

# Quality, Safety and Efficacy of Follow-on Biologics

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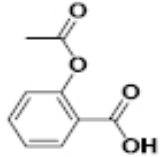
# Quality, Safety and Efficacy of Follow-on Biologics

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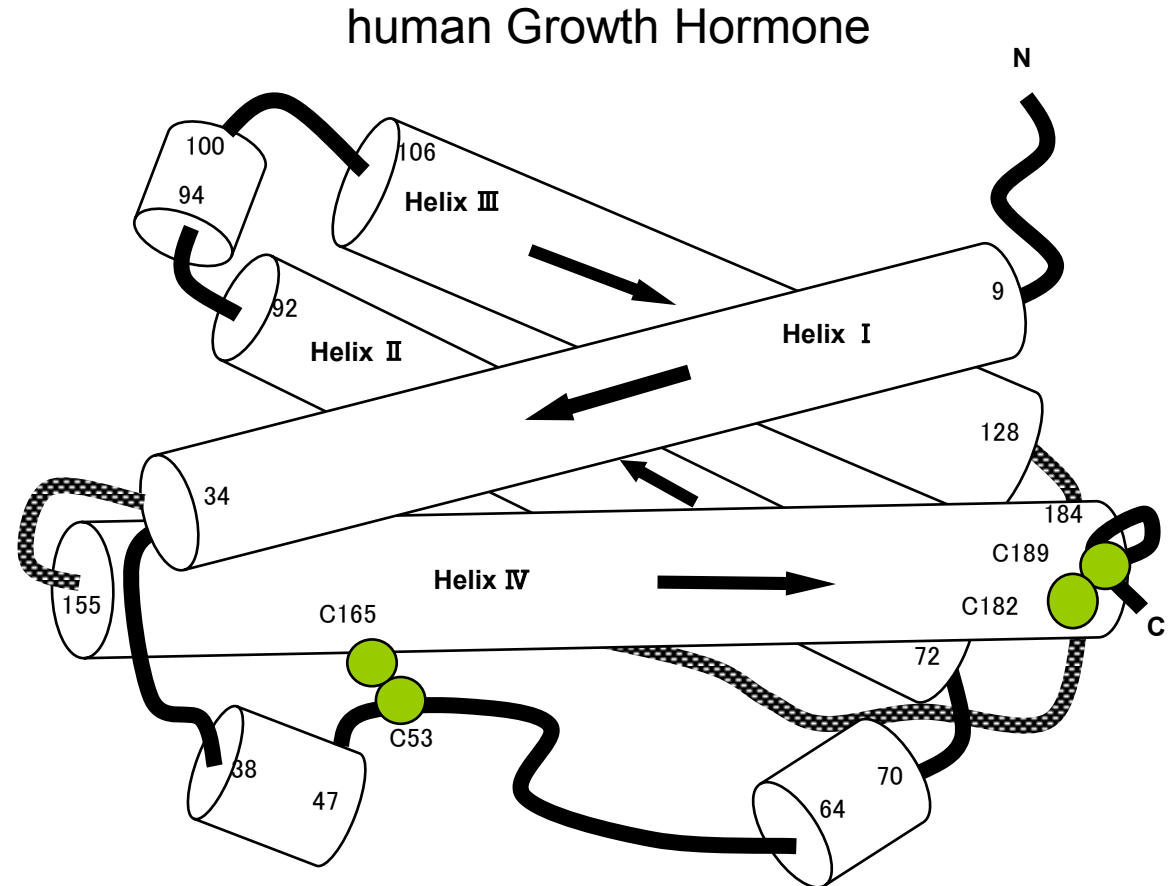
- Key issues to be discussed
- Key points to ensure the quality, safety and efficacy of Follow-on Biologics

# Biotechnological Products Have Complex Structure

aspirin



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

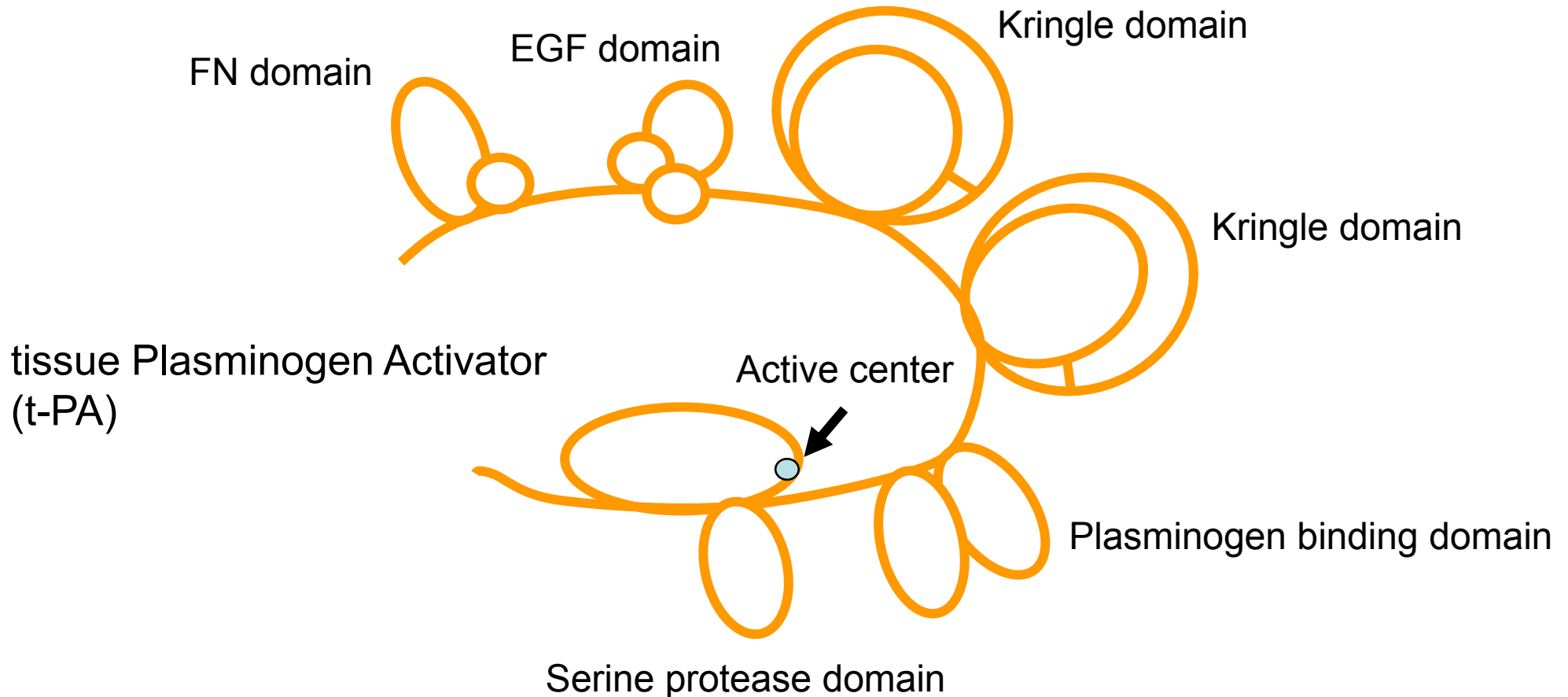


# Some Biotechnological Products Have Multiple Domains

Each domain has its own function.



A set of relevant functional assays are required.



# 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

# Immunogenicity Issues in Development of Follow-on Biologics


- In clinical studies with the earlier formulation of Omnitrope, up to 60% of the enrolled patients developed anti-hGH antibodies and all patients developed anti-ECP antibodies.
- ECP are known to be able to enhance the antibody reaction against GH.
- Downstream manufacturing process was modified to improve the ECP clearance.

## Anti-hGH antibody development in Omnitrope (improved formulation) clinical studies

|               | Number of patients tested for antibodies | Number of patients with positive test results | Estimated incidence (%) |
|---------------|--|---|-------------------------|
| Omnitrope     | 51                                       | 0   | 0                       |
| Genotropin    | 44                                       | 1   | 2.27                    |
| (Literature*) | 229                                      | 4   | 1.75                    |

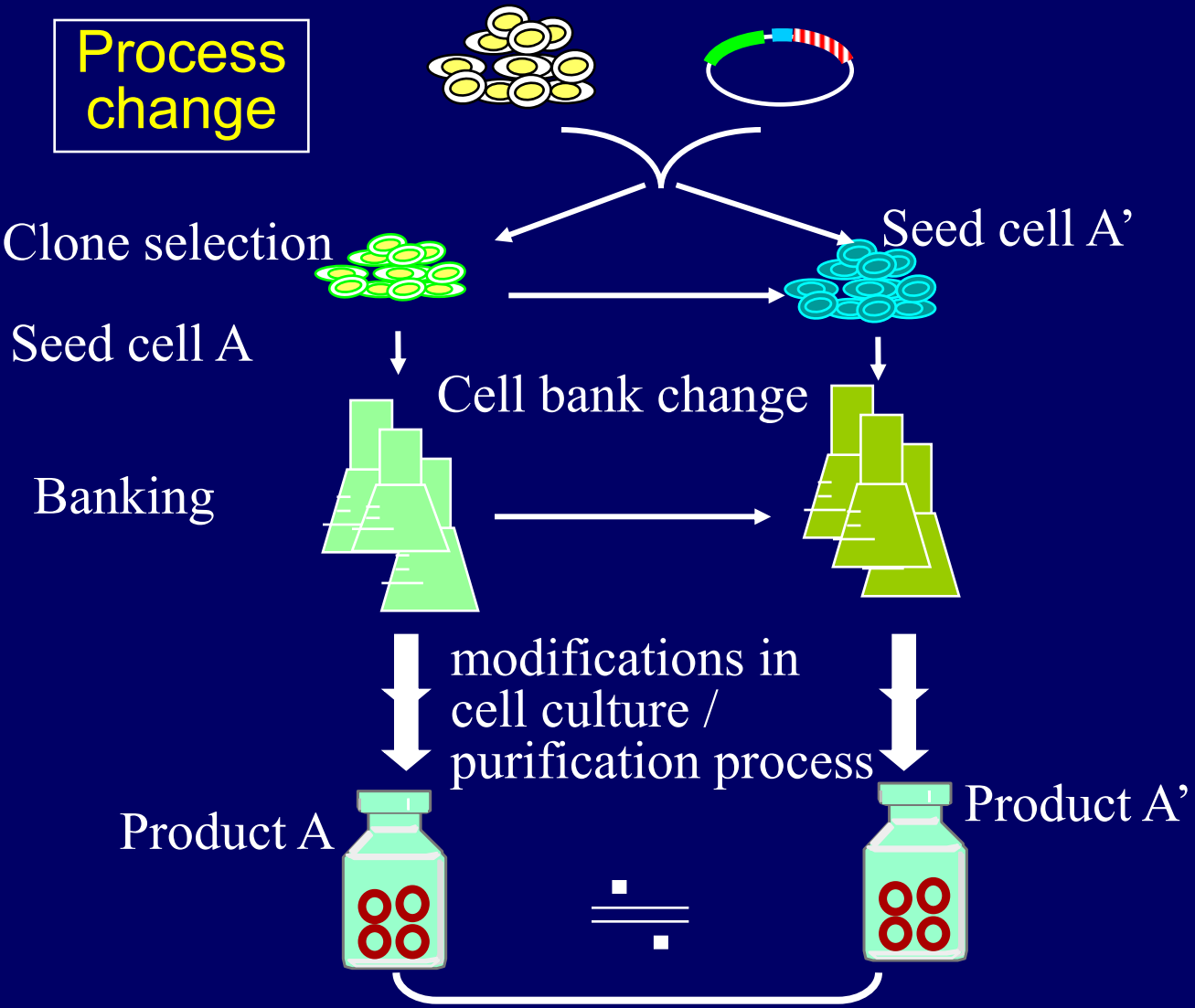
\*One year results published in: Lundin K, Berger L, Blomberg F, et al. Development of anti-hGH antibodies during therapy with authentic human growth hormone. Acta Paediatr Scand (Suppl) 1991;372:167-8.

# Identity of Cell Substrates

- “CHO cell” has several strains.
    - CHO-K1
    - CHO-DUKX
    - CHO-DG44
    - CHO-Pro5
  - Cellular characteristics may be modified by adapting cells to serum free and/or suspension culture during the process development stage.
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- Published information is not enough to identify the exactly same cell line / strain as that used for the production of the reference product.
  - Optimum media differ depends on the strains.

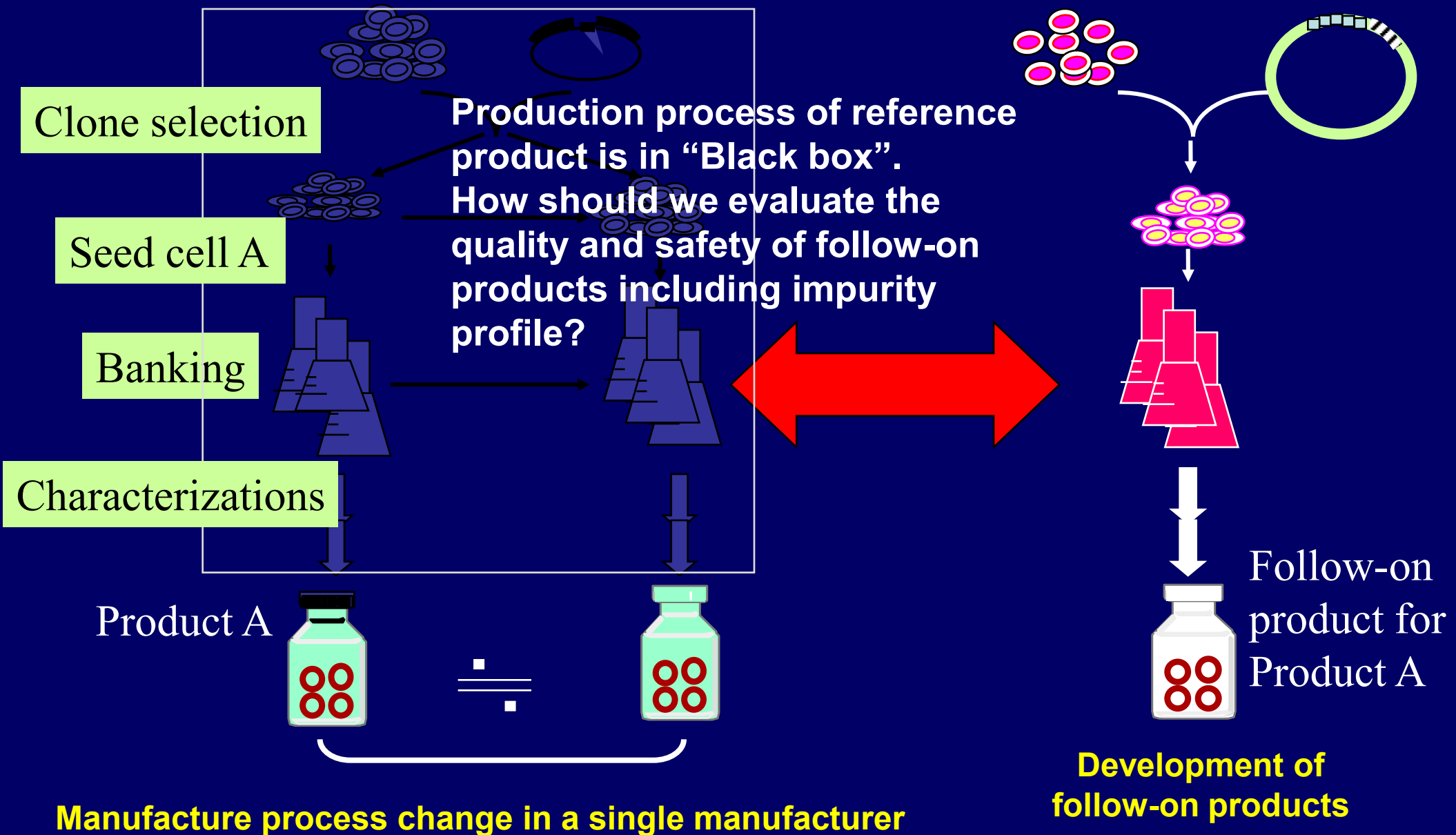
# Manufacturing Process Change and Comparability Studies

Process change



In case of manufacturing process change in a single manufacturer, quality attributes of pre-change and post-change products can be compared in head-to-head studies, and the comparability studies can be performed for each manufacturing process change. Comparability in **impurity profile** and heterogeneity can be easily evaluated.

# Manufacturing Process Affects the Product Quality Attributes



# Innovator's Products with Multi-indications

Human Growth Hormone (INN: somatropin)

| Brand Name<br>/Cell Substrate | <u>Indications</u>    |                       |                       |                       |                       |
|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                               | Dwarfism,             | Turner's,             | Prader-Willi,         | hGH-<br>syndrome      | Weight-<br>loss (HIV) |
| •Genotropin<br>/E.coli        | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |                       |
| •Norditropin<br>/E.coli       | <input type="radio"/> | <input type="radio"/> |                       |                       |                       |
| •Humatrope<br>/E.coli         | <input type="radio"/> | <input type="radio"/> |                       | <input type="radio"/> |                       |
| •Saizen<br>/CHO cell          | <input type="radio"/> |                       |                       |                       | <input type="radio"/> |
| •Growject<br>/E.coli          | <input type="radio"/> | <input type="radio"/> |                       |                       |                       |

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

# Key Issues in Evaluating the Comparability between Follow-on Biologics and Reference Products

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How to evaluate the comparability in quality, safety, and efficacy of the products under the limited availability of information and samples used for the studies is the key issue.

# Quality, Safety and Efficacy of Follow-on Biologics

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- Key issues to be discussed
- Key points to ensure the quality, safety and efficacy of Follow-on Biologics

# Japanese Guideline on Follow-on Biologics

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- The guideline covers from establishment of production process to non-clinical/clinical studies.
- Ten to fifteen years scientific progress after the approval of the innovator's products should be considered in evaluating the product characteristics.
- Theoretically all kinds of follow-on biologics can be developed, however, the guideline deals with recombinant protein products in which the definition of desired product is clear, and the approach for characterization is relatively easy.

# 1. Introduction

- A “Follow-on biologics” is intended to refer to a biotechnological product that is produced by a subsequent-entry manufacturer and claimed to be comparable to a biotechnological product already approved in Japan (hereinafter “reference medicinal product”).
- A new Marketing Authorization Application (MAA) category different from the existing generic approach should be established.
- It is recommended to adopt the manufacturing processes which potentially improve the safety of the product.

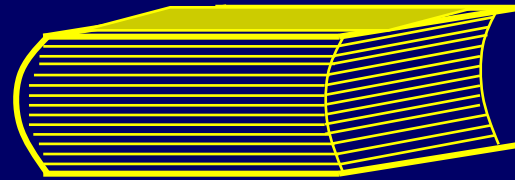
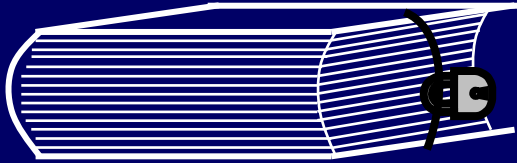
# Dossiers of Follow-on Biologics to be Submitted

Dossiers of the innovator product

Dossiers of the biosimilar product

**Manufacturing Process**

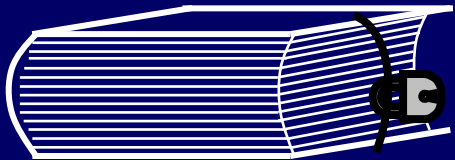
**Manufacturing Process**



To establish stable and robust manufacturing process

**Characterization of Quality Attributes**

**Characterization of Quality Attributes**



To analyze the quality attributes individually

**Non-clinical study**

**Non-clinical study**



**Comparability study**

+

**Individual study**

+

**Information**

**Clinical study**

**Clinical study**



# Guideline on Follow-on Biologics: Quality, Safety and Efficacy Issues (DRAFT)

Draft for public comment by MHLW  
September 17, 2008

# Contents

1. Introduction
2. Scope (Well-characterized recombinant protein products)
3. General principles for the development of follow-on biologics
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5. Comparability studies on quality attributes
6. Specifications
7. Non-clinical studies
8. Clinical studies
9. Post-marketing surveillance
10. Names
11. Glossary

## 2. Scope

- 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.

# Discussion on the scope of the guideline

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

\* e.g. proteins such as isolated from tissues or body fluids

### 3. 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.

# 3. 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.

# 4.1 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.

## 4.2 Quality Characterization

As with new biotechnology products, the products obtained should be fully characterized using the state of the art analytical methods.

- (1) Structural characterization
- (2) Physicochemical properties
- (3) Biological activities
- (4) Immunological properties
- (5) Impurities

## 4.3 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.

## 4.4 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.

## 5. 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) Immunological properties

# 6. 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.

# 7. 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.

# 7. 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.

# 8. 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.

## 8. 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.

# 9. Post-marketing Surveillance

- Data from preauthorization 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.

- Thank you for your attentions