Quality, Safety and Efficacy of Follow-on Biologics

Teruhide YAMAGUCHI
Division of Biological Chemistry and Biologicals
National Institute of Health Sciences

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Quality, Safety and Efficacy of Follow-on Biologics

• Current situation of follow-on biologics/biosimilar and Key issues to be discussed
• Key points to ensure the quality, safety and efficacy of Follow-on Biologics
Regulatory Topics on Follow-on Biologics

- "Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics“ (Yakushoku shinsahatu 0304007 by MHLW / March 4, 2009)
- “Revision of marketing approval application” (Yakushoku shinsahatu 0331015 by MHLW / March 4, 2009)
- “Nonproprietary name and brand name of Follow-on Biologics“ (Yakushoku shinsahatu 0304011 by MHLW / March 4, 2009)

Development of Follow-on Protein (Biosimilar Medicines) Products in Japan  (Sep. 2009)

<table>
<thead>
<tr>
<th>Reference products</th>
<th>Biosimilar products</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatropin</td>
<td>Genotropin</td>
<td>Omnitrope</td>
</tr>
<tr>
<td><strong>Under reviewing</strong></td>
<td>Epoetin kappa</td>
<td>Jepo</td>
</tr>
<tr>
<td><strong>Under development</strong></td>
<td>Follitropin alpha</td>
<td>Filgrastim</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Interferon a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interferon b</td>
</tr>
</tbody>
</table>
Biotechnological Products Have Complex Structure

- aspirin
- human Growth Hormone

- primary / secondary / tertiary / quaternary structure
- heterogeneity
- molecular size, charge
- posttranslational modification such as glycosylation
- heterogeneity in bioengineered structure such as pegylation
- biological activity
- immunogenicity

Some Biotechnological Products Have Multiple Domains

Each domain has its own function. → A set of relevant functional assays are required.

- FN domain
- EGF domain
- Kringle domain
- tissue Plasminogen Activator (t-PA)
- Active center
- Serine protease domain
- Plasminogen binding domain
Biotechnological Products Consist of Multiple Components
→ Important Issues in Characterization of Follow-on Biologics

**Desired Product**
- heterogeneity (e.g. glycosylation)

**Product-related substances**
- deamidated products
- oxidized products
- N/C terminal deleted products

**Product-related impurities**
- aggregates
- degradation products

**Process-related impurities**
- host cell proteins
- serum components
- infectious agents
- purification-process related impurities

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**Can Q5E apply the comparability study of follow-on biologics?**

- **Clone selection**
- **Seed cell A**
- **Banking**
- **Characterizations**

Production process of reference product is in "Black box". How should we evaluate the quality and safety of follow-on products including impurity profile?

Product A

Manufacture process change in a single manufacturer

Developed of follow-on products
Innovator’s Products with Multi-indications

Human Growth Hormone (INN: somatropin)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin</td>
<td>Dwarfism, Turner’s, Prader-Willi syndrome, hGH-deficiency, Weight-loss (HIV)</td>
</tr>
<tr>
<td>/E.coli</td>
<td></td>
</tr>
<tr>
<td>Norditropin</td>
<td></td>
</tr>
<tr>
<td>/E.coli</td>
<td></td>
</tr>
<tr>
<td>Humatrope</td>
<td></td>
</tr>
<tr>
<td>/E.coli</td>
<td></td>
</tr>
<tr>
<td>Saizen</td>
<td></td>
</tr>
<tr>
<td>/CHO cell</td>
<td></td>
</tr>
<tr>
<td>Growject</td>
<td></td>
</tr>
<tr>
<td>/E.coli</td>
<td></td>
</tr>
</tbody>
</table>

Key issues: Can follow-on biologics be approved for the multi-indication?

Quality, Safety and Efficacy of Follow-on Biologics

- Current situation of follow-on biologics/biosimilar and Key issues to be discussed
- Key points to ensure the quality, safety and efficacy of Follow-on Biologics
Dossiers of Follow-on Biologics to be Submitted

<table>
<thead>
<tr>
<th>Dossiers of the innovator product</th>
<th>Dossiers of the biosimilar product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing Process</td>
<td>Manufacturing Process</td>
</tr>
<tr>
<td>Characterization of Quality Attributes</td>
<td>Characterization of Quality Attributes</td>
</tr>
<tr>
<td>Non-clinical study</td>
<td>Non-clinical study</td>
</tr>
<tr>
<td>Clinical study</td>
<td>Clinical study</td>
</tr>
<tr>
<td></td>
<td>To establish stable and robust manufacturing process</td>
</tr>
<tr>
<td></td>
<td>To analyze the quality attributes individually</td>
</tr>
<tr>
<td></td>
<td>Comparability study + Individual study + Information</td>
</tr>
</tbody>
</table>

Guideline on Follow-on Biologics: Quality, Safety and Efficacy Issues

Published by MHLW
March 4, 2009
Definition of Follow-on Biologics

- A “follow-on” biologic is a biotechnological drug product developed by a company to be comparable to an approved biotechnology-derived product (hereinafter “original biologic”) of a different company.

- A follow-on biologics can generally be developed on the basis of data that demonstrates comparability between the two biologics with respect to quality, safety and efficacy, or other relevant data.

- It is recommended to adopt the manufacturing processes which potentially improve safety of the product.
Scope of Follow-on Biologics (1)

- The guideline applies to recombinant proteins and polypeptides, their derivatives, and products of which they are components, (e.g., conjugates).
- These proteins and polypeptides are produced from recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

Scope of the guideline (2)

<table>
<thead>
<tr>
<th>Decision</th>
<th>Products</th>
<th>Reasons</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Recombinant plasma proteins</td>
<td>There is no reason to exclude recombinant plasma proteins from the scope, even though some proteins have highly complicated structure.</td>
<td>Some patients might prefer non-recombinant products. Blood product supply might be affected, even though overlapped product development ensures the consistent supply.</td>
</tr>
<tr>
<td></td>
<td>Recombinant vaccines</td>
<td>Well characterized recombinant vaccine can be possibly developed as follow-on biologics.</td>
<td>Vaccine is administrated to healthy humans. Lot-to-lot variation of adjuvant activity is relatively large.</td>
</tr>
<tr>
<td></td>
<td>PEGylated recombinant proteins</td>
<td>Conjugates are in the scope as is in ICH Q6B.</td>
<td>Development of PEGylated protein as follow-on biologics might be difficult due to the structural complexity.</td>
</tr>
<tr>
<td>No</td>
<td>Synthetic peptides</td>
<td>Impurity profile is different from that of recombinant proteins.</td>
<td>Synthetic peptides can be generic drugs, because desired product can be easily defined by structural analyses.</td>
</tr>
<tr>
<td></td>
<td>Polyglycans</td>
<td>Characterization is difficult.</td>
<td>Several polyglycan products have been approved as generic drugs in Japan.</td>
</tr>
<tr>
<td>Case by case</td>
<td>Non-recombinant proteins*</td>
<td>Proteins that are highly purified and characterized could be developed as follow-on biologics.</td>
<td>Several urine-derived protein products have been approved as generic drugs in Japan.</td>
</tr>
</tbody>
</table>

* e.g. proteins such as isolated from tissues or body fluids
General Principles for the Development of Follow-on Biologics (1)

- As with new biotechnological products, establishment of the well-defined manufacturing process, and extensive characterization studies to reveal the molecular and quality attributes of the follow-on biologics are required.
- Demonstration of the high similarity in quality attributes with the reference medicinal product is also required.
- Comparability between the follow-on biologics and reference medicinal product should be evaluated based on the data from non-clinical and clinical studies in addition to the data of quality characteristics.

General Principles for the Development of Follow-on Biologics (2)

- The objective of ICH Q5E guideline is to provide the principles for assessing the comparability of biotechnological/biological products where changes are made on manufacturing processes. Manufacturers can compare the both products head-to-head in such a case.
- Since the information of innovator’s products are generally not disclosed, approaches by ICH Q5E can not always be applied to the evaluation of follow-on biologics.
- Based on the concept of Q5E, sponsors intending to develop the follow-on biologics should consider the comprehensive approach including comparability studies and other approaches that utilize public information or existing experiences.
Development of Manufacturing Process

- It is necessary to establish the highly consistent and robust manufacturing process.
- If the host cell line used for the production of reference medicinal product is disclosed, it is desired to use the same cell line.
- For the establishment and characterization of the cell banks, ICH Q5A, Q5B, Q5D guidelines should be referred.
- It is recommended to adopt the manufacturing processes potentially improve the safety of the product insofar as these do not affect efficacy.

Optimization of manufacturing process according to the comparability studies (1)
Optimization of manufacturing process according to the comparability studies (2)

Characterization of eluted fractions

Drug Product Design

- In principle, it is necessary for the dosage form and route of administration to be the same as that of reference medicinal product.
- Provided that safety and efficacy are not affected, **it is not essential for the follow-on biologics to have the same formulation as the reference medicinal product.**
Stability Testing

- Long-term, real-time, real-condition stability studies are required. The expiration dating of follow-on biologics should be determined based on the data of real-time/real-temperature studies.

- Since identical storage condition and storage period to the reference medicinal product are not prerequisite, a comparison of stability with reference medicinal product therewith will not necessarily be required.

- These stability tests should follow the ICH Q5C Guideline.

Comparability Studies on Quality Attributes

In addition to elucidating the quality attributes of the follow-on biologics, comparability exercises about quality attributes between the follow-on biologics and the reference medicinal product should be conducted.

For example, comparability exercises are conducted to examine the following aspects:

1. Structural characterization and physicochemical properties
2. Biological activities
3. Others
Quality Attributes of Biologics

Desired Product

Product-related impurity

Product Related Substances

HCP etc.

Infectious Agents

Evaluation of extraction method on active ingredient from product

RBP from market

Analysis of formulation

• ingredient
• mannitol
• buffer
• salt

Drug substance of FBP candidate

• mannitol
• buffer
• salt

Manufacturing of drug products similar to RBP
**Immunogenicity**

- Non-clinical study can not fully predict immunogenicity of follow-on biologics in human.
- Comparative study on immune-reactivity during the repeated toxicity study will provide useful information as follows;
  - Difference of quality attributes
  - Effect of antibody production on data interpretation of toxicity and pharmacological studies
  - Impact of antibody on clinical studies

**Specifications**

- Setting of specifications is required principally based on the results of characterization and lot analyses. It also be considered to reflect the results of the comparability studies between follow-on biologics and reference medicinal product appropriately. For this it may be useful to conduct comparability studies using several lots of the products if applicable.
- In setting the specifications, the ICH Q6B guideline should be followed.
Non-clinical Studies

- Non-clinical studies that can ensure the safety for administration to humans should be performed and completed prior to initiation of the clinical studies.

- Both “comparability assessment” and “individual assessment” are applicable, depending the purpose of the study. For example, comparability assessment may be conducted for pharmacological activity studies, whereas individual assessment is made to address the safety issues on impurities.

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**Graph**

- The graph illustrates the relationship between sialic acid content and specific activity in vitro.
- Points labeled A1 to A7 represent desialylated erythropoietins, while NG(0), (1), (2) represent de-N-glycosylated erythropoietins.
- Key: A1; Intact erythropoietin
  - A1~A7; Desialylated erythropoietins
  - NG(0),(1),(2); De-N-glycosylated erythropoietins

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Follow-on biologics – Effect of heterogeneity on efficacy and PK

Tissue Distribution of Radioactivity After a Single Intravenous Administration of Radioiodinated Control EPO or EPO-bi in Male Rats

Comparison of in vitro activity and in vivo activity.
Non-clinical Studies - impurities

- For product- and process-related impurities, it may be more rational to assess safety on the basis of an established manufacturing process per se and characteristics of impurities than simply to compare impurities of follow-on biologics with reference medicinal products.

- It may be acceptable to compare the toxicity profiles between follow-on biologics with reference medicinal products in spite of difference of impurities.

Target for comparability study of Follow-on Biologics

<table>
<thead>
<tr>
<th>Desired Product</th>
<th>Product-related impurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Related Substances</td>
<td>HCP etc.</td>
</tr>
<tr>
<td>Infectious Agents</td>
<td>Process-related impurity could be different between FBP and the innovator products</td>
</tr>
</tbody>
</table>
Clinical Studies (1)

- In general, clinical studies are required in development of follow-on biologics since the data from quality characterization and non-clinical studies will be insufficient to evaluate the comparability with reference medicinal product.

- Clinical studies should be designed based on the data of quality characterizations, non-clinical studies and comparability studies.

Clinical Studies (2)

- Where the data sufficient to assure the comparability in clinical endpoint has been obtained through the clinical pharmacokinetic (PK), pharmacodynamic (PD) or PK/PD studies, further clinical studies could be reduced in some cases.

- In general, the well-designed cross-over study should be consider to evaluate the comparability between follow-on biologics and reference medicinal products.

- However, the cross-over study may not be suitable for the long half-life products or products which may cause the antibody formation.
Clinical Studies (3) Indications

• In the case of an originator biologics with more than one indication

• The efficacy and pharmacological effects of the follow-on have been demonstrated to be comparable to the originator biologics

• In certain case it may be possible to extrapolate from one indication to the other indications of the originator biologics used as the reference product.

Approval of multi-indications for follow-on biologics

<table>
<thead>
<tr>
<th>Indications</th>
<th>Genotropin, in EU</th>
<th>Omnitrope in USA</th>
<th>Omnitrope in Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Growth hormone deficiency in children (CGHD),</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>• Growth hormone deficiency in adult (AGHD),</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>• Turner syndrome (TS),</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>• Chronic renal insufficiency deficiency</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>• Prader-Willi syndrome</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>• Short for gestational age</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
</tbody>
</table>
Post-marketing Surveillance

- Data from pre-authorization clinical studies normally are insufficient to identify the all potential safety profiles, post-marketing surveillance (PMS) of the safety profile including immunogenicity is required.
- The specific method and design of the PMS study and risk management plan should be discussed with the regulatory authorities and be submitted together with the application for approval.
- The findings of the PMS should be reported to the regulatory authorities.

PMS for Omnitrope

- Clinical data about Turner syndrome and Chronic renal insufficiency of omnitrope are required during PMS.
- The sponsor should analyze adverse effects possibly due to expression of antibodies against either somatropin or host cell protein.
- All patient data should be collected for 2 years as PMS.
Thank you for your attentions!