Recent Regulations of Biosimilars in Japan

Teruyo ARATO, Ph.D.
Review Director
PMDA

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DIA®
www.diahome.org

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Agenda

- Outline of Guideline for Biosimilar Products in Japan
- Review process for Biosimilar Products in Japan
- Datapackage of Biosimilar Products approved in Japan

Outline of Guideline for Biosimlar Products in Japan

Regulatory Topics on Biosimilar Products

- **"Guidelines for the Quality, Safety and Efficacy Assurance of follow-on biologics" (Yakushoku shinsahatu 0304007 by MHLW / March 4, 2009)**

Biosimilar products as EU terminology

- **"Nonproprietary name and brand name of follow-on biologics" (Yakushoku shinsahatu 0304011 by MHLW / March 4, 2009)**

- **"Revision of marketing approval application" (Yakushoku shinsahatu 0331015 by MHLW / March 4, 2009)**

application category

1. New drug	2. New combination	3. New route	4. New indication	5. New formulation	6. New dosage	7. FOB	8. Additional formulation	9. Similar composition	10. Other (generic drugs)

Contents of Guideline for Biosimilar Products in Japan

1. Introduction
2. Scope
3. General principles for the development of biosimilars
4. Manufacturing process and quality characterization
5. Comparability studies on quality attributes
6. Specifications
7. Non-clinical studies
8. Clinical studies
9. Post-marketing surveillance
10. Glossary

Definition of Biosimilar Products in Japan

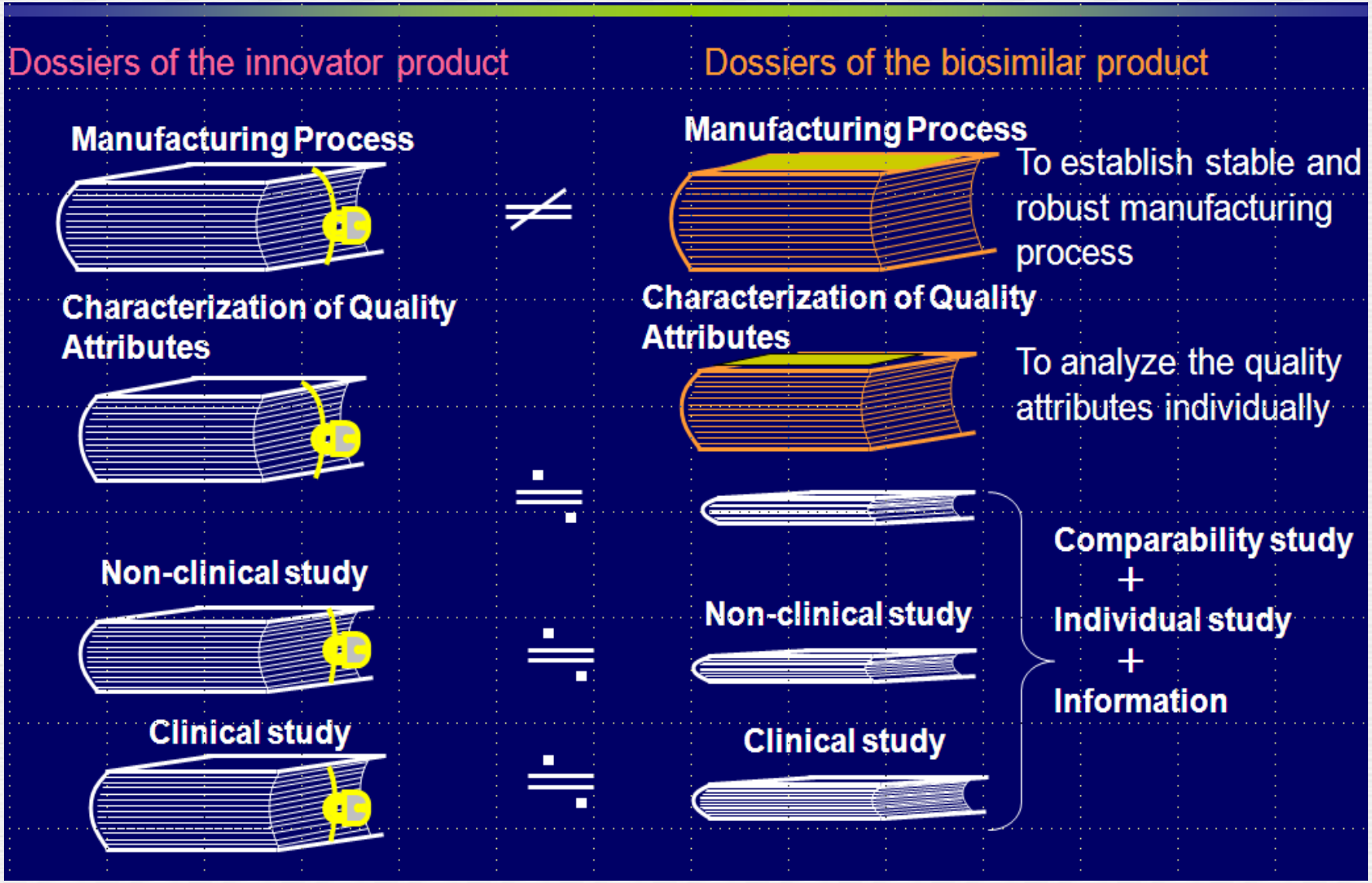
- **A biosimilar product is a biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived product (hereinafter "reference product") of a innovator.**
- **A biosimilar product can generally be developed on the basis of data that demonstrates the comparability between the biosimilar product and the reference product with respect to quality, safety and efficacy, or other relevant data.**

	Scope
Japan	**recombinant proteins and polypeptide products, their derivatives, and products of which they are components, e.g., conjugates. those proteins and polypeptide products that are produced from recombinant expression systems using microorganisms or cultured cells and can be highly purified and well-characterized using an appropriate set of analytical procedures.**
EU	**any biological medicinal product, e.g.: medicinal products containing biotechnology-derived proteins as active substance, immunologicals such as vaccines, blood-derived products, monoclonal antibodies, etc. more likely to highly purified products, which can be thoroughly characterized (such as some biotechnology-derived medicinal products).**
Canada	**biologic drugs that contain well characterized proteins derived through modern biotechnological methods such as use of recombinant DNA and/or cell culture.**
Korea	**all types of biological products. specifically to biological products that contain well-characterized protein**
WHO	**well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins.**

LMWH is generic

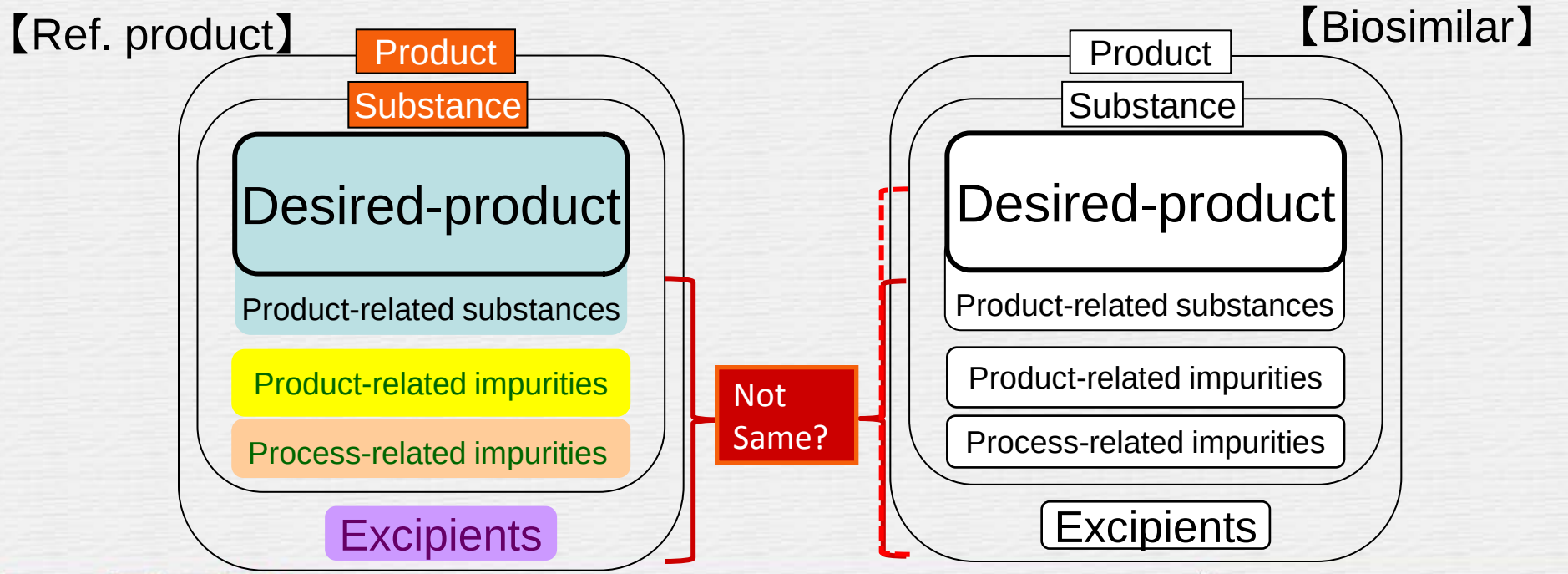
	Reference product
Japan	The reference products should be drugs approved in Japan and be the same product throughout the development period of the biosimilar products.
EU	The chosen reference medicinal product, defined on the basis of its marketing authorization in the Community, should be used during the development of a similar biological medicinal product.
Canada	The reference biologic drug should be authorized and marketed in Canada, and should be used throughout the studies. In appropriate circumstances, a biologic drug that is not authorized for sale in Canada may be used as a reference biologic drug
Korea	The reference product should be a biological product authorized in Korea. However, if a reference product authorized in Korea is not commercially available or if there are other justifiable reasons, the same biological product as the one authorized in Korea may be purchased from overseas markets and used as the reference product
WHO	The rationale for the choice of a RBP should be provided by the manufacturer of the SBP in the submission to the National Regulatory Authority.

General principles for the Development in Japan



Drug Product Formulation (Japan)

- **The dosage form and route of administration of biosimilar products should be the same as that of reference product .**
- **It is not essential for the biosimilar product to have the same formulation as the reference product.**



Stability testing (Japan)

- **The expiration dating of biosimilar products should be determined based on the data of real-time/real-temperature studies.**
- **A comparison of stability with reference product will not necessarily be required.**
- **Accelerated and stress stability studies are recommended to obtain useful data for evaluating the properties of the biosimilar product.**

Non-clinical studies (Japan)

- **PK: It is useful to compare the non-clinical PK in some glycoprotein.**
- **Pharmacological studies: Comparability of the pharmacological action should be directly evaluated.**
- **Toxicity studies:**
  - **Repeated dose-toxicity studies may be valuable to evaluate both single-dose and repeated-dose toxicity.**
  - **Local tolerance could be evaluated (in repeated-dose toxicity studies).**
  - **A direct comparative study of the toxicity profile may not always be necessary (e.g. process-related impurities) .**
  - **Other general non-clinical safety studies are generally unnecessary.**

Clinical studies

	PK
Japan	The sponsor should conduct the comparability exercise of PK studies.
EU	Comparative PK studies are an essential part of the comparability exercise.
Canada	Comparative PK studies should be conducted.
Korea	The PK profile should always be investigated. PK studies must be comparative in nature.
WHO	The PK profile should always be investigated. PK studies must be comparative in nature.

	PD studies
Japan	If possible, it is necessary to select PD markers for clinical efficacy & to conduct the comparability studies using the appropriate PD marker.
EU	The PD markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product.
Canada	PD studies may be combined with PK studies. The PD studies should be comparative in nature.
Korea	In general, the PD studies may be performed in combination with PK studies and the PD parameters should be selected on the basis of their relevance to demonstrate clinical efficacy.
WHO	It may be advisable for the manufacturer to ensure similar PD profiles before proceeding to clinical trials

	Efficacy studies
Japan	The comparability of biosimilar products should be evaluated through the clinical studies. In case PK/PD studies are sufficient to assure comparability in clinical endpoint of interest, additional clinical studies might be omitted.
EU	Comparative clinical trials are required for the demonstration of clinical comparability. In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability.
Canada	Comparative clinical trials are critically important to demonstrate the similarity in efficacy and safety profiles
Korea	Clinical trials are required to demonstrate similar efficacy Comparative PK/PD studies may be appropriate for the following cases: ・・・
WHO	Clinical trials are required to demonstrate similar efficacy. In certain cases, comparative PK/PD studies may be appropriate.

	Safety (Immunogenicity)
Japan	Clinical safety studies, including a study on immunogenicity should be considered. At an appropriate stage of the clinical development, studies should be conducted to evaluate antibody formation & other immunogenicity.
EU	Pre-licensing safety data should be obtained. The immunogenicity of SBMP must always be investigated.
Canada	The nature, severity and frequency of adverse events should be compared. The immunogenicity of the SEB should be evaluated
Korea	Pre-authorization safety data should be obtained The frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared before authorization.
WHO	Pre-licensing safety data should be obtained The frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared

Extraporation (multiple indication)

Japan	**In certain cases it may be possible to extrapolate from one indication to other indications of the reference product Where each relevant indication has different mechanism of action, the comparability of efficacy should be demonstrated for each indication without extrapolation.**
EU	**Demonstration of the clinical comparability in one indication will allow the extrapolation of the other indications of the RMP if the mechanism of action is the same.**
Canada	**In some situations, proposals for additional indications held by the reference biologic drug may be granted to the SEB in the absence of such clinical data.**
Korea	**Extrapolation of these data to other indications of the reference products for which post-marketing survey was completed may be possible**
WHO	**Extrapolation of these data to other indications of the RBP (not studied using independent clinical studies with the SBP) may be possible**

	Post-marketing surveillance
Japan	The clinical safety of biosimilar products should be followed and monitored on an ongoing basis during post-marketing surveillance.
EU	Clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.
Canada	It is important that a Risk Management Plan be presented prior to issuance of marketing authorization.
Korea	Further characterization of the immunogenicity profile may be necessary post-marketing
WHO	Further close monitoring of the clinical safety of these products in all approved indications and a continued benefit-risk assessment is necessary in the post-marketing phase.

Datapackage of Biosimilar Products to be submitted in Japan

		NMEs	Biosimilar	Generic
Quality	Manufacturing Process	○	○	△
	Characterization (Quality Attribute)	○	○	–
	Specification	○	○	○
Stability	Long term test	○	○	–
	Stress test	○	△	–
	Accelerated test	○	△	○
Pharmacology	Primary PD	○	○	–
	Safety Pharmacology	○	–	–
	Others	△	–	–
PK	ADME (non-clinical)	○	△	–
	BE (human)	–	–	○
	Others	△	△	–
Toxicology	Single-Dose Toxicity	○	△	–
	Repeat-Dose Toxicity	○	○	–
	Genotoxicity	○	–	–
	Carcinogenicity	△	–	–
	Reproductive & Developmental	○	–	–
	Local Tolerance	△	△	–
	Others	△	△	–
Clinical	Clinical Studies	○	○	–

Nonproprietary & Brand Names of Biosimilar Products in Japan

Nonproprietary Name:
○○○○○(genetical recombination)[×××××　Biosimilar 1]

Brand Name: ×××××BS　Inj Content Company-Name

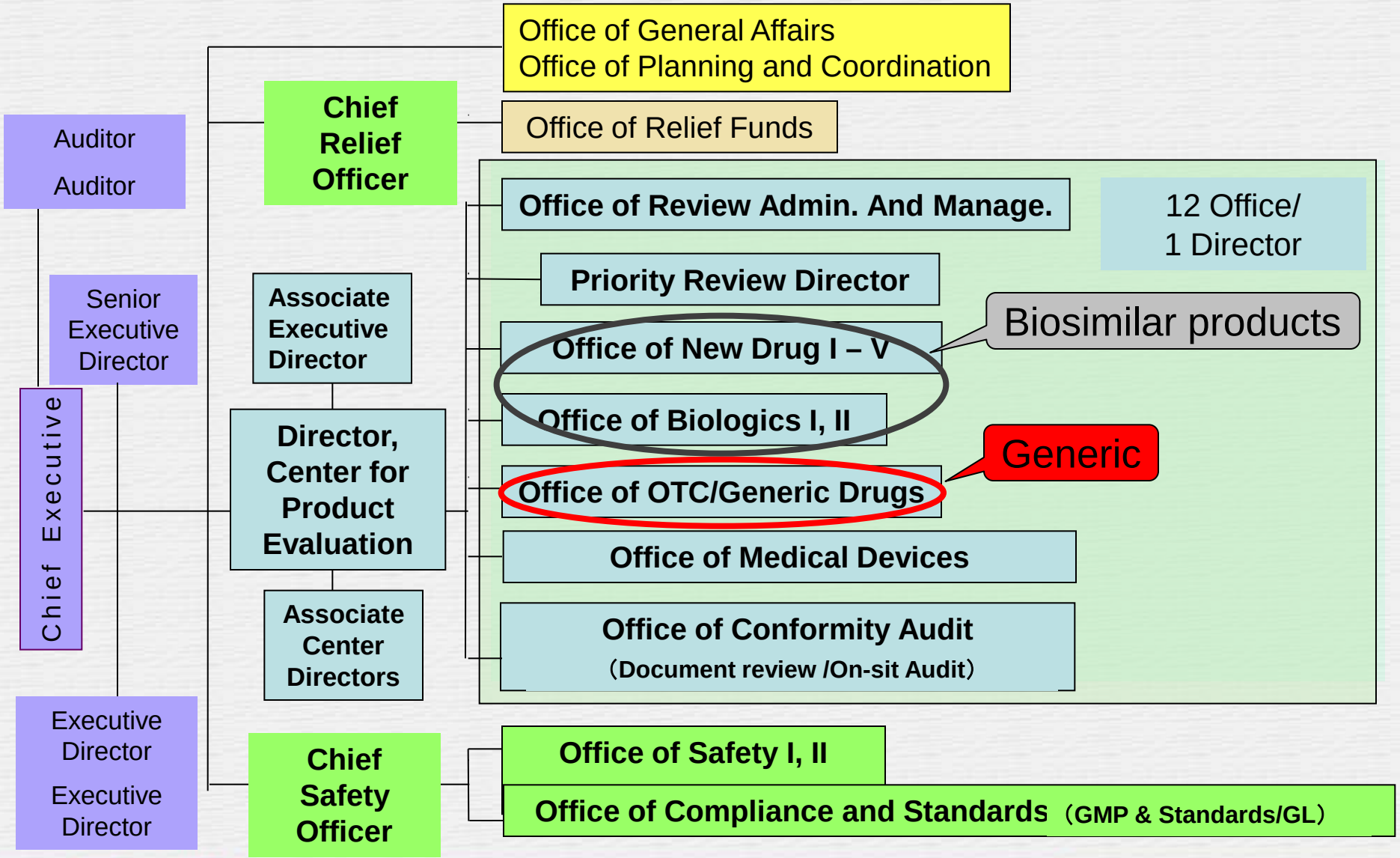
×××××　excludes "genetical recombination" from the Nonproprietary Name of original biologic.

【Example】

Nonproprietary Name:
Epoetin Kappa(Genetical Recombination) [Epoetin Alfa Biosimilar 1]
Brand Name: Epoetin Alfa BS Inj 750 "JCR"

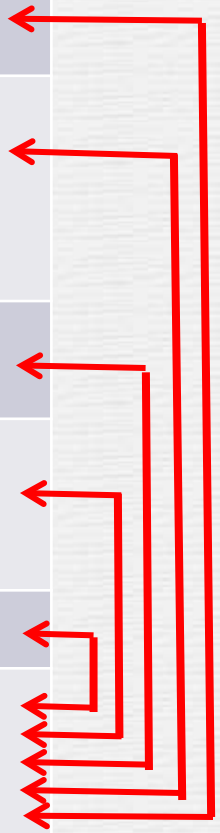
Review process for Biosimilar Products in Japan

PMDA Organizational Chart

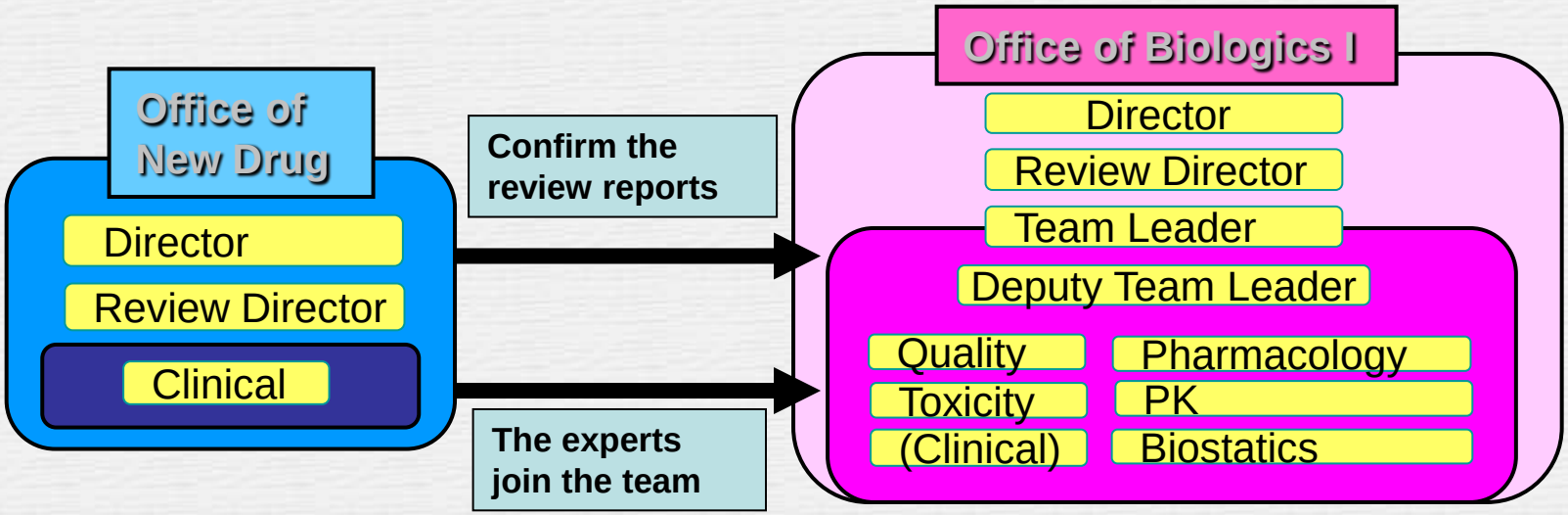


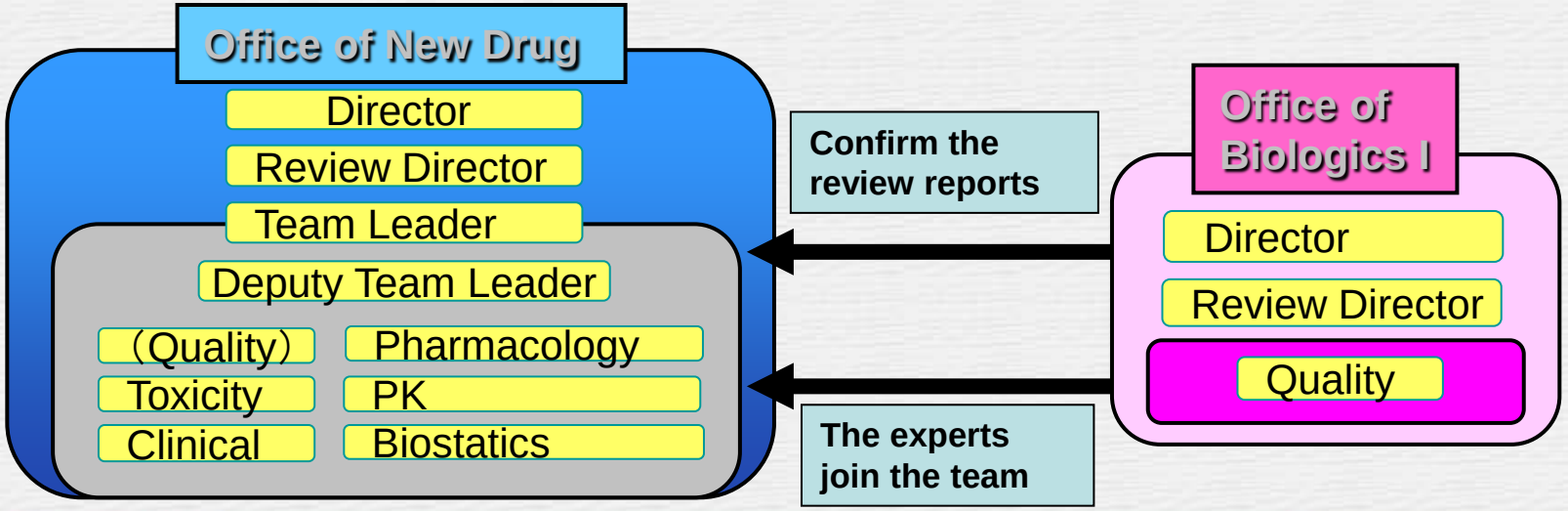
Work of the offices of new drug

Department	Therapeutic Category	
Office of New Drug I	Team 1 Team 6-2	Gastrointestinal drugs etc. Hormone drugs
Office of New Drug II	Team 2 Team 5 Radiopharmaceuticals In vivo diagnostics	Cardiovascular drugs etc. Drugs for urogenital system etc. Radiopharmaceuticals Contrast medium
Office of New Drug III	Team 3-1 Team 3-2	Central/peripheral nervous system drugs etc.
Office of New Drug VI	Team 4 Anti-AIDS drugs Team 6-1	Antibacterial agents etc. Anti-HIV agents Respiratory tract drugs etc
Office of New Drug V	Oncology drugs	Anti-cancer drugs
Office of Biologics I	Blood products (Serum albumin, blood coagulation factors etc.) Gene therapy products (=pre IND) CMC of biotech-products, Biosimilar products	
Office of Biologics II	Vaccines etc. Cellular & Tissue-derived products	

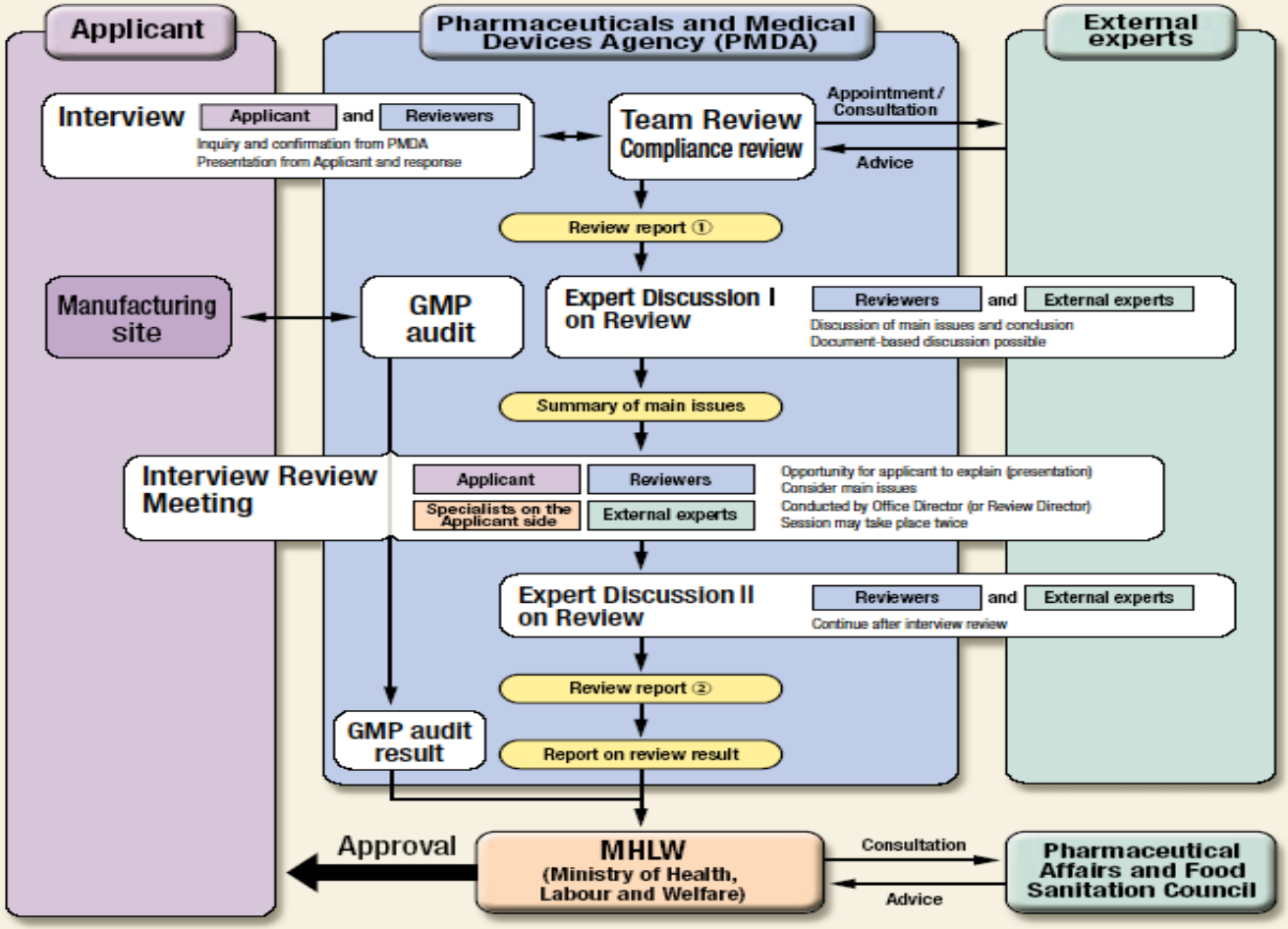


Structure of a review team of Biosimilar Products





Review Process for Pharmaceuticals and Medical Devices



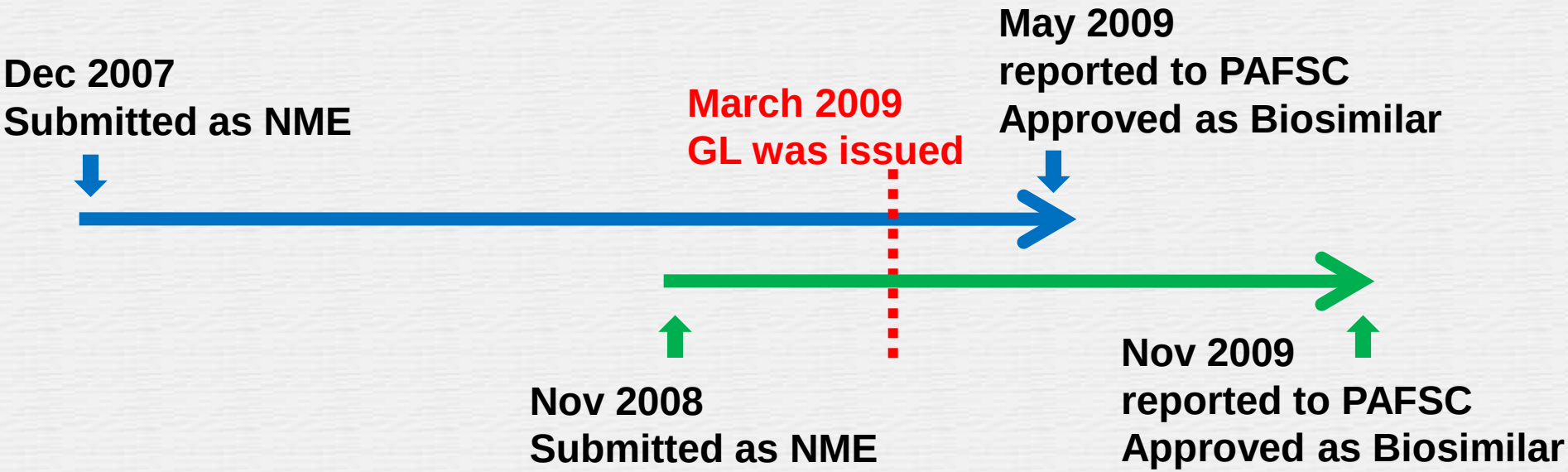
The review Process for biosimilar products is almost same as the review process of NMEs.
In case of NMEs, MHLW consults the PAFSC about the approval of them.
In case of biosimilar products, the review results is reported to the PAFSC.

Datapackage of Biosimilar Products approved in Japan

Two biosimilar products have been approved in Japan.

Somatropin BS s.c. "Sandoz"

Original biologic: Genotropin



Epoetin alfa BS "JCR"

Original biologic: Espo

Datapackage of Biosimilar Products approved in Japan

		GL	Somatropin BS	EPO BS
Quality	Manufacturing Process	○	○	○
	Characterization (Quality Attribute)	○	○	○
	Specification	○	○	○
Stability	Long term test	○	○	○
	Stress test	△	–	○
	Accelerated test	△	○	○
Pharmacology	Primary PD	○	○	○
	Safety Pharmacology	–	–	○
	Others	–	–	–
PK	ADME	△	–	○
	BE	–	–	–
	Others	△	–	–
Toxicology	Single-Dose Toxicity	△	△	○
	Repeat-Dose Toxicity	○	○	○
	Genotoxicity	–	–	○
	Carcinogenicity	–	–	–
	Reproductive & Developmental	–	–	○
	Local Tolerance	△	○	○
	Others	△	–	–
Clinical	Clinical Studies	○	○	○

Clinical Datapackage of Somatropin BS s.c.“Sandoz”(=Omnitrope)

【PK/PD studies】

Study Number	Study Design	Subjects	Japan	EU	Canada	USA
EP00-106	A 3-arm cross-over trial to compare Omnitrope solution (5mg/1.5mL), Omnitrope solution (10mg/1.5mL) vs Genotropin powder	54 Healthy volunteers (Japanese, Male)	○			
EP00-104	A 3-arm cross-over trial to compare Omnitrope powder (5.8mg/vial), Omnitrope solution (5mg/1.5mL) vs Genotropin powder	36 Healthy volunteers	△		○	
EP00-105	A 3-arm cross-over trial to compare Omnitrope powder (5.8mg/vial), Omnitrope solution (10mg/1.5mL) vs Genotropin powder	36 Healthy volunteers	△		○	
EP2K-99-PhISUSA	A placebo-controlled 2-arm cross-over trial of Omnitrope powder (5.8mg/vial)	12 Healthy volunteers	△	○	○	○
EP2K-99-PhIUSA	A 2-arm cross-over trial to compare Omnitrope powder (5.8mg/vial) vs Genotropin powder	24 Healthy volunteers	△			○
EP2K-00-PhI[AQ]	A 2-arm cross-over trial to compare Omnitrope powder (5.8mg/vial) vs Omnitrope solution (5mg/1.5mL)	24 Healthy volunteers	△	○	○	○

Clinical Datapackage of Somatropin BS s.c.“Sandoz”(=Omnitrope)

【PhIII studies】

Study Number		Subjects	Japan	EU	Canada	USA
EP2K-99-PhⅢ/ EP2K-00-PhⅢFo	Sequential randomized open–label parallel study to compare Omnitrope powder (5.8mg/vial) vs Genotropin powder	89 GHD children	△	○	○	○
EP2K-00-PhⅢ^{AQ} （Part A）	Sequential randomized open–label parallel study to compare Omnitrope powder (5.8mg/vial) vs Omnitrope solution (5mg/1.5mL)	86 GHD children	△	○	○	○
EP2K-00-PhⅢ^{AQ} （Part B）	Sequential study to confirm the safety and efficacy of Omnitrope solution (5mg/1.5mL)	86 GHD children	△	○	○	○
EP2K-00-PhⅢb-E	A single-arm study to confirm long-term safety and efficacy of Omnitrope solution (5mg/1.5mL)	70 GHD children	△		○	
EP2K-02-PhⅢLyo	A single-arm study to confirm long-term safety and efficacy of Omnitrope powder (5.8mg/vial)	51 GHD children	△	○	○	

○：Evaluation Data, △：Reference Data

Indication of Somatropin BS s.c.“Sandoz”(=Omnitrope)

Indication	Genotropin (Japan)	Japan	EU	Canada	USA
GHD in Pediatric	○	○	○	○	○
Turner Syndrome	○	○	○		
Chronic renal insufficiency	○	○	○		
Prader-Willi syndrome	○		○		＊
Small for gestational age	○		○		＊
GHD in Adults	○	§	○	○	○
Idiopathic Short Status					＊

Ph III

＊ : new indication added 4 years after first approval without any clinical studies with Omnitrope.

§ : new indication added 2 years after first approval (=after re-examination period of “GHD in Adults” was finished) without any clinical studies with Somatropin BS s.c. “Sandoz”.

Datapackages of Epoetin Alfa Biosimilar Products

		GL（JP）	EPO BS（JP）	Abseamed et.al.	Retacrit et.al.
Quality	Manufacturing Process	○	○	○	○
	Characterization	○	○	○	○
	Specification	○	○	○	○
Stability	Long term test	○	○	○	○
	Stress test	△	○	?	?
	Accelerated test	△	○	?	?
Pharmacology	Primary PD	○	○	○	○
	Safety Pharmacology	–	○	–	–
	Others	–	–	–	–
PK	ADME (non-clinical)	△	○	○	–
	BE (human)	–	–	–	–
	Others	△	–	–	–
Toxicology	Single-Dose Toxicity	△	○	–	–
	Repeat-Dose Toxicity	○	○	○	○
	Genotoxicity	–	○	–	–
	Carcinogenicity	–	–	–	–
	Reproductive & Developmental	–	○	–	–
	Local Tolerance	△	○	○	○
	Others	△	–	–	–
Clinical	Clinical Studies	○	○	○	○

Compared to Reference products

Clinical Datapackage of Epoetin Alfa Biosimilar Products

【PK/PD studies】

	Epoetin Alfa BS“JCR”	Abseamed et.al.	Retacrit et.al.
Non-comparative	A placebo-controlled trial to confirm the safety & PK ・single IV dose ・24 healthy volunteers	Supportive data for PK ・multiple SC doses ・6 healthy volunteers	
		Characterization of PK ・single and multiple SC doses ・72 healthy volunteers	
comparative		pilot study (PK & PD) ・IV and SC ・6 healthy volunteers	
	A 2-arm cross-over trial to compare the safety & PK ・single IV dose ・24 HD patients	An open randomised parallel study to compare PK and PD ・multiple IV doses ・76 healthy volunteers	A two-period cross-over trial to compare the PK profiles ・single IV dose ・24 healthy volunteers
	A 2-arm cross-over trial to compare the safety & PK ・single SC dose ・32 healthy volunteers	An open randomised parallel study to compare PK and PD ・multiple SC doses ・74 healthy volunteers	A three-period cross-over trial to compare the PK profiles etc. ・single SC dose ・48 healthy volunteers

Clinical Datapackage of Epoetin Alfa Biosimilar Products

【PhIII studies】

		Epoetin Alfa BS“JCR”	Abseamed et.al.	Retacrit et.al.
Renal Anaemia (IV)	comparative	A double blind trials to compare the safety & efficacy ･329 HD patients	A randomised, double-blind parallel trial (+ safety after 28 wks) ･403 HD patients	A randomised, double-blind parallel-group trial (Correction phase) ･541 HD patients
				A randomised, double-blind cross-over trial (Maintenance phase) ･239 HD patients
	long term ／safety	A single-arm study to confirm long-term safety and efficacy ･143 HD patients		an open-label safety trial with focus on the anti-EPO antibodies ･745 patients
Chemotherapy-induced Anaemia (SC)			A randomised double-blind study to evaluate the efficacy and safety (not comparative) ･60 cancer patients	A safety trial to provide information on thrombotic events ･216 cancer patients

Indication of Epoetin Alfa Biosimilar Products

		Epoetin Alfa BS"JCR"			Abseamed et.al.			Retacrit et.al.		
		Ref. *1	Ph III	Indi-cation	Ref. *2	Ph III	Indi-cation	Ref. *2	Ph III	Indi-cation
Renal anaemia	Hemodialysis	○	○	○	○	○	○	○	○	○
	Peritoneal dialysis									
	Maintenance Phase		○			○			○	
	Correction Phase					○				
Renal anaemia not yet undergoing dialysis					○		○	○		○
Anaemia of Prematurity		○		○						
Autologous blood predonation					○		○	○		○
Cancer chemotherapy-induced anaemia					○	○	○	○	○	○
Orthopaedic surgery					○		○	○		

＊1: ESPO750, 1500, 3000IU　＊2：From Package leaflet of Eprex 2000, 4000, 10000IU/mL in UK

PMS for Biosimilar Products in Japan

Somatropin BS

- Patients' data (≧300) were required collect as PMS.
- Clinical data about Turner syndrome (≧18) and Chronic renal insufficiency (≧3) were collected during PMS.
- The sponsor should analyze the lack of efficacy & immune response adverse possibly due to expression of antibodies against somatropin/HCP.

Epoetin alfa BS

- Patients' data (≧500) were required to collect for 5 years as PMS.
- Clinical data about PD patients and Anemia of prematurity were required to collect during PMS.
- The sponsor should analyze the lack of efficacy possibly due to expression of antibodies.

Thank you for your attention.