<td>Patient Protection &amp; Innovative Biologic Medicine Act (Apr 07)</td>
<td>no</td>
</tr>
<tr>
<td>Biologics Price Competition &amp; Innovation Act (June 07)</td>
<td>yes</td>
</tr>
<tr>
<td>Pathway for Biosimilars Act (March 08)</td>
<td>yes</td>
</tr>
<tr>
<td>Promoting Innovation &amp; Access to Life-saving Medicines Act (March 09)</td>
<td>yes</td>
</tr>
<tr>
<td>Affordable Health Choice Act (July 09)</td>
<td>yes</td>
</tr>
</tbody>
</table>
# Entry of FOBs into the US Market

## Anticipated Biosimilar Entry Dates for Selected Biologic Brands

<table>
<thead>
<tr>
<th>Biologic Class</th>
<th>Branded Biologic</th>
<th>USA Biosimilar Entry</th>
<th>Europe Biosimilar Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>hGH</td>
<td>Genotropin, Humatrope</td>
<td>2006</td>
<td>2006</td>
</tr>
<tr>
<td>TNF-alpha inhibitor</td>
<td>Enbrel Remicade Humira</td>
<td>2014 NE 2014 2016</td>
<td>NE 2014 2018</td>
</tr>
</tbody>
</table>

Notes: a = Sandoz filed Omnitrope via the 505(b)(2) pathway in the United States; an abbreviated BLA pathway (ABLA, "biosimilars pathway") will not be available until 2010. Date reflects the launch of agents filed via an ABLA pathway. hGH = human growth hormone, ESP = erythropoiesis stimulating protein, G-CSF = granulocyte colony stimulating factor, TNF = tumor necrosis factor, MAb = monoclonal antibody, NE = None expected.

© Decision Resources, Inc., 2009

Source: Decision Resources, Inc.

- Patent expiration of major bioproducts starts in 2013
- Abbreviated BLA (ABLA) will be established after 2010
  (Decision Resource, 2009)

- Biologics in the US prescription drug market amount for 45 billion USD in 2008年
- 25% of new drugs are biologics
  (Washington Post, July 2009)

- Patent expirations of the 27 top biologics* will happen soon after 2015
- Global bio-market totals 112 billion USA. The top 27 products account for 87% share
  (FTC report, June 2009)

*27 top biologics: Avastin, Enbrel, Remicade, Humira, Rituxan, Herceptin, Lantus, Epogen/Procrit, Neulasta, Novolog, Erbitux, Aranesp, Recombinate, Lucentis, Avonex, Novolin, Humalog, Pegsys, Rebif, Crezyme, Tysabri, NovoSeven, Synagis, Neupogen, Betaseron, Humulin Kognate FS
“Competition between a biologic drug and a FOB is much more likely to resemble Brand-to-Brand competition” (FTC Report, June 2009)
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Possibility of FOBs of antibodies

Toward biosimilar monoclonal antibodies

Christian K Schneider & Ulrich Kalinke

To what extent is the existing framework for biosimilars in Europe likely to be applicable to monoclonal antibodies?

May be possible but outstanding challenge!!
More challenges along with technology advancements
Needs of in-depth scientific advices by the authority

CKS is a member of the CHMP of EMEA
Reditux vs. MabThera (Rituxan)

Reditux (Dr. Reddy)

Approved in India
April 30, 2007

- Same Amino Acid Sequence
- Host Cell Protein content much higher
- Content of aggregates not comparable
- Glycosylation not comparable
- Effector function not comparable
- Charge distribution not comparable
- Published clinical data with Reditux in NHL comprised only 17 patients

Different manufacturing -
Different drug -
Different safety/efficacy profile !?

Development of Antibody FOBs

Not available for FOB developer

Comparability data required by ICH Q5E

Comparability to the comparator

Manufacturing process
Quality
Non-clinical
PK/PD
Efficacy
Safety
Post-marketing

quality
clinical
PK/PD
Efficacy
Safety
Post-marketing

° May be possible to comparatively analyze of qualities by technology advancements of protein analysis
° Still difficult to prepare similar (comparable) products from different manufacturing process
° Needs to confirm efficacy/safety profile by clinical studies (Stand-alone approach)

° Next generation against the same antigen
° Cost reduction by high expression system

° May be possible to comparatively analyze of qualities by technology advancements of protein analysis
° Still difficult to prepare similar (comparable) products from different manufacturing process
° Needs to confirm efficacy/safety profile by clinical studies (Stand-alone approach)
Global Major’s Biosimilar Strategies

Integrated Type
- Johnson & Johnson: Rx+MD/Dx+OTC
- Abbott: Rx+npsrition+MD/Dx+vascular
- GlaxoSmithKline: Rx/vaccine+OTC+GE (alliance with Aspen)

Hybrid Type
- Roche: Rx+MD/Dx
- Schering-Plough + Merck: RX/Vaccine
- Lilly: Rx+animal
- AstraZeneca: Rx

Specific Type
- Pfizer + Wyeth: Rx+Vaccine + animal + OTC + nutrition
- Rx+animal+GE (Its subsidiary Greenstone plans to launch competing product GE in addition to self-product GE)

New Drug
- Rx/Vaccine+GE+Dx+OTC+Ox/GE/surgery/OTC (buyout of Alcon)
- Rx/vaccine + nutrition/OTC (buyout of Symbion) + GE (buyout of Zentiva)
- Rx+animal+GE (Its subsidiary Greenstone plans to launch competing product GE in addition to self-product GE)
Today’s Summary

- Brand and follow-on bioproducts are different substances
- Bioproduct is a mixture consisting of heterogeneous proteins and impurities and profile of the final product is much controlled by the manufacturing process.
- Traditional process for abbreviated approval of generic drugs cannot be applied. New guidelines for development of follow-on biologics entering after patent expiration are (being) established in many countries.
- Patent expiration of bioproducts in the US, the biggest market of biologics, starts from 2013.
- FOB guideline will be established after 2010, however, its contents are not predictable. (level of data requirement)
- According to existing guidelines (EU, Japan), FOBs of antibodies would be required considerable evaluations by clinical trials on efficacy and safety.
- Main arena of FOBs/biosimilars will be the antibody drug market. Players are likely to be limited to current brand manufacturers and companies with similar capabilities.

Patient’s benefits (efficacy/safety) should be the top prioritized issue.
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