PMDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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Deputy Director General of the Office of Review Innovation

PMDA, Japan

Today's Presentation

1. Our Recent Efforts
2. Quality by Design
3. Biosimilars
4. Future Directions

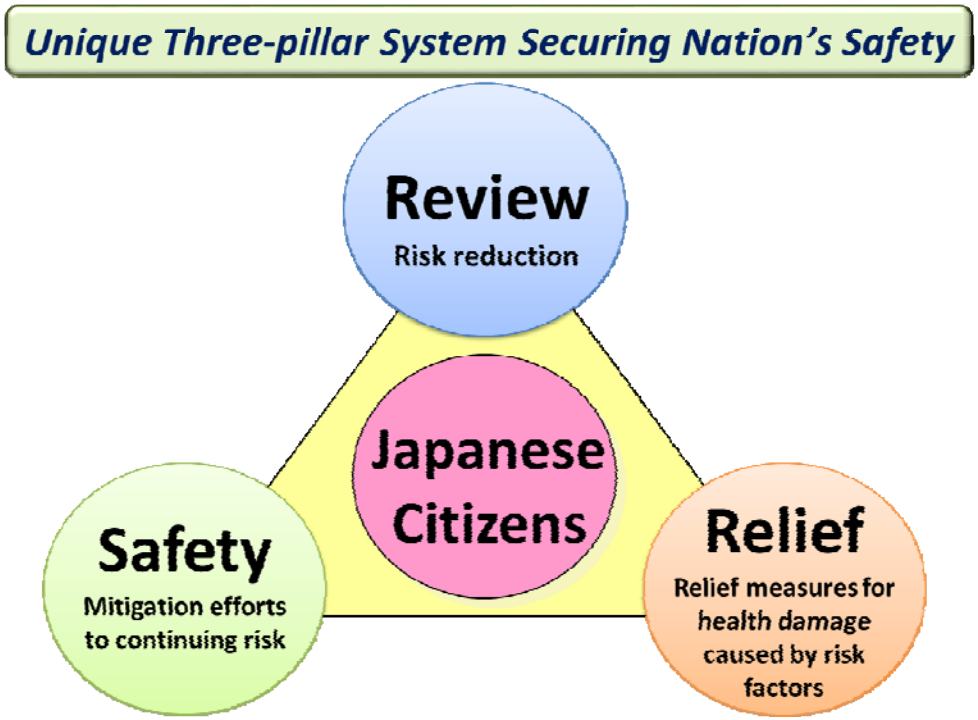
Introduction of PMDA

Tokyo, JAPAN

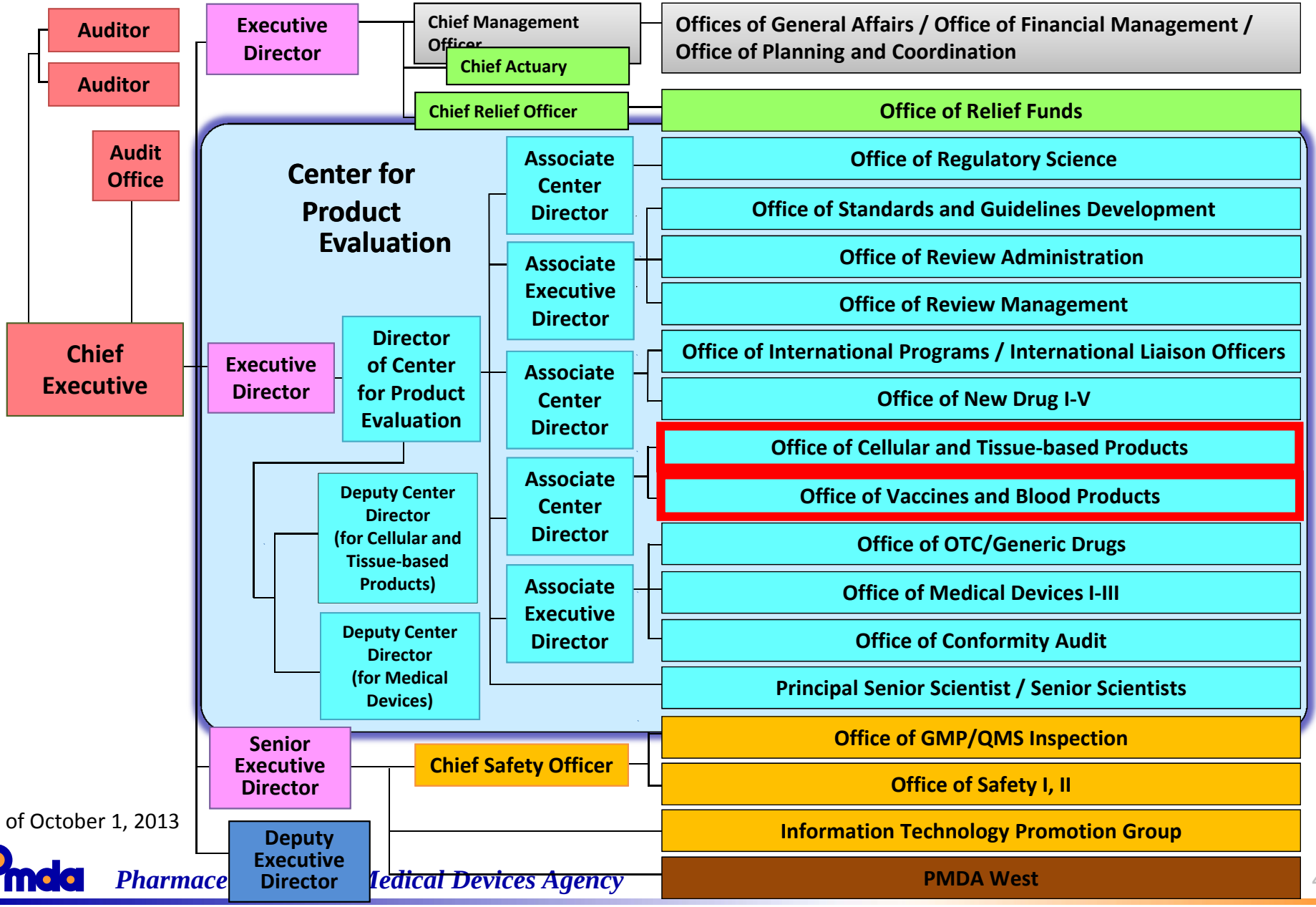
Pharmaceuticals and Medical Devices Agency (PMDA)

- an Incorporated Administrative Agency (IAA)

PMDA's Safety Triangle

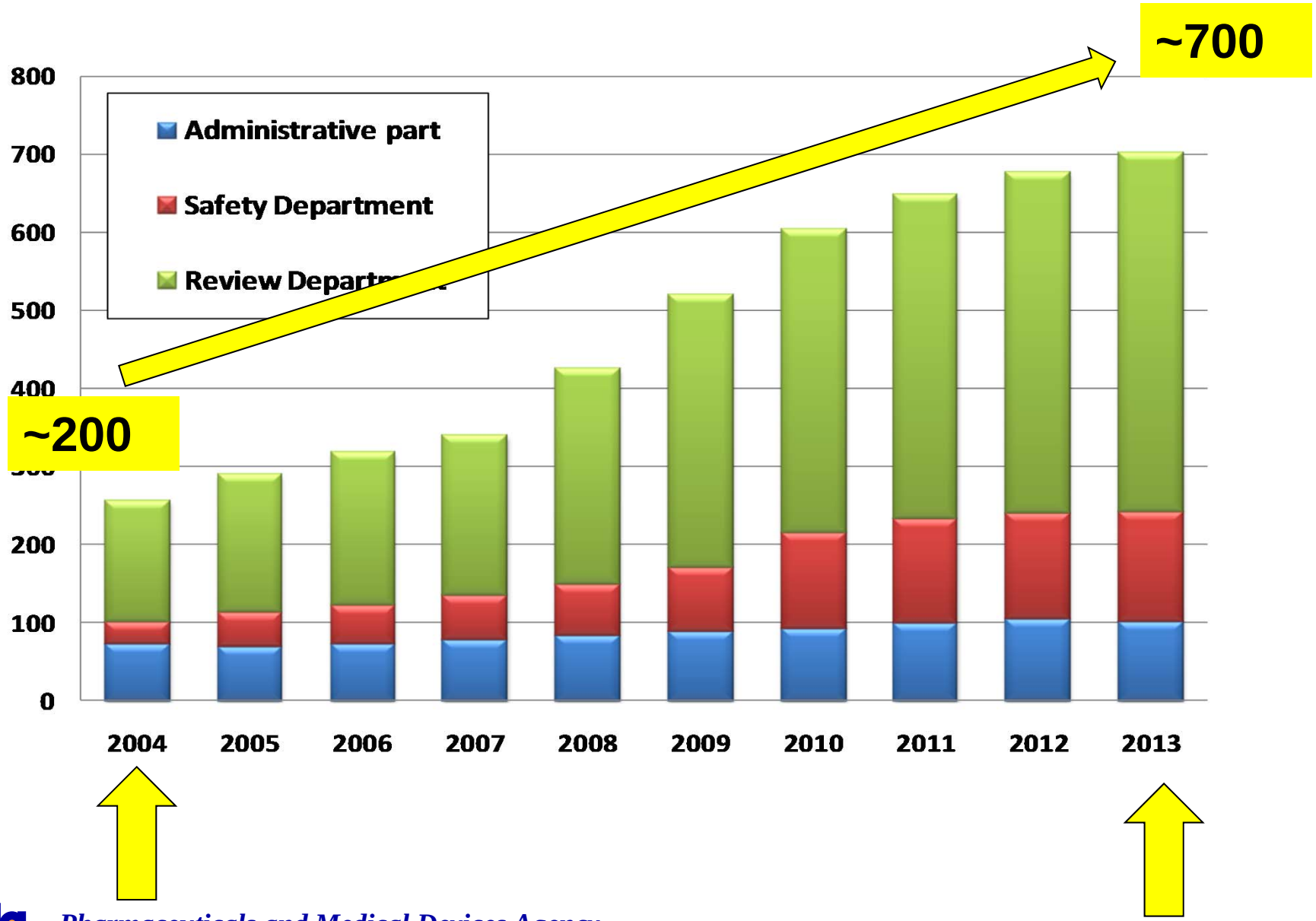


Organization of PMDA

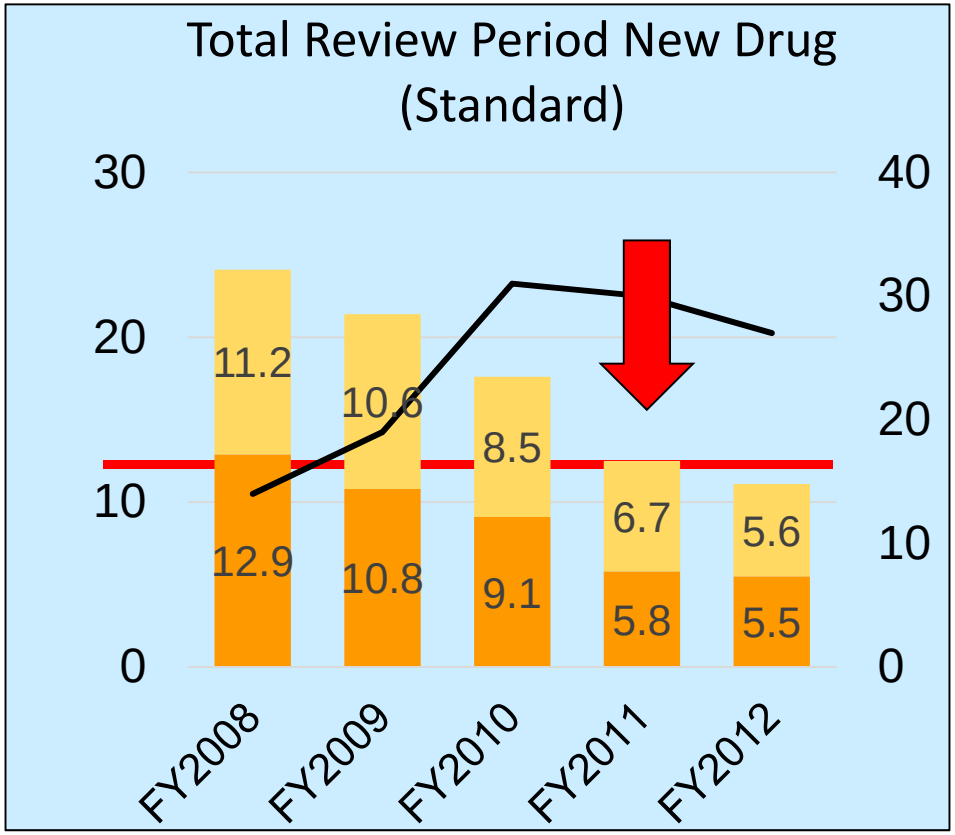


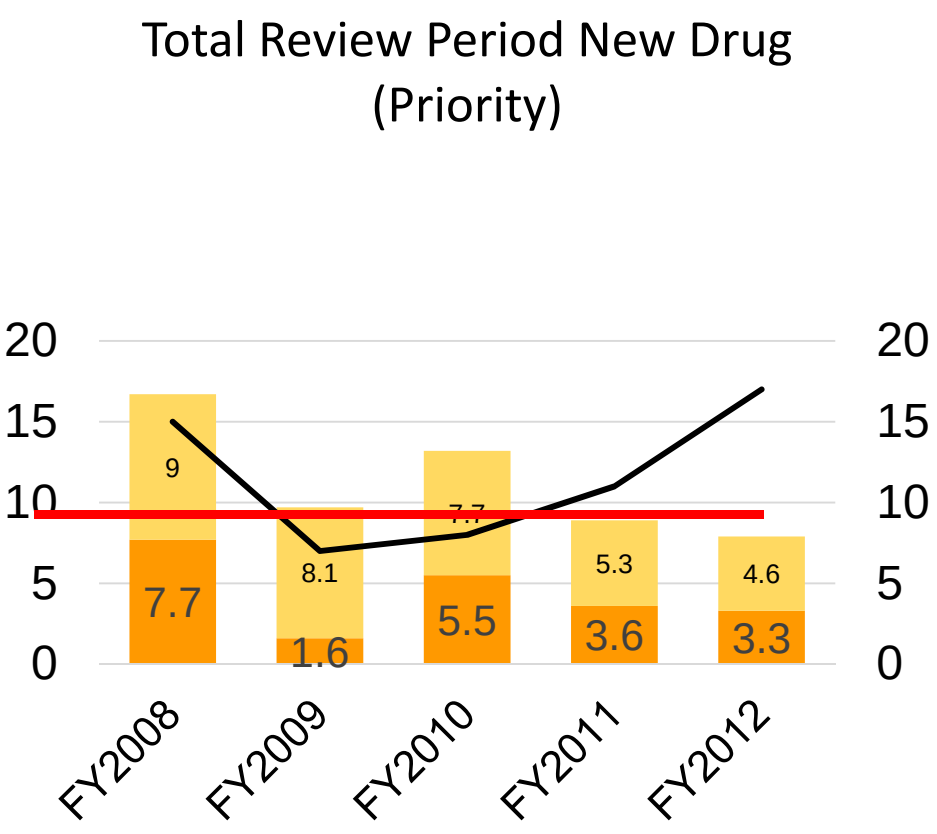
As of October 1, 2013

PMDA Staff Size



Accelerating Review Period





	Percentile						Total Review Period
	2013	2014	2015	2016	2017	2018	
Standard	50	60	70	70	80	80	12mo.
Priority	50	60	60	70	70	80	9 mo.

Applicant
Regulatory
Number of application
Target Period

Issues of PMDA

1. Conducting review and consultation understanding of the research activities in state-of-the-art technologies,

2. Conducting review and consultation in the state-of-the-art technologies from early stage of development,

3. Training reviewers to catch up on the accelerating innovative technologies and contributing in the establishment of practical use of state-of-the-art technologies.

Science Board in 2012

For PMDA To Be More Science-Based

Basic Research

Seeds of new drug / medical devices

Quality Tests → Non-clinical tests → Clinical Trial → Review → Approve → Post Marketing

Practical use

Innovative medical products

Pharmaceutical consultation on R&D Strategy | Clinical Trial Consultation | Review | Post Marketing Safety Measure

Offices of Review (Drugs & Medical Devices), Office of Safety

Office of Review Innovation

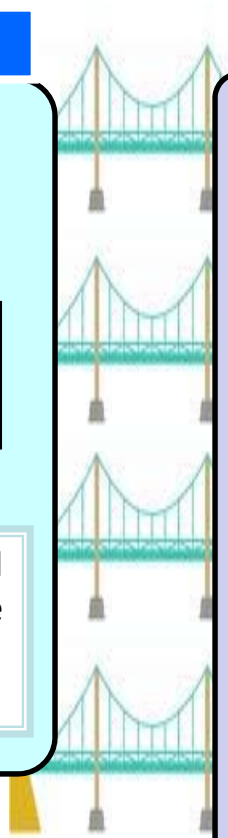
Establishment of the Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage such as basic research, development support, product review, and post market safety measures.

Board members

Academia

Science Board and Office of Review Innovation



Office of Review Innovation

Director General

Secretariat Director

Associate Director General

Mission

Reform PMDA review system and related services based on science with consideration of actual medical practices

PMDA Office

Review/ Audit/ Inspection

RS

Safety

SGD

Science Board

- **Committee members: External experts from Academia**
- **Declare Conflicts of Interest**
- **Not involved in the Review Process of individual products**

Committee

- Recommendation on PMDA tasks
- Improvements in the scientific aspects of review

Subcommittee

- Deliberation on problems in each field
- Collaboration with PMDA working team

Pharmaceuticals | Medical Devices | Bio-based Products | Cellular & Tissue-based products

Projects Across Multi-Offices in PMDA

RS: Office of Regulatory Science
SGD: Office of Standards and Guidelines Development

Working Policy of Discussion on Subcommittee

Pharmaceuticals　Bio-based Products

Aiming at summary of " Recommendation for the review policy of the pharmaceuticals regarding personalized medicine" and discuss needed items in order of priority.

Cellular & Tissue-based Products

Discussing how to ensure the safety of cellular and tissue-based products and aiming at revealing the predictable risks in the products as possible.

Medical Devices

Starting from discussion about the common issues as many kind of medical devices as possible because of big differences among product attributes of the medical devices.

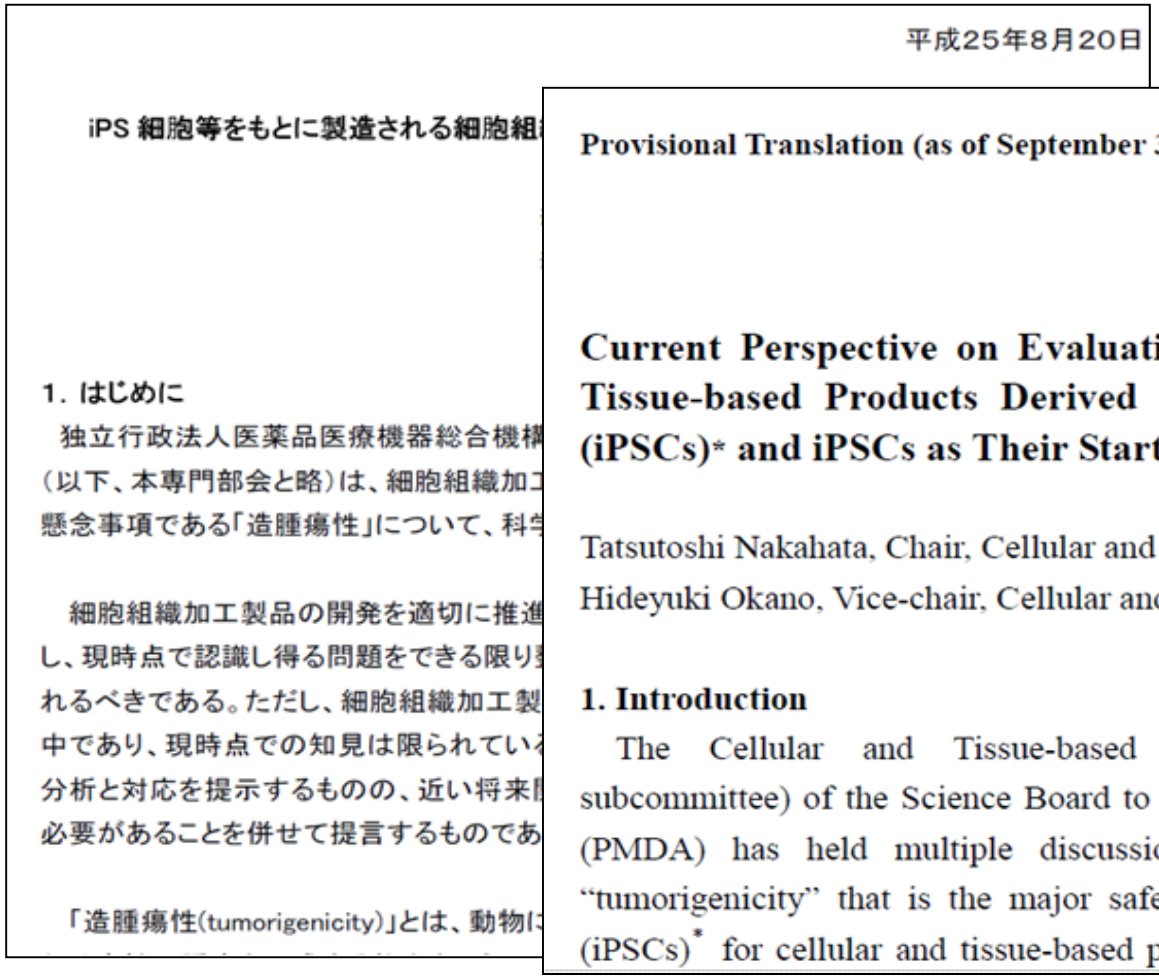
Cellular & Tissue-based Products

Theme: Scientific methods for examining tumorigenicity regarding the capabilities and limits of each test method, and presented the points for consideration.

- ➢ Discussed assay for appearing undifferentiated cells/tumorigenic cell contaminants as a cause of “tumorigenicity” in the products.
- ✓ Undifferentiated pluripotent cells are assessed by cell culture or animal model
  - The methods have to be more sensitive or quantified.

- ➢ Genetic abnormality that induces persistent cell proliferation
- ✓ Validate that the pluripotency inducing transgenes used for generation of iPSCs are not inserted into the host genome regardless of the approach used for transgene delivery.
- ➢ Genomic instability
- ✓ Confirm that the genomic mutation rate is not increased in iPSCs

Outcome of the Science Board



平成25年8月20日

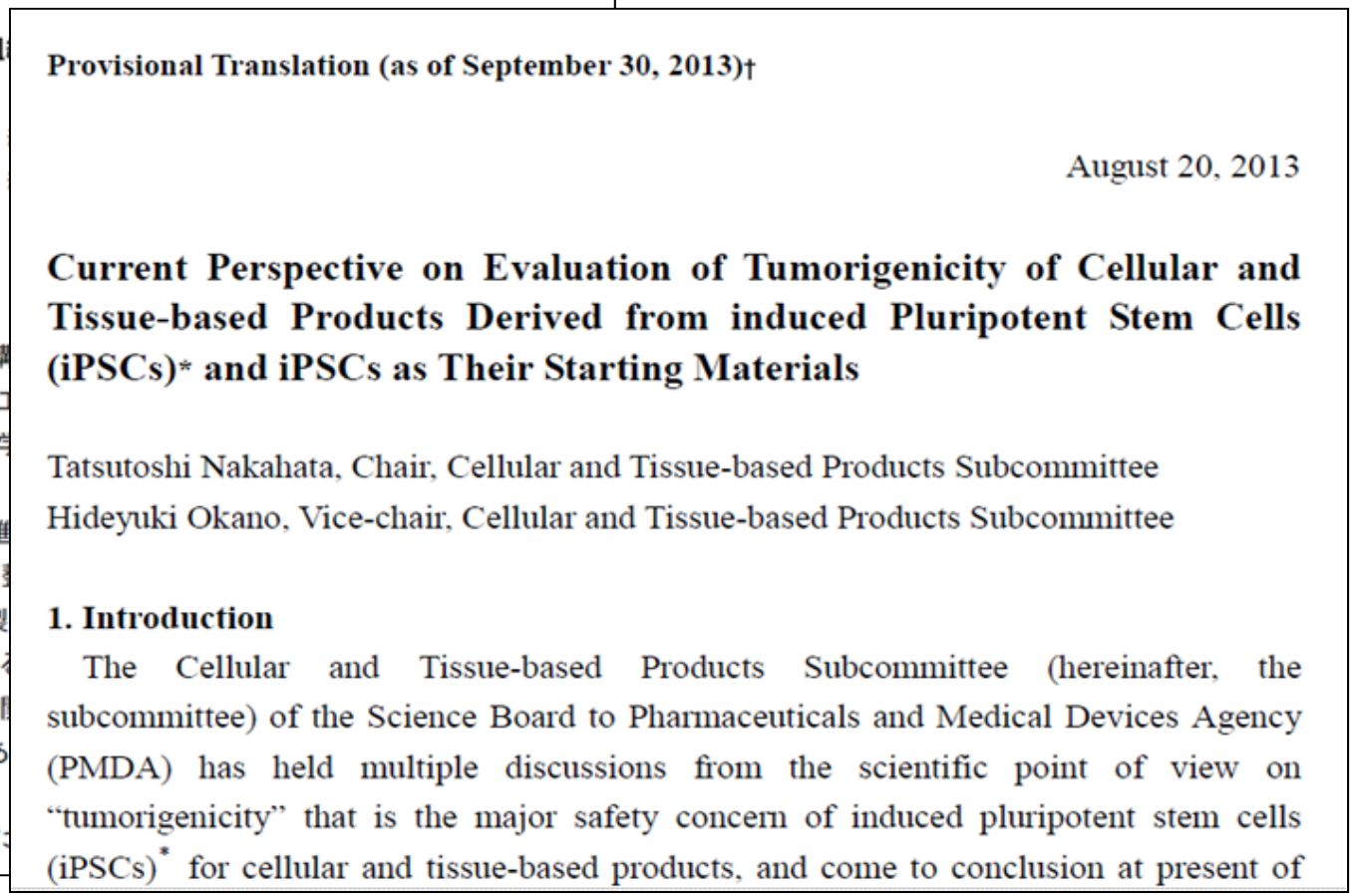
iPS 細胞等をもとに製造される細胞組

1. はじめに

独立行政法人医薬品医療機器総合機構
（以下、本専門部会と略）は、細胞組織加工
懸念事項である「造腫瘍性」について、科学

細胞組織加工製品の開発を適切に推進
し、現時点で認識し得る問題をできる限り
れるべきである。ただし、細胞組織加工製
中であり、現時点での知見は限られてい
分析と対応を提示するものの、近い将来
必要があることを併せて提言するものであ

「造腫瘍性(tumorigenicity)」とは、動物に



Provisional Translation (as of September 30, 2013)†

August 20, 2013

Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials

Tatsutoshi Nakahata, Chair, Cellular and Tissue-based Products Subcommittee
Hideyuki Okano, Vice-chair, Cellular and Tissue-based Products Subcommittee

1. Introduction

The Cellular and Tissue-based Products Subcommittee (hereinafter, the subcommittee) of the Science Board to Pharmaceuticals and Medical Devices Agency (PMDA) has held multiple discussions from the scientific point of view on "tumorigenicity" that is the major safety concern of induced pluripotent stem cells (iPSCs)* for cellular and tissue-based products, and come to conclusion at present of

Japanese

English（Provisional Translation）

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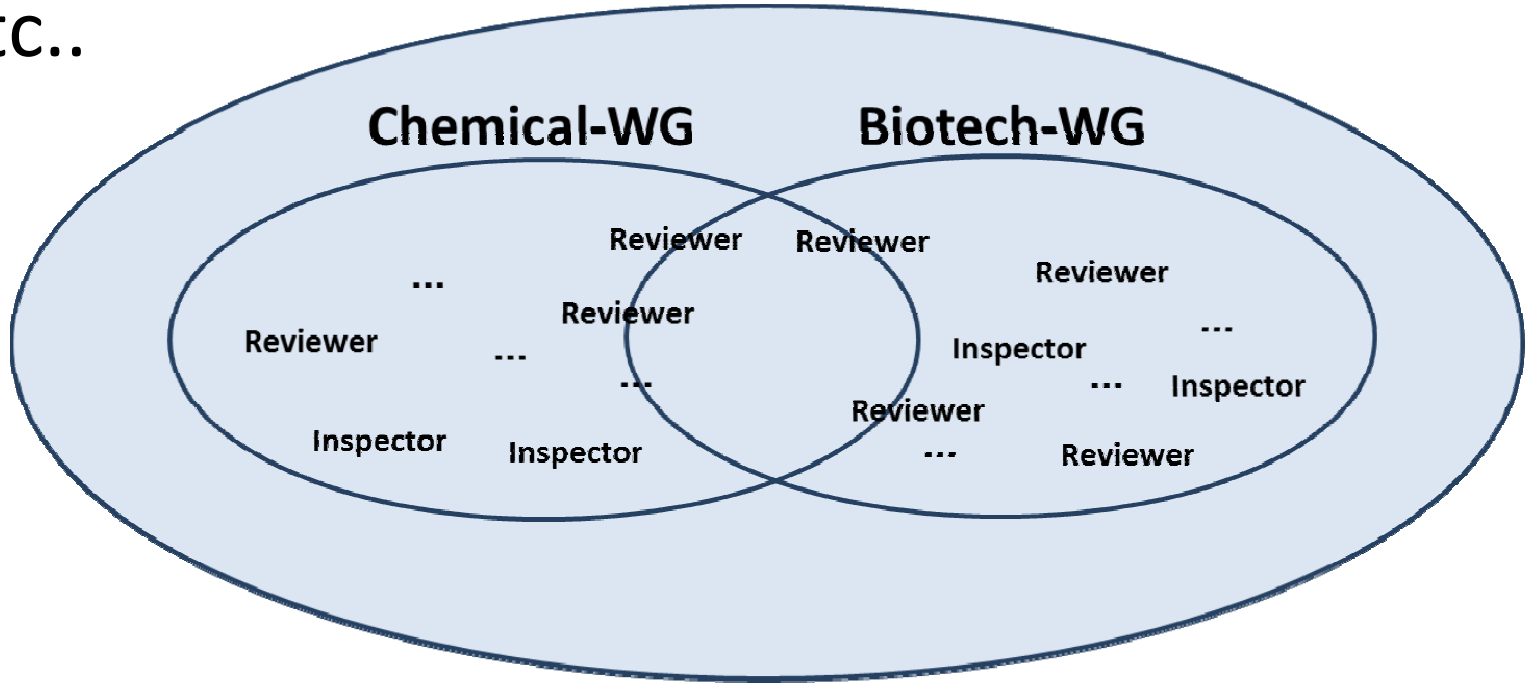
QbD Assessment Project (1)

- In November 2011, PMDA launched a new project team to handle the participation in the EMA-FDA pilot program as an observer.
- The project team consists of reviewers, inspectors, etc..



QbD Assessment Project (2)

- The team participates in teleconferences, supports core reviewers of each QbD application, and shares the experiences learnt from the project with CMC reviewers in PMDA.

- With the agreement of applicant, PMDA participated in…

- 2 parallel assessment applications
- Comments on 2 sets of Q&As (total 15) published by EMA&FDA on Aug 20 and Oct 24, 2013.

What PMDA learnt

- Many our concerns about QbD applications were basically same as the EMA and FDA.
- The different regulatory framework might result in the different decision, especially in the different post approval change actions.

Post-approval change Procedure

Risk of Changes	Japan	US	EU
High	**Partial change application (PCA)** (Application for approval of variation)	Prior Approval Supplement	Type II variation
Moderate	**Minor change notification (MCN)** (Notification within 30 days after shipping)	Changes-being-effected-in-30-Days (CBE-30)	Type IB variation
Low		Changes-being-effected (CBE-0)	Type IA_{IN} variation
		Annual report	Type IA_{AR} variation

Quality Review/Regulation in Japan

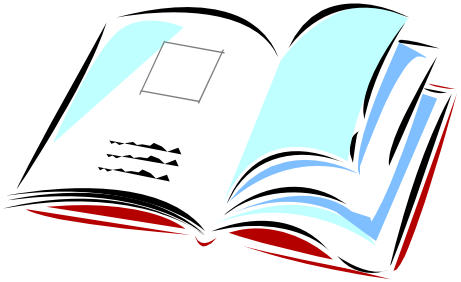
Approval Matters | **Major review document**

Module 1
Application form
(in Japanese)

- Specification
- Shelf life
- Mfg. process
- Mfg. site
- Etc.

PCA/MCN

Module 2 (QOS)
(in Japanese)



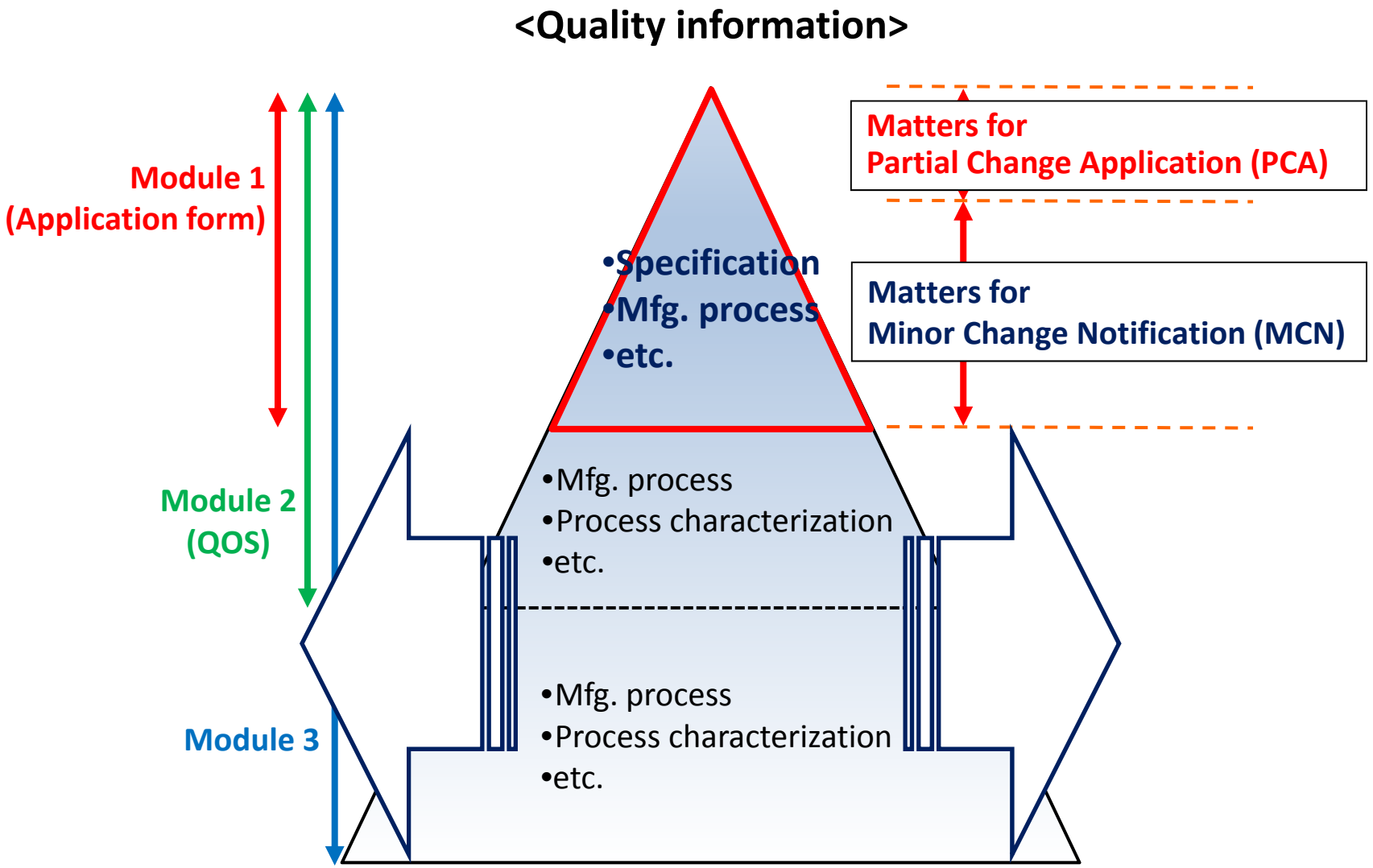
2.3.S.1 General Information
2.3.S.2 Manufacture
2.3.S.3 Characterisation
2.3.S.4 Control of Drug Substance
2.3.S.5 Reference Standards or Materials
2.3.S.6 Container Closure System
2.3.S.7 Stability
.....

Module 3
(in Japanese or English)

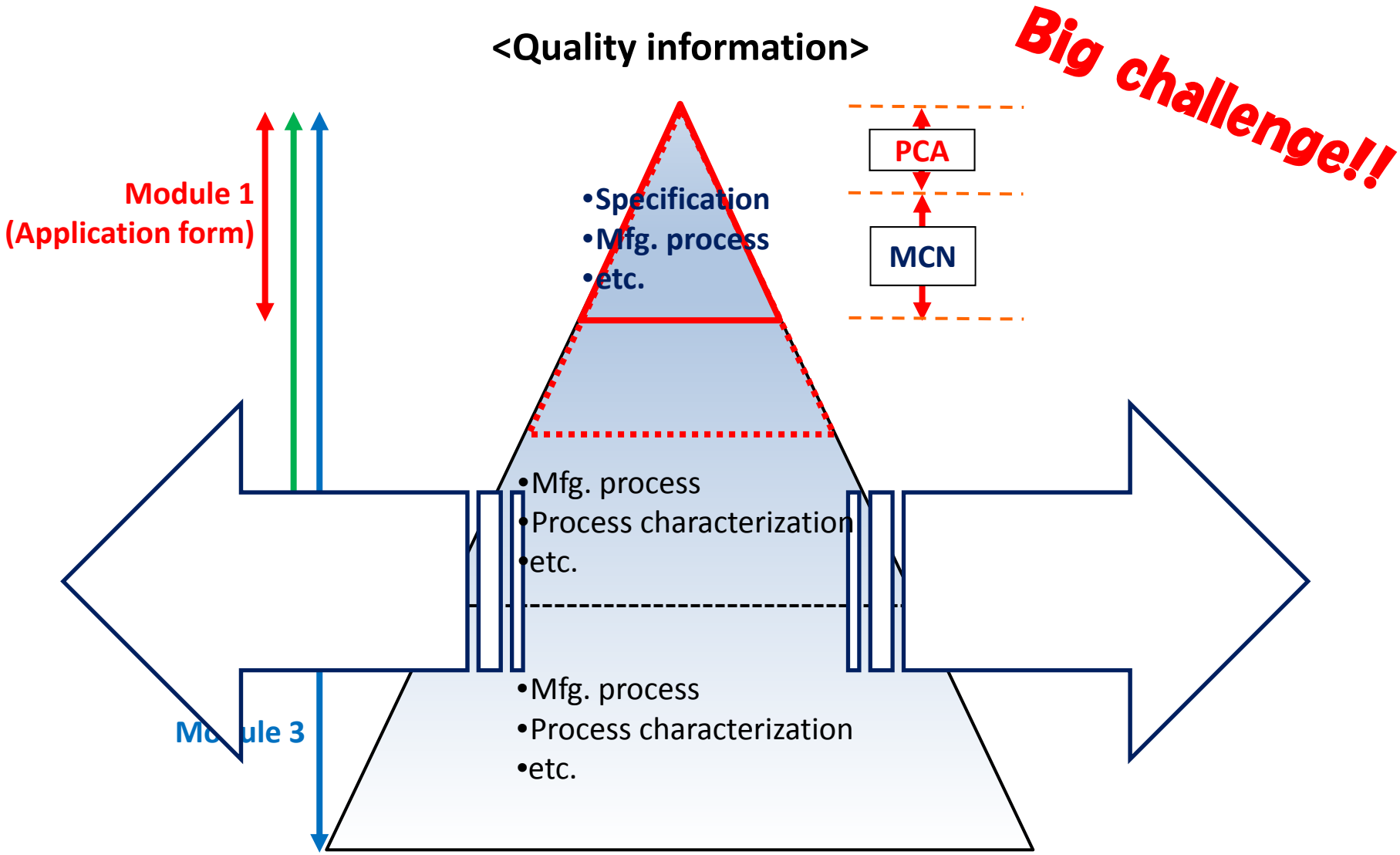
3.2.S.1 General Information
3.2.S.2 Manufacture
3.2.S.3 Characterisation
3.2.S.4 Control of Drug Substance
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability
.....

Raw data

QbD gives more flexibility in Post-approval changes in Japan?



QbD gives more flexibility in Post-approval changes in Japan?



PMDA Continues QbD Assement Project

06/03/2014

EMA and FDA extend pilot programme for parallel assessment of quality-by-design applications

As of 1 April 2014 the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) have agreed on a two-year extension of their joint pilot programme for the parallel evaluation of quality-by-design (QbD) applications.

This follows the success of the first phase of this programme initiated in April 2011 during which the agencies assessed in parallel the QbD elements of one marketing authorisation application and several scientific advice requests submitted by medicines developers.

Both agencies found these parallel assessments extremely useful and reached agreement on a wide range of QbD aspects leading to the publication of two guidance documents for the industry. Further guidance is being developed and is expected to be published in 2014.

Quality by design is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of the medicines; these concepts are described in the international guidelines ICH Q8, Q9, Q10 and Q11.

The objective of this parallel assessment is to share knowledge, facilitate a consistent implementation of the international guidelines on QbD aspects and promote the availability of pharmaceutical products of consistent quality throughout the European Union and the United States.

The programme is open to selected procedures, including applications for initial marketing authorisations, type-II variations and scientific advice. Participation in the pilot is voluntary. Applicants and sponsors should express their interest in participating in the programme to both agencies at least three months prior to submission of an application.

Applicants volunteering for this parallel assessment benefit from a harmonised evaluation of their application and receive a common list of questions/information requests or an agreed list of issues to be addressed from the two agencies for the parts of the application subject to the pilot.

With the agreement of the applicants, experts from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) participate as observers in the programme.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002035.jsp&mid=WC0b01ac058004d5c1

About the extension of the EMA-FDA pilot program of QbD

PMDA is ready for the participation of the extended EMA-FDA pilot program for Quality by Design as an observer.

In March 2014, EMA and FDA announced the two-year extension of the joint pilot program for the parallel evaluation of QbD applications. (EMA web site / FDA web site)

PMDA has been participating in the pilot program since December 2011, and involved in one parallel assessment application and one biotech product that followed the consultative advice pathway. In addition, we gave some comments on two sets of Q&As which have already published.

Now, PMDA is willing to participate in the pilot program as an observer again, expecting that our activity would facilitate QbD applications and harmonization in assessment among three regions.

PMDA believes that it brings a good opportunity for sponsors to get each regulator's perspective and comments on QbD , and that it will become a driving force for the efficient global development.

PMDA welcomes for sponsors participating in the pilot program. If you would expect to obtain feedback from PMDA, we recommend you to ask EMA or FDA for PMDA's participation as an observer.

http://www.pmda.go.jp/english/service/qbd_extension.html

- **PMDA Keens on Participating in this Program (as an observer).**

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Regulatory History and Status of Biosimilars

- Guideline
- Application Category for biosimilars
- Nomenclature rules

Q&A Q&A

Revision of Nomenclature rules

2005 2009 2010 2011 2012 2013 2014

Somatropin BS[Sandoz]

Epoetin alfa BS[JCR]

Filgrastim BS [F], [MOCHIDA]

Filgrastim BS [Sandoz]

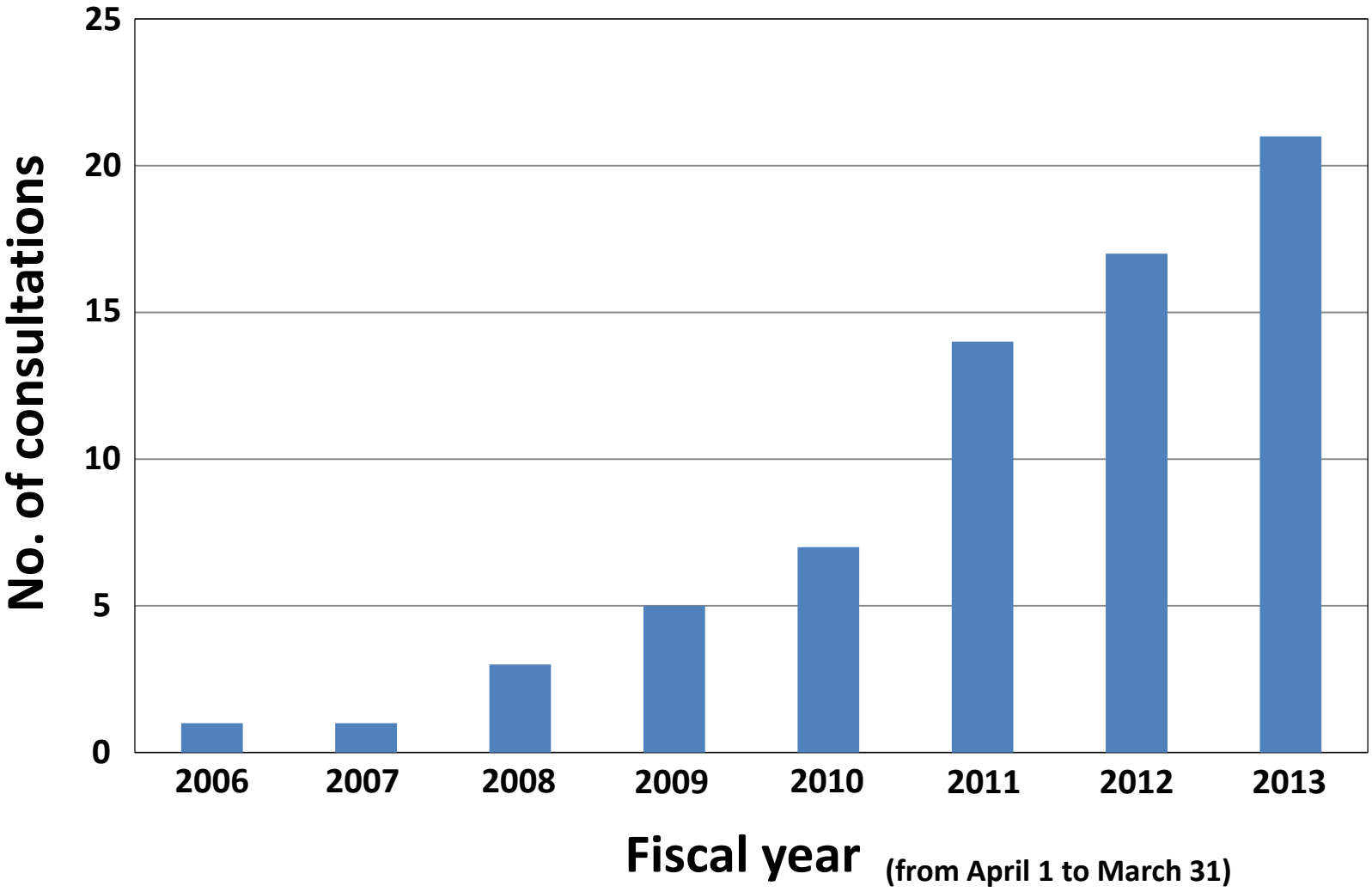
Filgrastim BS [NK], [TEVA]

List of Approved Biosimilars in Japan

Drug name	Japanese Accepted Name (JAN)	Manufacturer (Country)	Reference product	Approved year
Somatropin BS s.c. Injection 5mg [SANDOZ] etc.*1	Somatropin (genetical recombination)	SANDOZ(Austria)	Genotropin (Somatropin) (Pfizer)	2009.5
Epoetin alfa BS Injection 750 syringe [JCR] etc. *1	Epoetin Kappa (genetical recombination) [Epoetin Alfa Biosimilar 1]	JCR Pharmaceuticals (Japan)	Espo (Epoetin alfa) (Kyowa Hakko Kirin)	2010.1
Filgrastim BS Injection 75μg syringe [F] etc. *1,2	Filgrastim (genetical recombination) [Filgrastim Biosimilar 1]	Fuji Pharma (Japan)	Gran (Filgrastim) (Kyowa Hakko Kirin)	2012.11
Filgrastim BS Injection 75μg syringe [MOCHIDA] etc. *1,2	Filgrastim (genetical recombination) [Filgrastim Biosimilar 1]	Mochida Pharmaceutical (Japan)	Gran (Filgrastim) (Kyowa Hakko Kirin)	2012.11
Filgrastim BS Injection 75μg syringe [NK] etc. *1,3	Filgrastim (genetical recombination) [Filgrastim Biosimilar 2]	NIPPON KAYAKU (Japan)	Gran (Filgrastim) (Kyowa Hakko Kirin)	2013.2
Filgrastim BS Injection 75μg syringe [TEVA] etc. *1,3	Filgrastim (genetical recombination) [Filgrastim Biosimilar 2]	Teva Pharma Japan (Japan)	Gran (Filgrastim) (Kyowa Hakko Kirin)	2013.2
Filgrastim BS Injection 75μg syringe [SANDOZ] etc. *1	Filgrastim (genetical recombination) [Filgrastim Biosimilar 3]	SANDOZ(Austria)	Gran (Filgrastim) (Kyowa Hakko Kirin)	2014.3

*1: etc. means different presentations. *2: Same active substance, different applicants *3: Same active substance, different applicants

Number of Consultation for Biosimilars



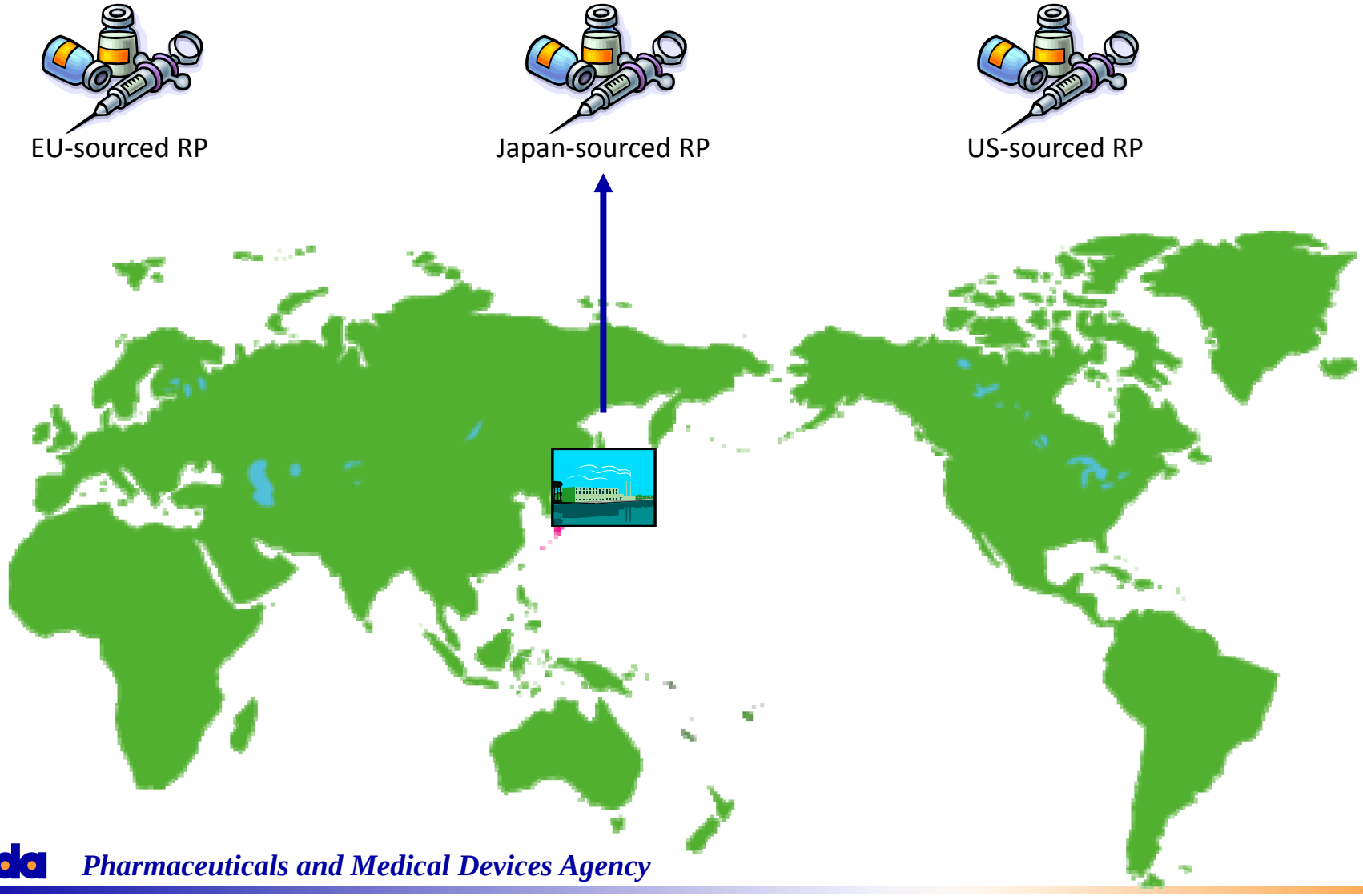
Based on date of application

What should be considered for the global development of biosimilars?

- Reference Product
- Clinical Trial

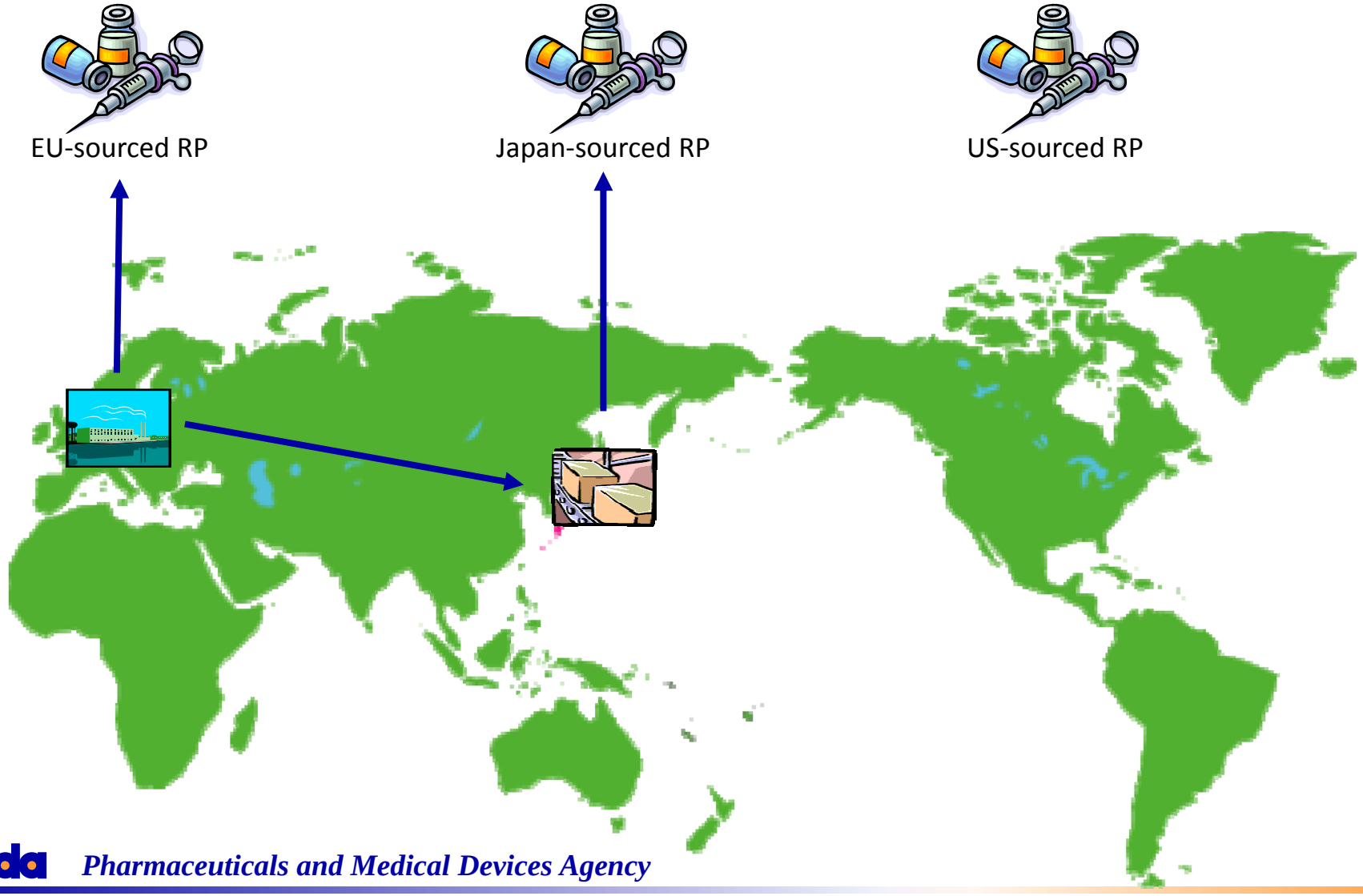
Reference Product (1)

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



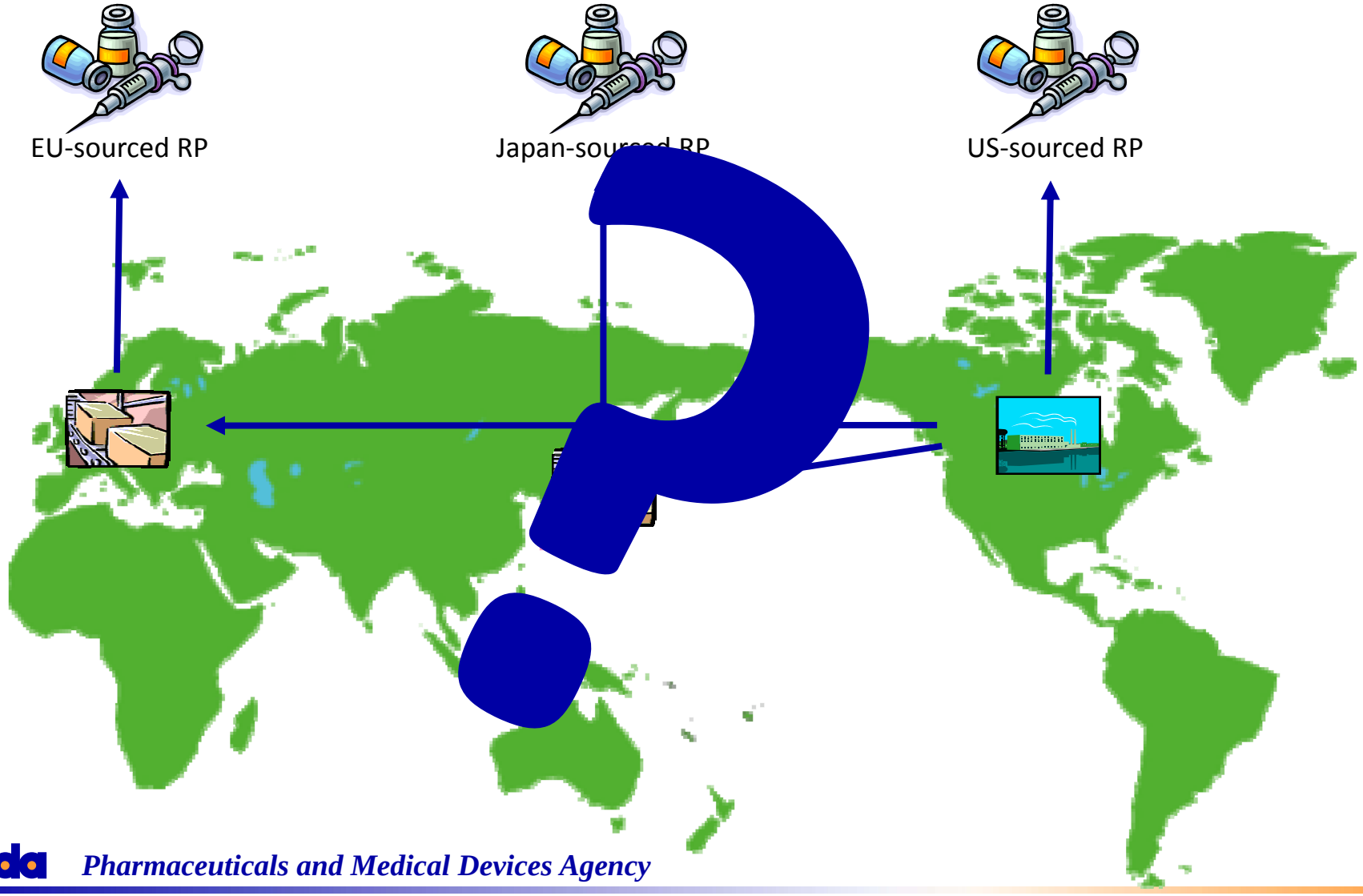
Reference Product (2)

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



Reference Product (3)

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



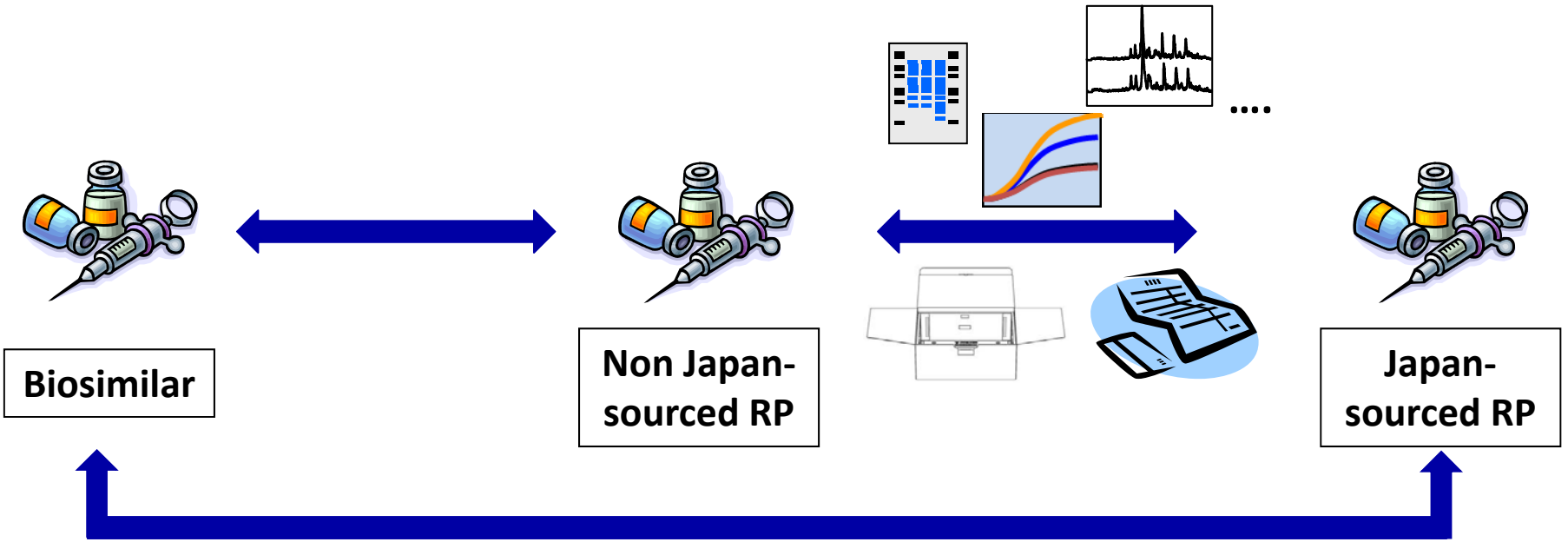
Reference Product

- Guideline

PMDA thinks the applicant should confirm the comparability to the reference product which is approved (and used by healthcare providers and patients) in Japan.

Reference Product

- However, if applicant 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 other available information.



What should be considered for the global development of biosimilars?

- Reference Product
- Clinical Trial

Global Clinical Trial (GCT)

Guidance

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

  (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 when GCT is designed.
- A global trial 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.

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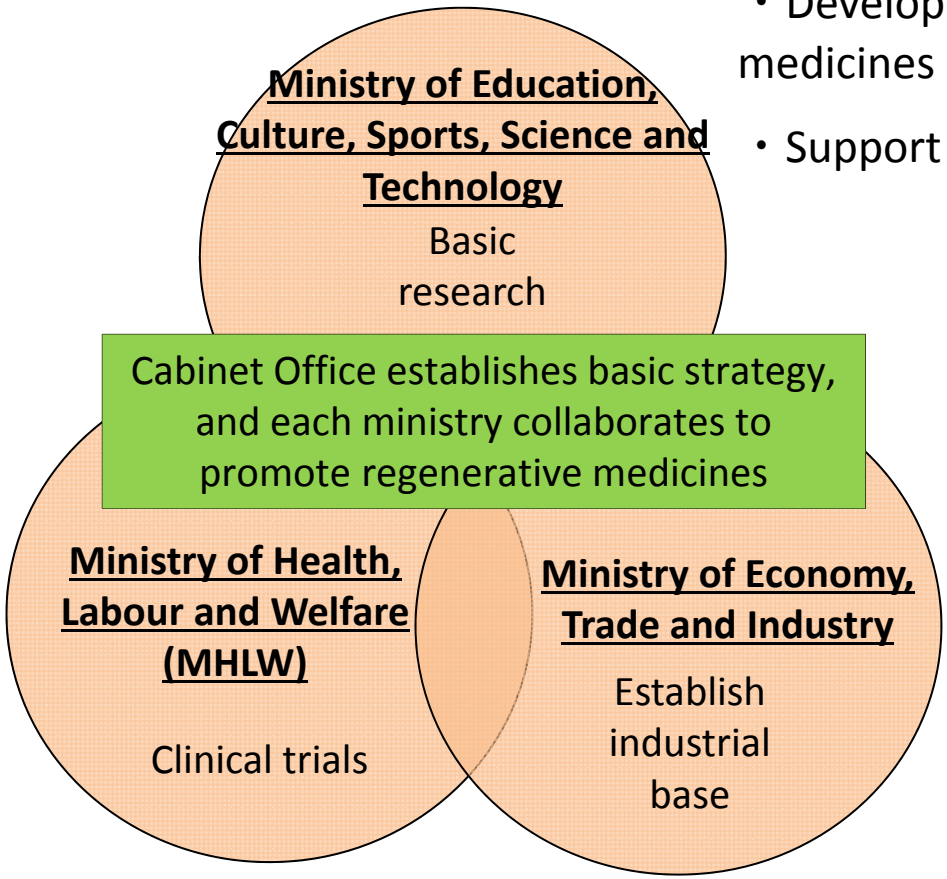
   - Regenerative Medicine
   - Advanced Review/Consultation

Government's Policy

Regenerative Medicine Promotion Law (Enacted in May 2013)

- Integrated supports from basic to clinical researches
- Development of infrastructure to promote regenerative medicines
- Support utilizing iPS cells as a drug-discovery tool



Goals for the next 7 years

- To apply new drugs developed by iPS cell technology to clinical trials
- To increase the number of approved cellular therapeutic products
- To expand the target diseases in clinical trials
- To develop equipment or devices related to regenerative medicine

→2 Acts have been passed the Diet in Nov. 2013

Revision of Pharmaceutical Affairs Law

◆ Revisions of Drugs and Medical Devices Articles

- Relevant party's obligations are specified to ensure quality, safety, and efficacy of drugs and medical devices.
- MAH's obligation to notify labeling and its revision, reflecting the latest findings

◆ Revisions of Medical Devices Articles

- Independent Chapter for "Medical Devices"
- Expansion of Third party certification system to higher risk devices
- Quality Management System (QMS) adherent to ISO 13485
- Other revisions related to medical devices

◆ Additions for Regenerative Medical Products

- Definition and independent chapter for Regenerative Medical Products
- Introduction of conditional/time limited approval system

The Act on Pharmaceuticals and Medical Devices (PMD Act)

Background of additions for regenerative medical products

Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells

→ To secure timely provision of safe regenerative medicines, a new framework is needed

Expedited approval system for regenerative medical products

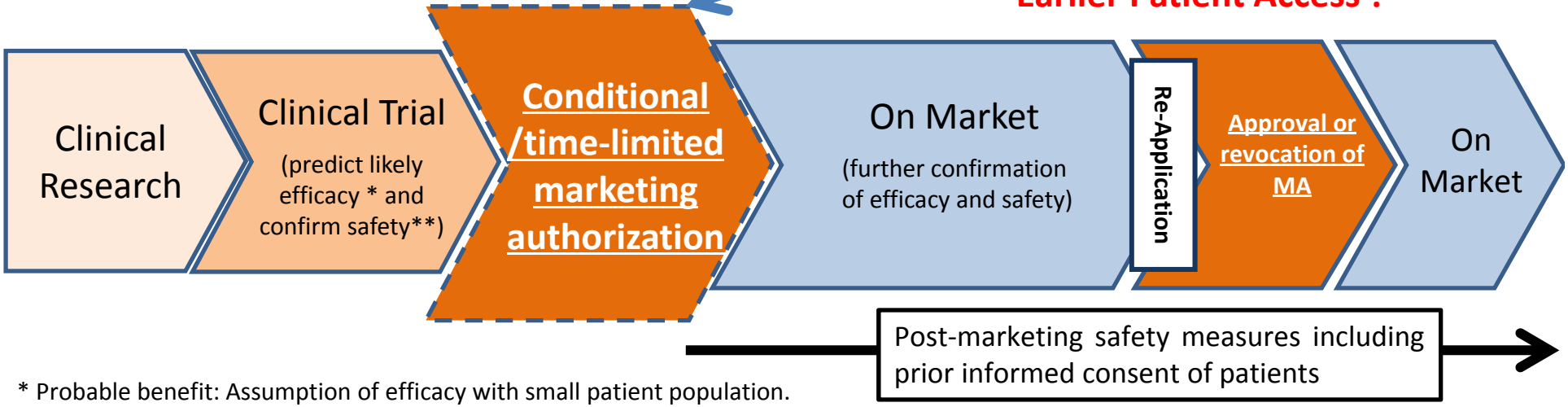
After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.

New Marketing Authorization in PMD Act

【Traditional Pathway of approval】

【New Pathway for regenerative medical products】

※ Leading to Earlier Patient Access !



* Probable benefit: Assumption of efficacy with small patient population.
** Safety: Earlier detection and evaluation of adverse events.

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   - Regenerative Medicine
   - Advanced Review/Consultation System

Advanced Review/Consultation System

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

A rational & effective evaluation process for regulatory decision

Practical use of Innovative Medical Products

NDA etc.

e-Submission of study data

Accumulation data

Database

Sophisticated NDA review

- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis

- Innovative evaluation methods
- Active utilization of Modeling & Simulation
  - ➢ Disease model
  - ➢ Objective B/R assessment
  - ➢ Identifying AE-related factors etc.

Sophisticated Consultation

- More evidence-based consultation

Effective and High Quality Review

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific regulatory decision

Effective and Successful Development

- Epoch-making proposal leading the world
- Proactive publication of guideline

We look forward to welcoming you!

CMC Strategy Forum Japan 2014

Monday, December 08 - Tuesday, December 09, Tokyo

JPMA

Thank you for your attention !

http://www.pmda.go.jp/