1st Malaysia-Japan Symposium on Pharmaceutical Regulatory System, March 10-11, 2015,
ALOFT KUALA LUMPUR SENTRAL , Kuala Lumpur, Malaysia

Regulatory Framework for Biotherapeutic Products including Similar Biotherapeutic Products

Yasuhiro Kishioka, Ph.D.

Principal Reviewer

Office of Cellular and Tissue-based Products

Pharmaceuticals and Medical Devices Agency (PMDA)

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

1. Introduction

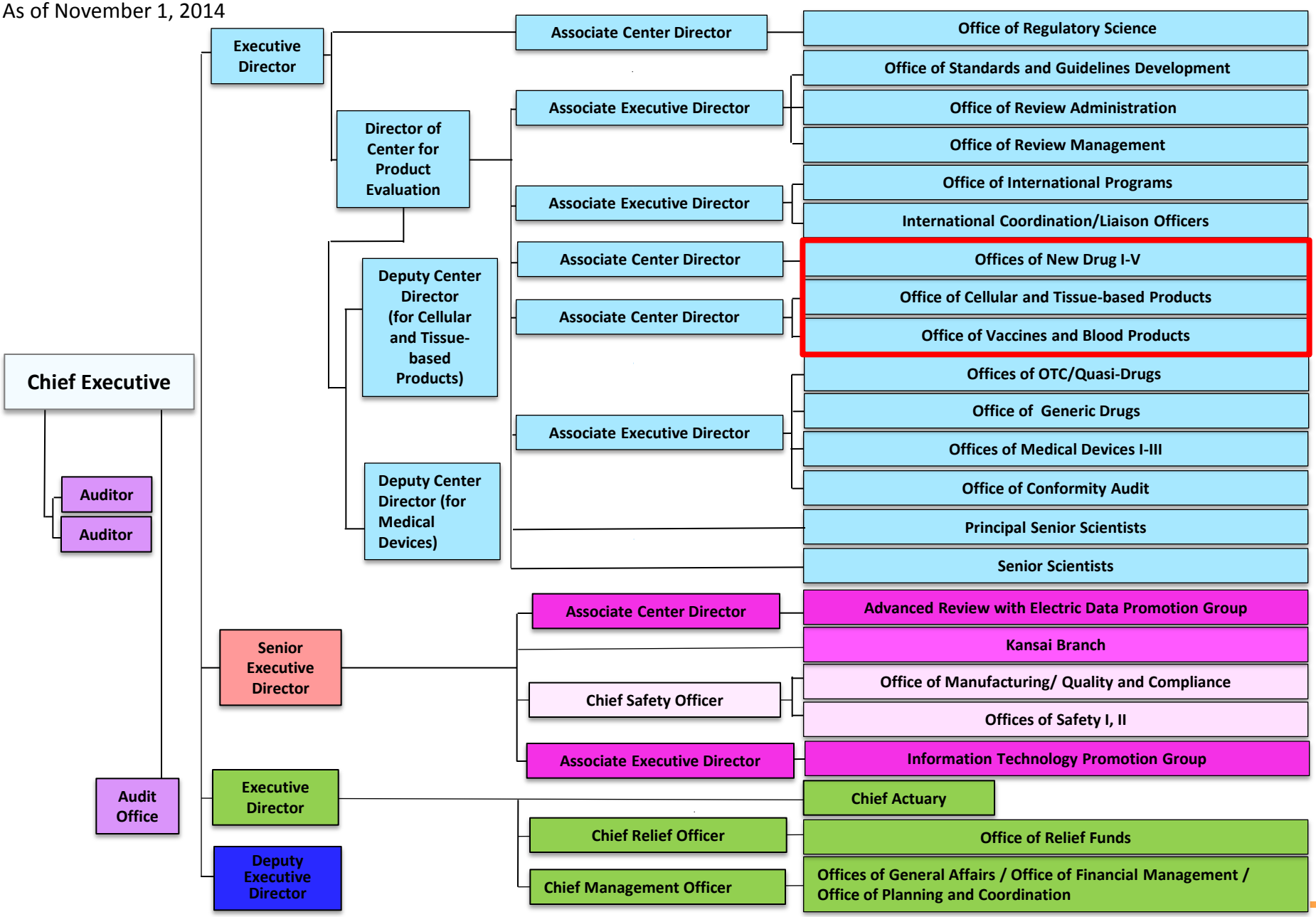
2. Regulatory Framework for Biotherapeutic Products

   - Pharmaceuticals and Medical Devices Act
   - Standard for Biological Ingredients
   - Minimum Requirements for Biological Products

3. PMDA Experience and Perspectives on the Development and Approval of Biosimilars

Organization Chart of PMDA

As of November 1, 2014



Review Categories of New Drugs

Office	Review Category	Products
Office of New Drug I	Team 1 Team 6-2	Gastrointestinal drugs, Dermatologic drugs Hormone drugs, Drugs for metabolic disorders
Office of New Drug II	Team 2 Team 5 Radiopharmaceuticals In vivo diagnostics	Cardiovascular drugs, Antiparkinsonian drugs, Antithrombotics, Anti-Alzheimer's drugs Reproductive system drugs, Drugs for urogenital system, combination drugs Radiopharmaceuticals Contrast media
Office of New Drug III	Team 3-1 Team 3-2	Central/peripheral Nervous system drugs (excluding anesthetic drugs) Anesthetic drugs, Sensory organ drugs (excluding drugs for inflammatory diseases), Narcotics
Office of New Drug VI	Team 4 Anti-AIDS drugs Team 6-1	Antibacterial drugs, vermifuge, Antifungal drugs, Antiviral drugs (excluding AIDS drugs) Anti-HIV agents Respiratory tract drugs, Anti-allergy drugs (excluding dermatologic drugs), Sensory organ drugs for inflammatory diseases
Office of New Drug V	Oncology drugs	Antineoplastic drugs
Office of Cellular and Tissue-based Products	Bio-CMC Cellular and tissue-based products, Gene therapy products	Quality of biologics, Biosimilars Cellular and tissue-based products Quality and safety of gene therapy products
Office of Vaccines and Blood Products	Vaccines Blood products	Vaccines, Antitoxic serum Globulin, Blood coagulation factor products

Outline

1. Introduction

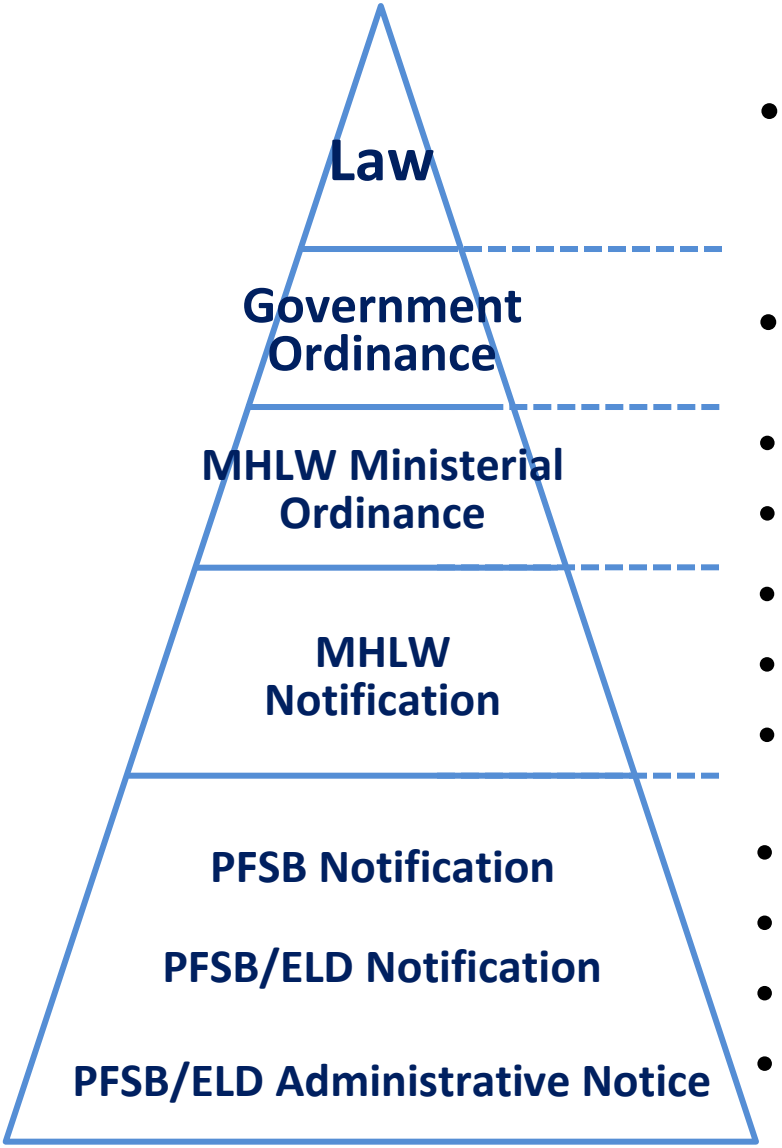
2. Regulatory Framework for Biotherapeutic Products

   - Pharmaceuticals and Medical Devices Act
   - Standard for Biological Ingredients
   - Minimum Requirements for Biological Products

3. PMDA Experience and Perspectives on the Development and Approval of Biosimilars

Overview of the Regulatory Framework

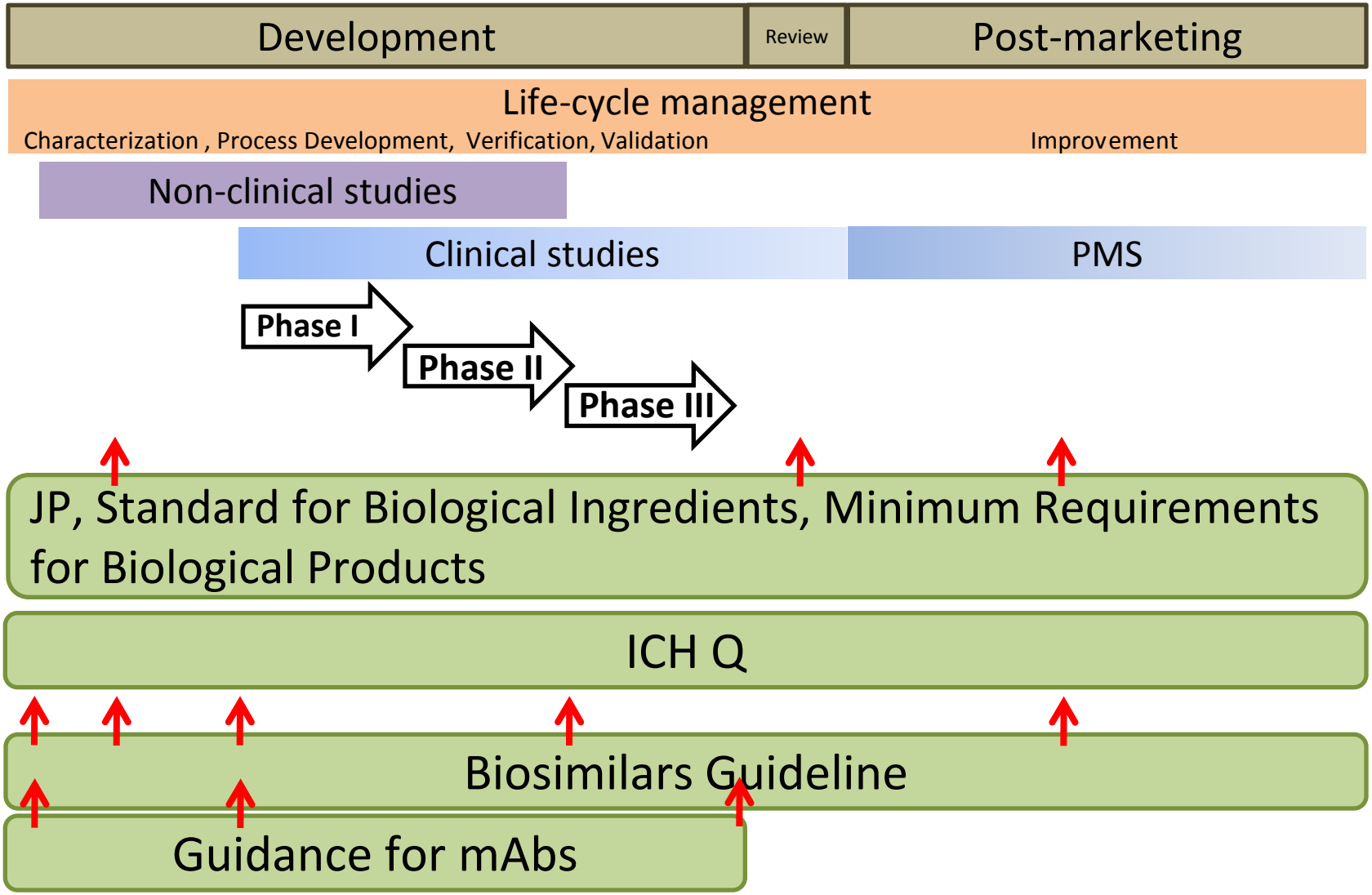
-Focus on Quality-



- Pharmaceuticals and Medical Devices Act (PMD. Act)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH guidelines
- Guidance for monoclonal antibodies
- Biosimilars Guideline
- Etc.

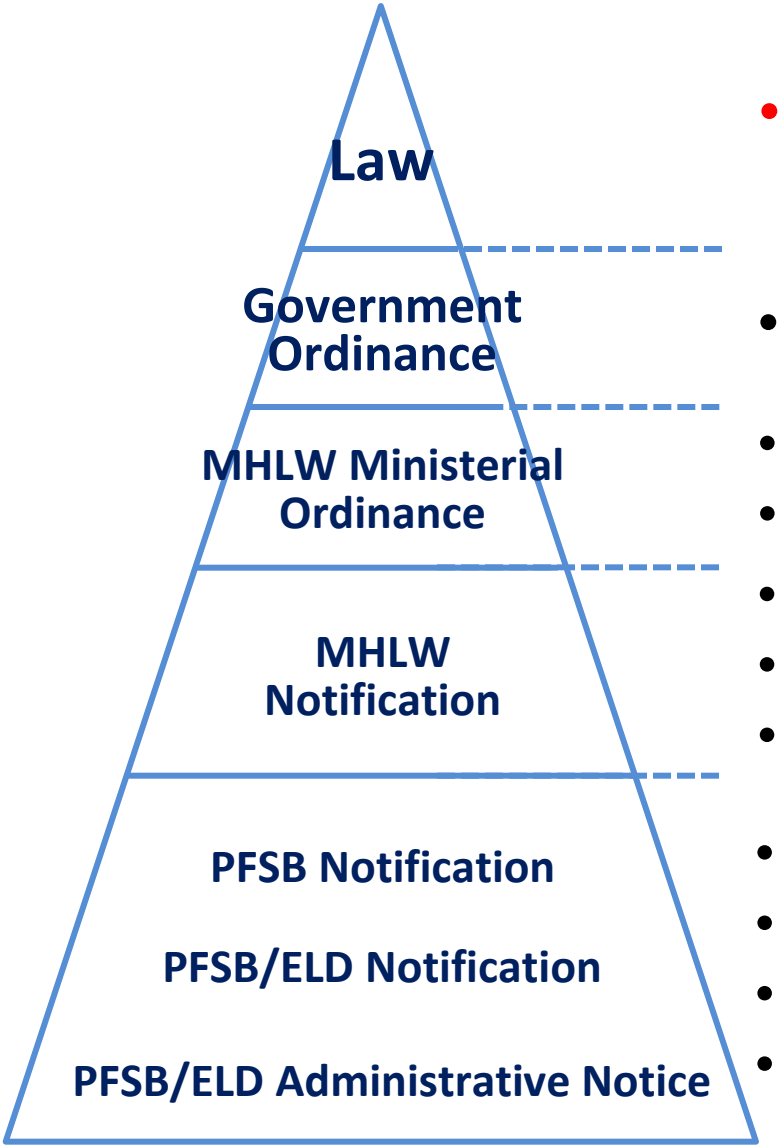
- MHLW: Minister of Health Labour and Welfare
- PFSB: Pharmaceutical and Food Safety Bureau
- ELD: Evaluation and Licensing Division

Japanese Strategies for Ensuring the Quality of Biotherapeutic Products



Overview of the Regulatory Framework

-Focus on Quality-

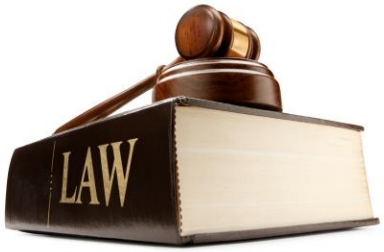


- Pharmaceuticals and Medical Devices Act (PMD. Act)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH guidelines
- Guidance for monoclonal antibodies
- Biosimilars Guideline
- Etc.

- MHLW: Minister of Health Labour and Welfare
- PFSB: Pharmaceutical and Food Safety Bureau
- ELD: Evaluation and Licensing Division

Pharmaceuticals and Medical Devices Act

Revision History:



- 1960
- 2002
- 2014

Past:

- HIV contaminated plasma derivatives
- Fibrinogen-transmitted Hepatitis C
- Iatrogenic CJD through transplantation of dura mater

Strengthening of Safety Measures for Biotherapeutic Products

Risk-based Safety Measures

How Do We Classify the Risk?

- MHLW classifies individual products including ingredients derived from human or biological source materials into three categories
  - "Specified Biological Products"
  - "Biological Products"
  - Others
- Product classification is done, based on sound scientific assessment of potential risk of infection transmission, according to the recommendation from PAFS* council.

*: Pharmaceutical Affairs and Food Sanitation Council

What are “Biological Products”?

“Biological Products”

Products including ingredients derived from human or biological source materials (excluding plants) , which are designated by the Minister ……. as requiring special precautions in terms of public health and hygiene

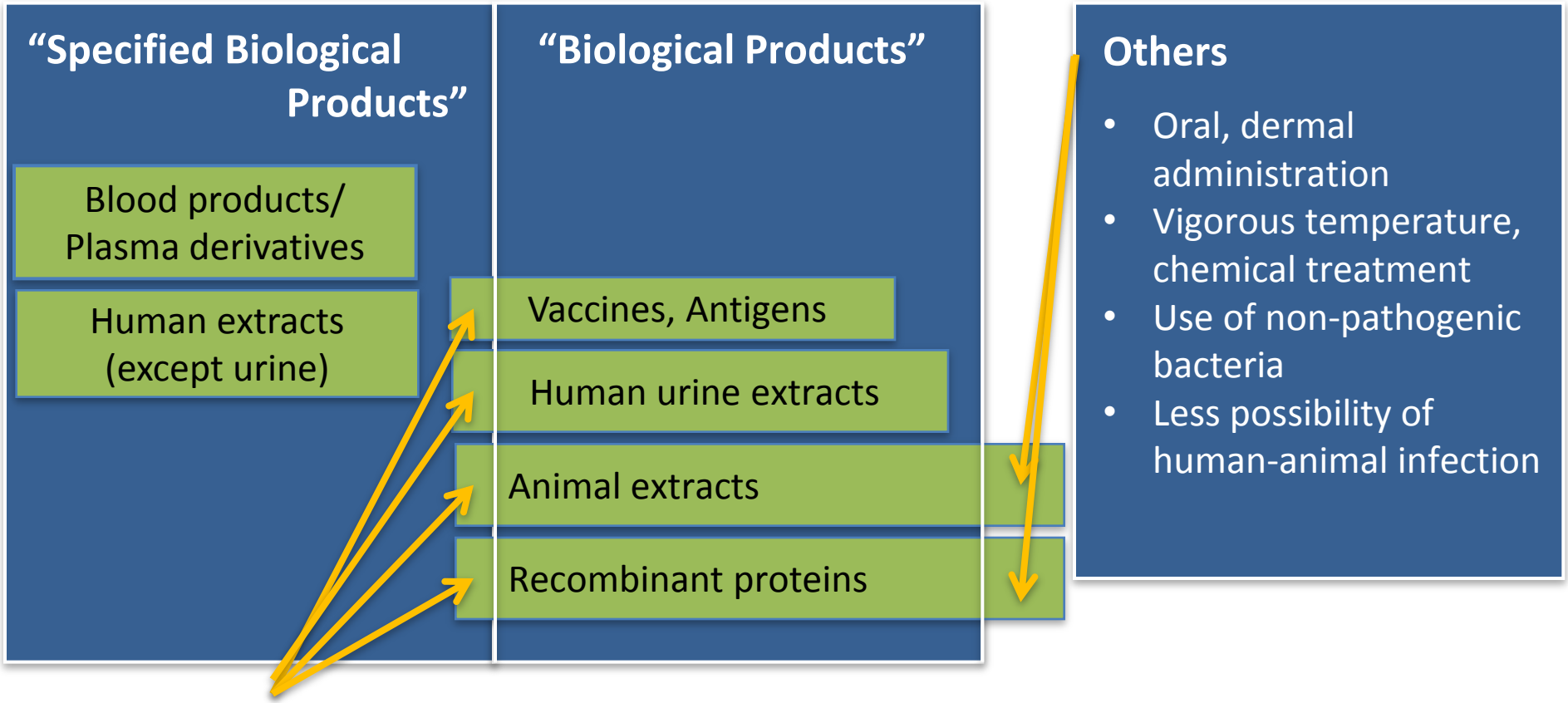
(Article 2.10 of PMD. Act)

“Specified Biological Products”

“Biological products” as requiring measures to prevent the onset or spread of risk to public health and hygiene

(Article 2.11 of PMD. Act)

Classification of “Biological Products”



Some of those containing human plasma derivative

If the risk is estimated to be equivalent to blood products/plasma derivatives in terms of usage, dose, quantities and duration, the product is designated as “Specified Biological Products”.

Post-Marketing Safety Measures for “Biological Products”

- Labeling
- Package insert

	Information
S.B.	Ingredients, Risk of infection, Risk-benefit etc.
B.P.	Ingredients etc.

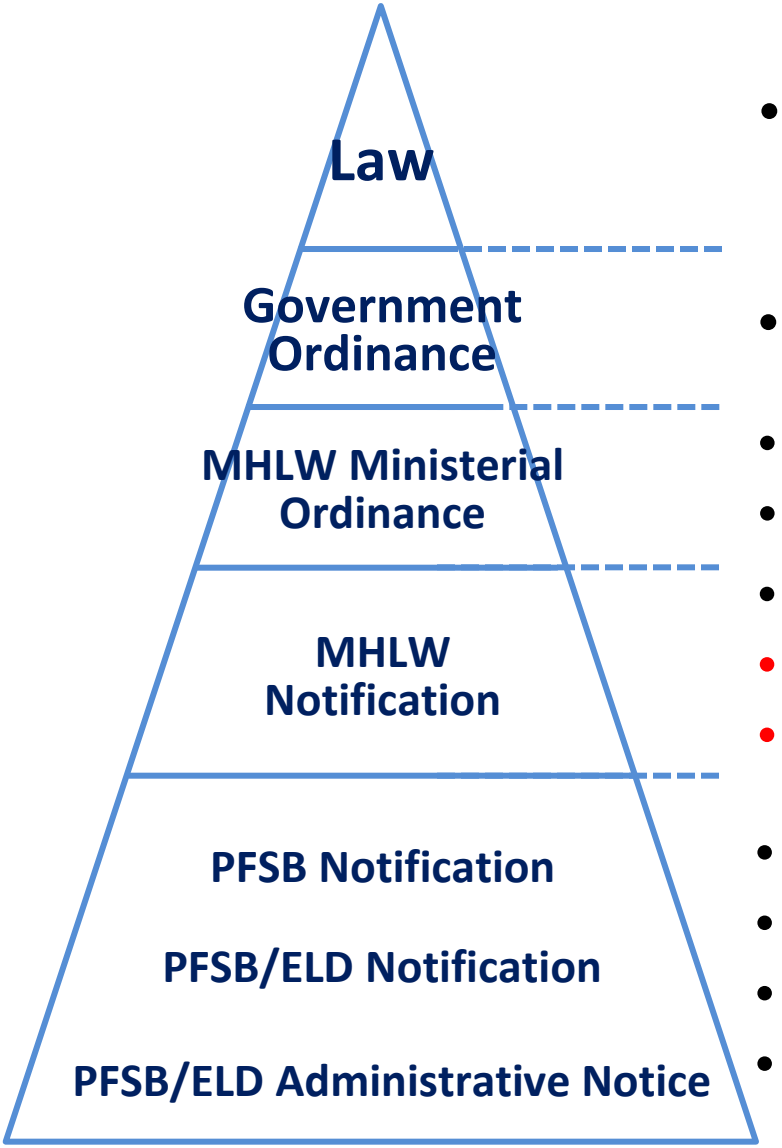
- Periodic surveillance report
- Retention of record

	Manufacturers	Health professionals
S.B.	30 yrs. (donor records, manufacturing records)	20 yrs. (patient records)
B.P.	10 yrs. (donor records, manufacturing records) If B.P. contains human plasma derivatives, 30 yrs.	-

S.B.: “Specified Biological Products” B.P.: “Biological Products”

Overview of the Regulatory Framework

-Focus on Quality-



- Pharmaceuticals and Medical Devices Act (PMD. Act)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH guidelines
- Guidance for monoclonal antibodies
- Biosimilars Guideline
- …Etc.

- MHLW: Minister of Health Labour and Welfare
- PFSB: Pharmaceutical and Food Safety Bureau
- ELD: Evaluation and Licensing Division

Japanese standards (Article 41, 42 of PMD. Act)

Chapter VIII Standards and Tests for Pharmaceuticals etc.

Article 41

For the purpose of regulating the properties and quality of pharmaceuticals, the Minister shall establish and publish the Japanese Pharmacopoeia, … .

Article 42

The Minister may lay down the necessary standards, …. , related to the manufacturing process, properties, quality, storage method, etc. of those pharmaceuticals and regenerative medicines that require special attention concerning public health and hygiene.

Standard for Biological Ingredients

MHLW Notification No.375 (2014)

1. General Rules
2. General Rules for Blood Products
   - i) General Rules for Blood Products for Transfusions
   - ii) General Rules for Blood Plasma Derivatives
3. General Rules for Human Derived Ingredients
   - i) Standard for Raw materials of Human Cellular/Tissue-based Products
   - ii) Standard for Human Urine-derived Raw Material
4. General Rules for Animal-derived Ingredients
   - i) Standard for Ruminant Animal-derived Raw Materials
   - ii) Standard for Raw Materials of Animal Cellular/Tissue-based Products
   - iii) Standard for Animal-derived Raw Materials

Purpose of the Standard

the purpose of this standard is to ensure the quality, efficacy and safety of products by establishing standards regarding raw materials used in the manufacturing process, which are derived from human or biological source materials (plants are excluded). *(General rules 1.1)*

Main points of the Standard

- **Eligibility of donors**

  e.g.) blood donors must be confirmed as eligible donors by means of medical examinations, interviews, etc. and… *(General Rules for Blood Products for Transfusions)*

- **Testing for raw materials**

  e.g.) the blood collected from each donor must be serologically tested for, at minimum, treponema pallidum, HBV, HCV, HIV-1, HIV-2 and HTLV-1.

  blood that is to be used as a source material for blood products for transfusions must be subjected to NAT for, at minimum, HBV DNA, HCV RNA, and HIV RNA. *(General Rules for Blood Products for Transfusions)*

- **Basic requirements for risk mitigation in manufacturing process**

  e.g.) for cells or tissue used as source materials (in case cell banks are used as a starting material for production culture, including cell line and cells after production culture), all necessary testing to detect viruses (virus tests) must be performed. Furthermore, at the unprocessed or unpurified bulk stages, appropriate virus tests must be implemented.*(Standard for Animal Derived Ingredients)*

- **Record retention**

Minimum Requirements for Biological Products

MHLW Notification No.439 (2014)

General Rules

Monograph

- Influenza Vaccine
- Influenza HA Vaccine
- Freeze-dried Inactivated Tissue Culture Hepatitis A Vaccine
- …Etc.

General Tests

A. Test procedure

B. Standards, Reference Preparations, Test Toxins and Units

C. Reagents, Test Solutions, etc.

D. Buffered Solutions and Culture Media

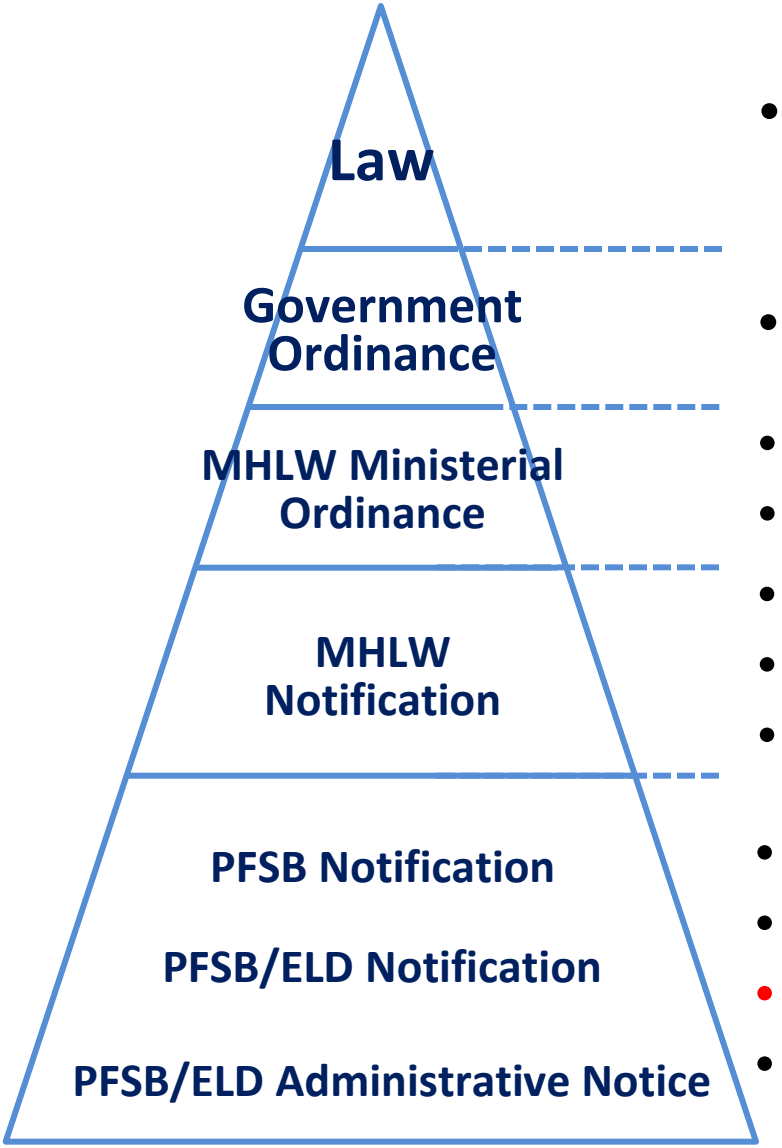
http://www.nih.go.jp/niid/en/mrbp-e.html (in English)

Purpose of the Standard

This standard specifies manufacturing methods, properties, quality, storage, and other matters for biological products listed in the monographs. *(General rules 1)*

Overview of the Regulatory Framework

-Focus on Quality-



- Pharmaceuticals and Medical Devices Act (PMD. Act)
- Enforcement Ordinance of the PMD. Act
- Enforcement Regulations of the PMD. Act
- GMP, GQP
- Japanese Pharmacopoeia
- Standard for Biological Ingredients
- Minimum Requirements for Biological Products
- ICH guidelines
- Guidance for monoclonal antibodies
- Biosimilars Guideline
- …Etc.

- MHLW: Minister of Health Labour and Welfare
- PFSB: Pharmaceutical and Food Safety Bureau
- ELD: Evaluation and Licensing Division

Regulations for Biosimilars in Japan

- Guideline for the Quality, Safety and Efficacy Assurance of Follow-on Biologics (FOBs)*
  (PFSB/ELD Notification No. 0304007 / March 4, 2009)
  http://www.pmda.go.jp/english/service/pdf/notifications/PFSB-ELD-0304007.pdf (GL in English)

  *: "Follow-on Biologics" in this guideline is a synonym for "Biosimilars".

- Marketing Approval Application for FOBs
  (PFSB Notification 0304004 / March 4, 2009)

- Nonproprietary Name and Drug Name of FOBs
  (PFSB/ELD Notification No. 0214-1, Administrative Notice / February 14, 2013)

- Questions & Answers regarding Guideline
  (PFSB/ELD Administrative Notice / July 21, 2009, March 31, 2010)

Outline

1. Introduction

2. Regulatory Framework for Biotherapeutic Products

   - Pharmaceuticals and Medical Devices Act
   - Standard for Biological Ingredients
   - Minimum Requirements for Biological Products

3. PMDA Experience and Perspectives on the Development and Approval of Biosimilars

Regulatory History and Status of Biosimilars

- Application Category for biosimilars
- Guideline
- Nomenclature rules

Q&A

Q&A

Revision of Nomenclature rules

2005 2009 2010 2011 2012 2013 2014 2015

Somatropin BS [Sandoz]

Epoetin alfa BS [JCR]

Filgrastim BS [F], [MOCHIDA]

Filgrastim BS [NK], [TEVA]

Filgrastim BS [Sandoz]

Infliximab BS [NK], [CTH]

Insulin glargine BS [Lilly]

List of Approved Biosimilars in Japan

Drug name	Japanese Accepted Name (JAN)	Manufacturer	Reference product	Approved year
Somatropin BS S.C. Injection 5mg [SANDOZ] etc.*	Somatropin (genetical recombination)	SANDOZ	Genotropin (Somatropin) (Pfizer)	2009.5
Epoetin alfa BS Injection 750 syringe [JCR] etc. *	Epoetin Kappa (genetical recombination) [Epoetin Alfa Biosimilar 1]	JCR Pharmaceuticals	Espo (Epoetin alfa) (Kyowa Hakko Kirin)	2010.1
Filgrastim BS Injection 75μg syringe [F] / [MOCHIDA] etc.*	Filgrastim (genetical recombination) [Filgrastim Biosimilar 1]	Fuji Pharma / Mochida Pharmaceutical	Gran (Filgrastim) (Kyowa Hakko Kirin)	2012.11
Filgrastim BS Injection 75μg syringe [NK] / [TEVA] etc.*	Filgrastim (genetical recombination) [Filgrastim Biosimilar 2]	NIPPON KAYAKU / Teva Pharma Japan	Gran (Filgrastim) (Kyowa Hakko Kirin)	2013.2
Filgrastim BS Injection 75μg syringe [SANDOZ] etc.*	Filgrastim (genetical recombination) [Filgrastim Biosimilar 3]	SANDOZ	Gran (Filgrastim) (Kyowa Hakko Kirin)	2014.3
Infliximab BS I.V. infusion 100mg [NK] / [CTH]	Infliximab (genetical recombination) [Infliximab Biosimilar 1]	NIPPON KAYAKU / Celltrion	Remicade (Infliximab) (Mitsubishi Tanabe Pharma)	2014.7
Insulin glargine BS Injection [Lilly] etc. *	Insulin glargine (genetical recombination) [Insulin glargine Biosimilar 1]	Eli Lilly Japan	Lantus (Insulin glargine) (Sanofi)	2014.12

*: etc. means different presentations.

Review Team for Biosimilar application

Office of Cellular & Tissue-based Products

Director

Deputy Director

Bio-CMC team

Review Director

Team Leader

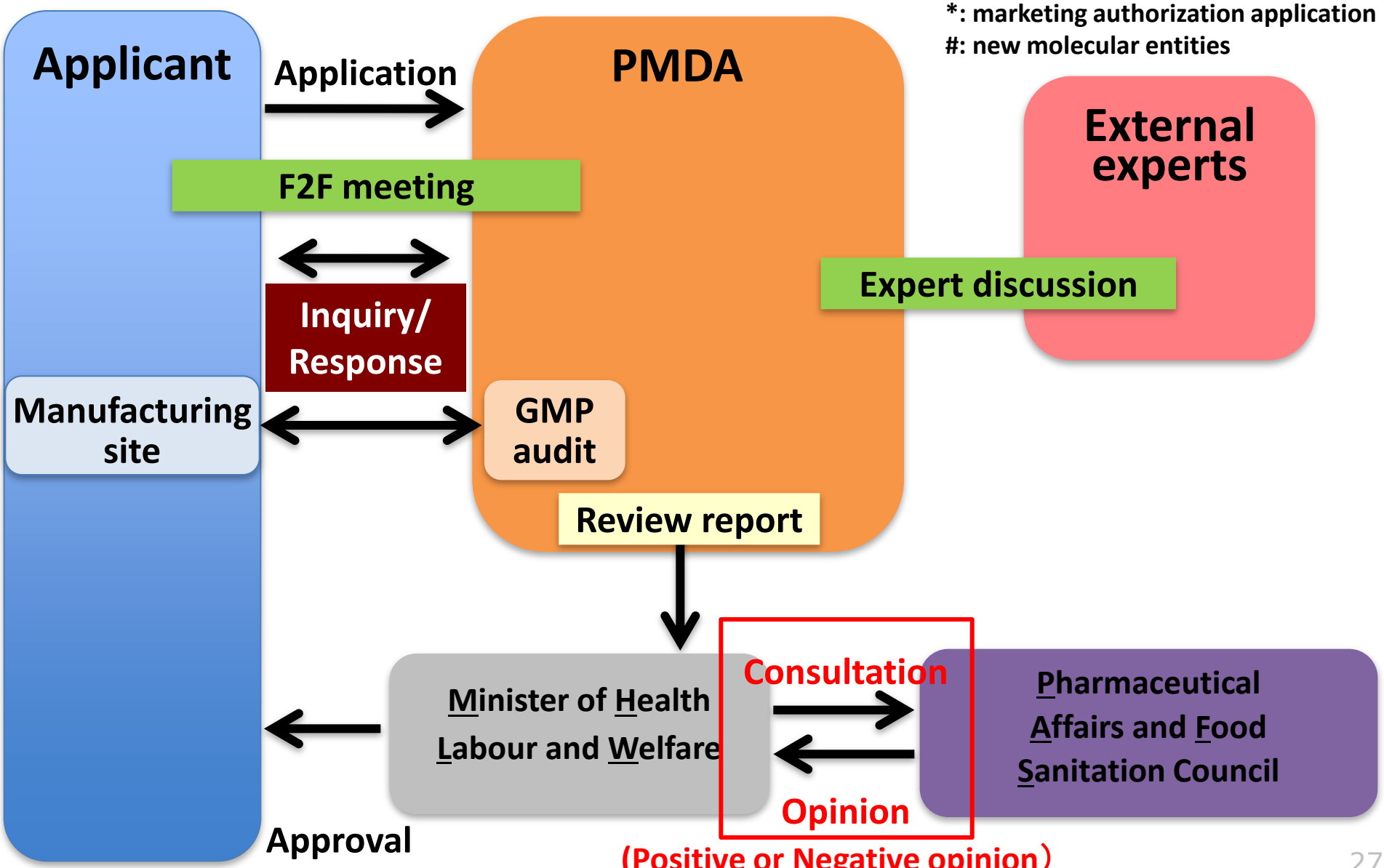
Deputy Team Leader

CMC | Toxicology | Pharmacology | PK/PD

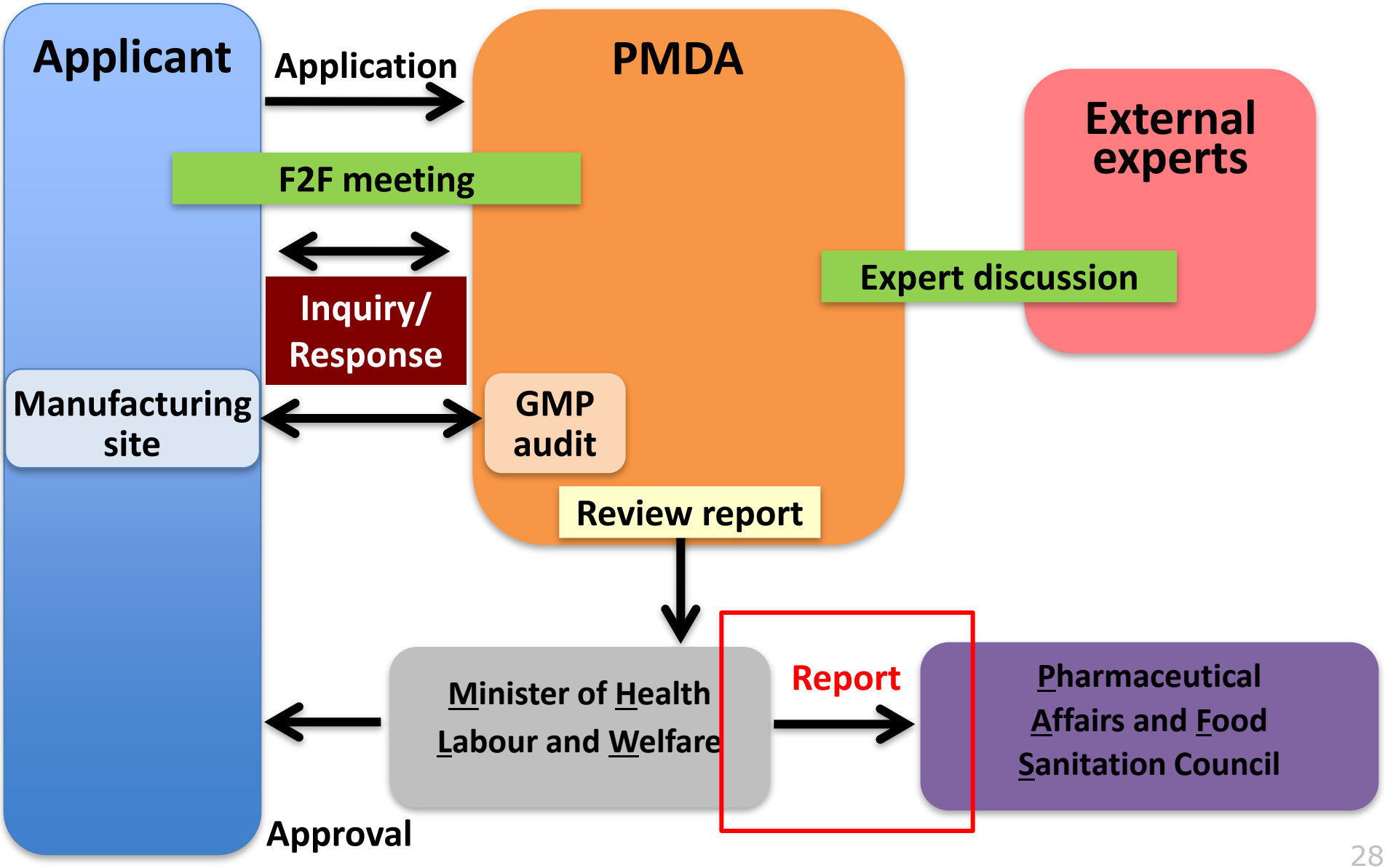
Biostatics | Clinical | PMS

Review Process of MAA* for NMEs# in Japan

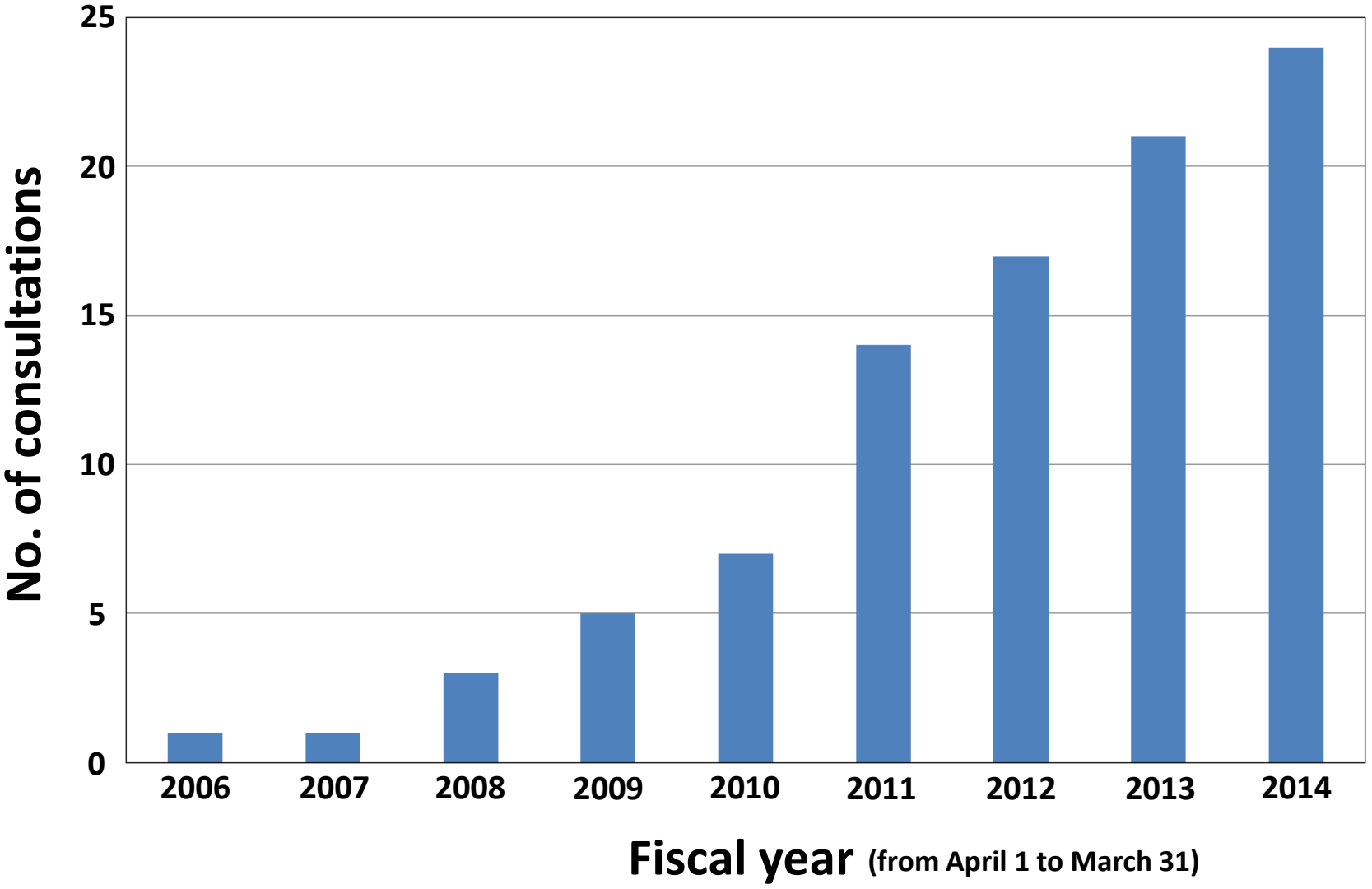
*: marketing authorization application
#: new molecular entities



Review Process of MAA for Biosimilars in Japan



Number of Consultation for Biosimilars



Based on date of application

Frequently asked Questions

- Can a sponsor use non-Japan sourced reference product in comparability exercise?
- What should a sponsor consider when utilizing foreign clinical trials or designing global clinical trials?

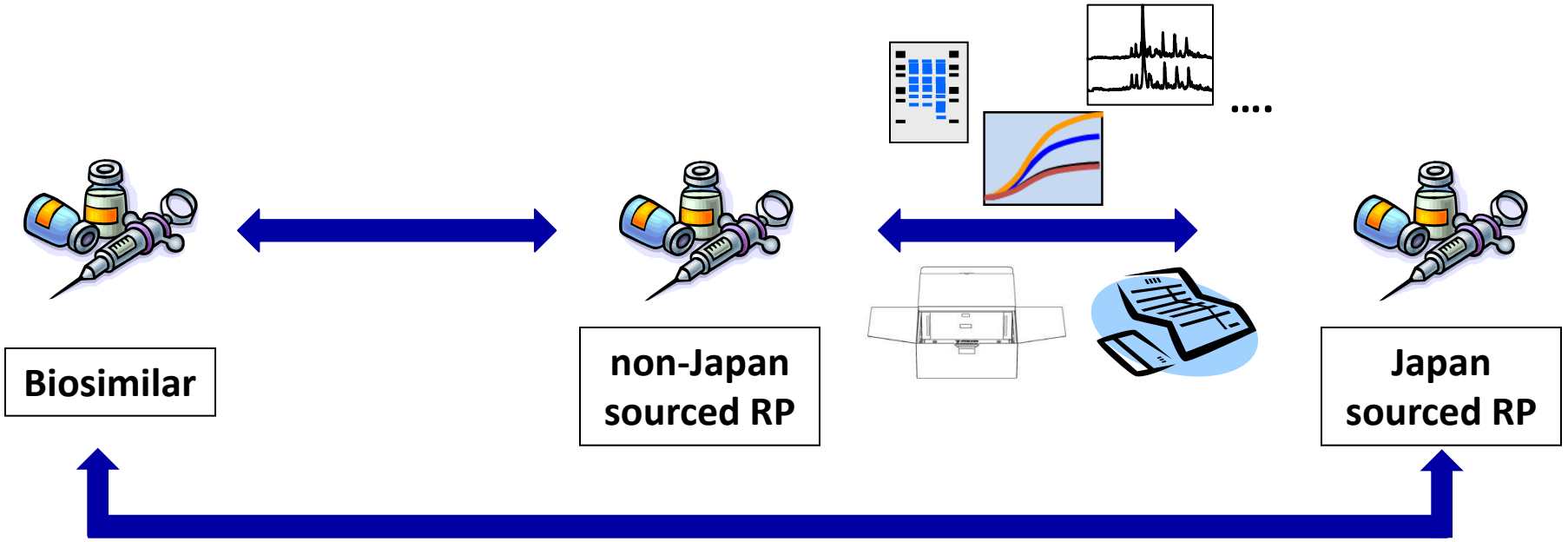
Can a sponsor use non-Japan sourced reference product in comparability exercise?

Guideline: The reference product (RP) should be already approved in Japan.

- PMDA thinks the sponsor should confirm the comparability to the RP which is approved (and used by healthcare providers and patients) in Japan.

Can a sponsor use non-Japan sourced reference product in comparability exercise?

- However, if a sponsor needs to use non Japan-sourced RP in comparability exercise, it is required to explain that the non-Japan sourced RP is the representative of the Japan sourced RP by analytical assays and publicly available information.



Frequently asked Questions

- Can a sponsor use non-Japan sourced reference product in comparability exercise?
- What should a sponsor consider when utilizing foreign clinical trials or designing global clinical trials?

What should a sponsor consider when utilizing foreign clinical trials or designing global clinical trial?

Guidance

- Ethnic factors in the acceptability of foreign clinical data *(ICH E5 (R1))*
- Basic principles on Global Clinical Trials (GCTs)

  (PFSB/ELD Notification No. 0928010 / September 28, 2007)

  http://www.pmda.go.jp/operations/notice/2007/file/0928010-e.pdf (in English)
- Basic principles on Global Clinical Trials (Reference Cases)

  (*PFSB/ELD Administrative Notice September 5, 2012*)

  http://www.pmda.go.jp/kijunsakusei/file/guideline/new_drug/GCT-jirei_en.pdf (in English)

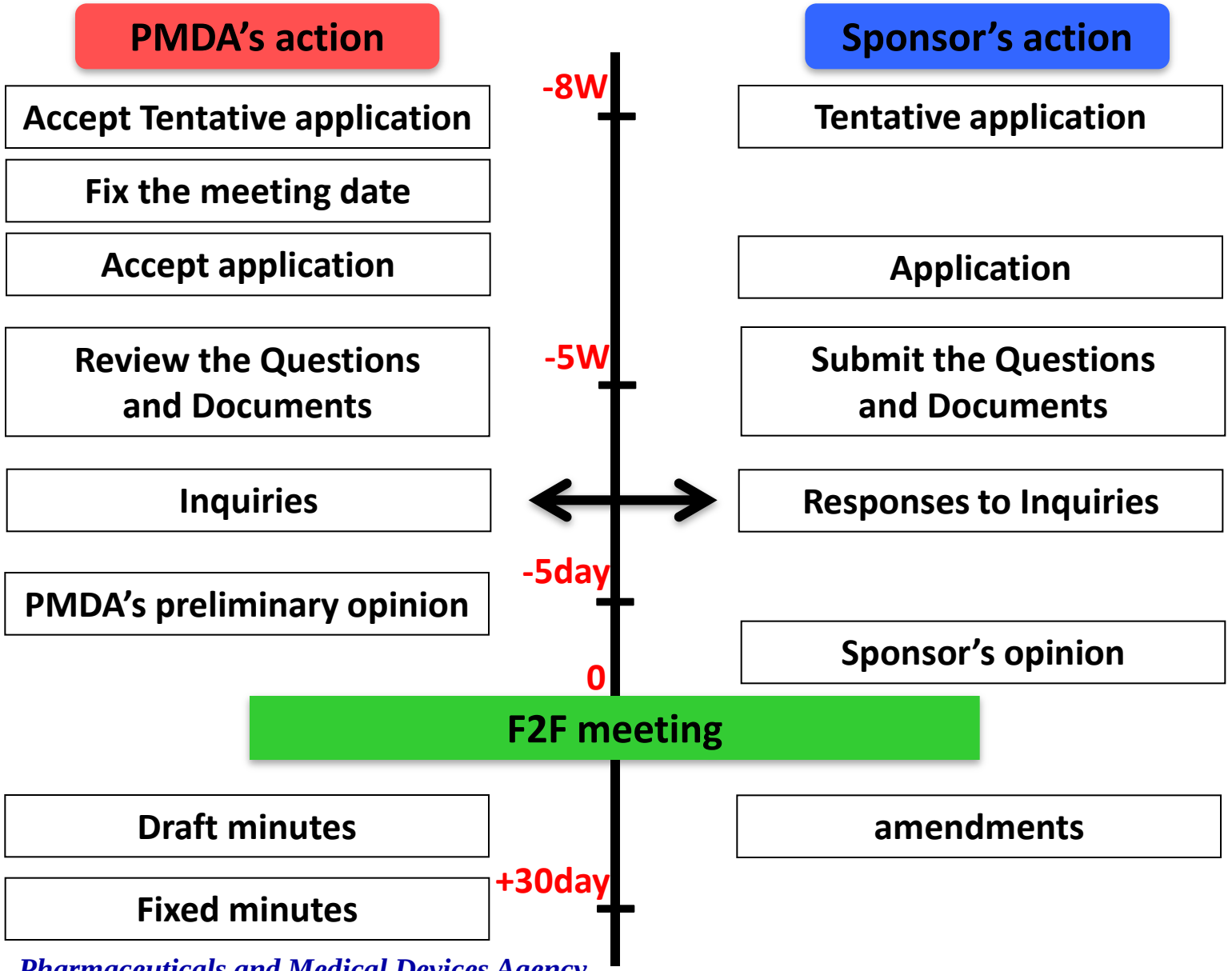
➡
- Ethic factors should be considered.
- A GCT should be designed so that consistency can be obtained between results from the entire population and the Japanese population, and by ensuring consistency of each region, it could be possible to appropriately extrapolate the result of full population to each region.

PMDA Consultation *(charged)*

- Application procedure consultation
- Quality consultation
- Safety consultation
- Consultation on bioequivalence testing, etc. for drugs
- Consultation Pre-phase I study for drugs
- Consultation Pre-phase IIa study for drugs
- Consultation Pre-phase IIb study for drugs
- Consultation after End of phase II study for drugs
- Pre-application consultation
- Additional consultation
- Etc…

For more information:
PMDA H.P. (in Japanese) http://www.pmda.go.jp/operations/shonin/info/consult/iyakuhintaimen.html

PMDA Consultation Flowchart



Sharing of Information, Experience and Knowledge is Valuable !!

World Health Organization

ICH harmonisation for better health

Regulatory Harmonization Steering Committee

APEC Life Sciences Innovation Forum

asean

PANDRH

…Others

Thank you for your attention!

TERIMA KASIH ATAS PERHATIAN ANDA

Yasuhiro Kishioka, PhD.

Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency

kishioka-yasuhiro@pmda.go.jp

Acknowledgements

- Colleagues in the Office of Cellular and Tissue-based Products