



Current Status and Perspectives on Pharmaceutical Products in Japan

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Agenda

- Introduction of PMDA
- Revised Pharmaceutical Affairs Act
- Revised Japanese Pharmacopoeia
- Collaboration with external organizations
- QbD applications in Japan
- ICH Q12

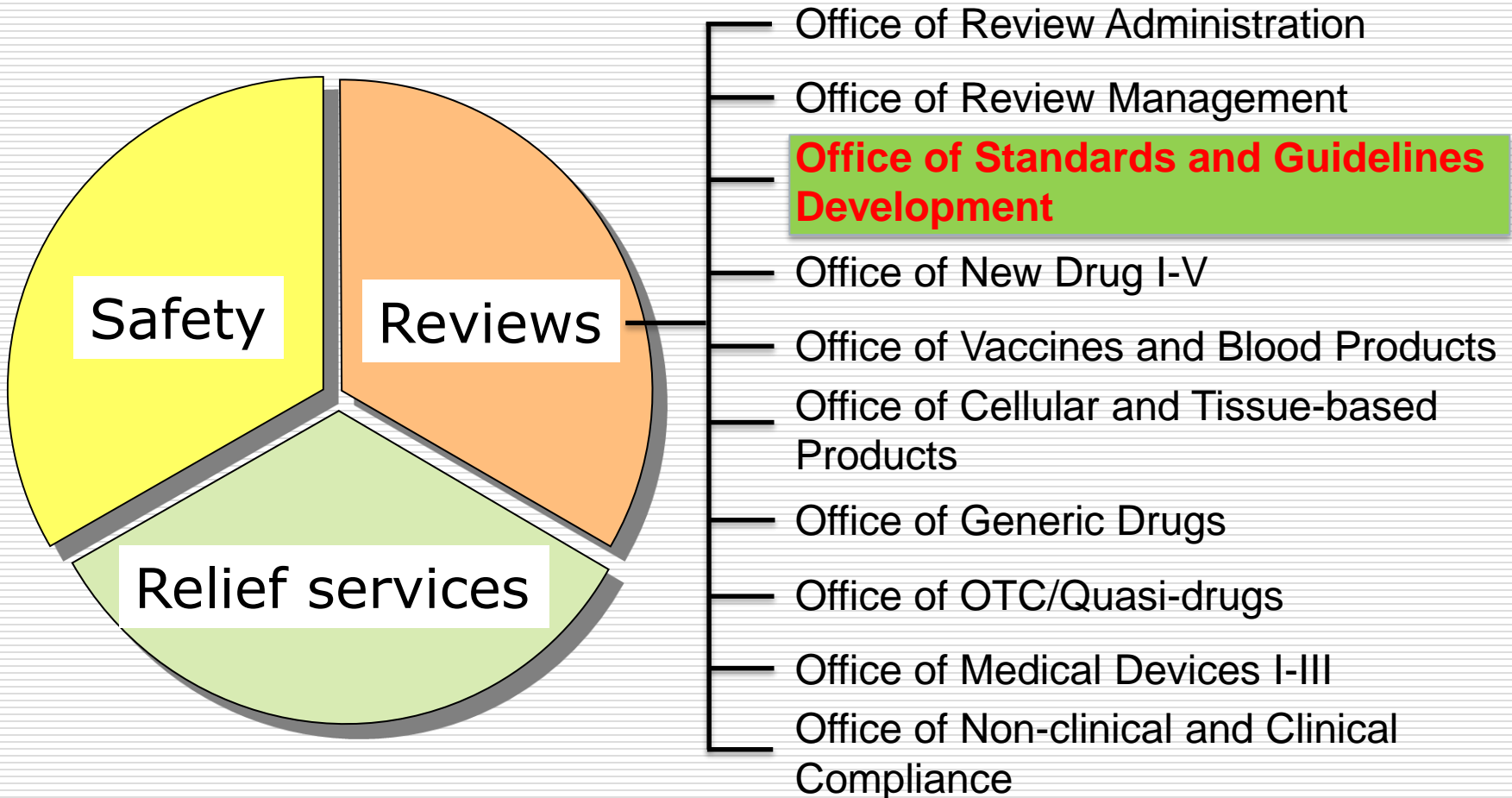
Introduction of PMDA



- ❑ Name : Pharmaceuticals and Medical Devices Agency
- ❑ Date of Establishment : In April 2004
- ❑ Established as an **Incorporated Administrative Agency**

<http://www.pmda.go.jp/english/index.html>

PMDA Organization



Introduction of the Office organization

Office of Standards and Guidelines Development

Division of Pharmacopoeia and Standards for Drugs

- Secretariat of Japanese Pharmacopoeia Expert committees
- **Projects Across Multi-Offices in PMDA** (ex. Review Guidelines)
- **Registration of Master Files for Drug Substances**

Division of Standards for Medical Devices

- Secretariat of Committees for Certification and Approval Standards
- Cooperation to Review Guidelines Development

The revision of Pharmaceutical Affairs Act (PAA)

- ❑ The revised PAA was enforced on November 25, 2014.
- ❑ Name of PAA was changed to “the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics”

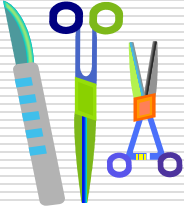
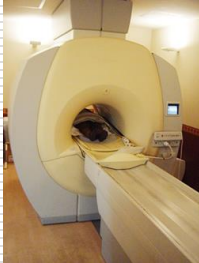




PMD Act

Safety Measures & Medical Devices

- **New Regulations** for Safety Measures
 - Pharmaceutical companies should notify the Ministry of Health, Labour and Welfare (MHLW) / PMDA about the contents of package inserts at the time of approval and revision.
 - Package inserts notified will be uploaded in a PMDA web-site.
- **New Regulations** for Medical Devices
 - Standalone Medical Device Software (SMDS) will be regulated as well as in US and EU.
 - Scope of third party certification will be expanded.

Overview of Medical Device Regulation

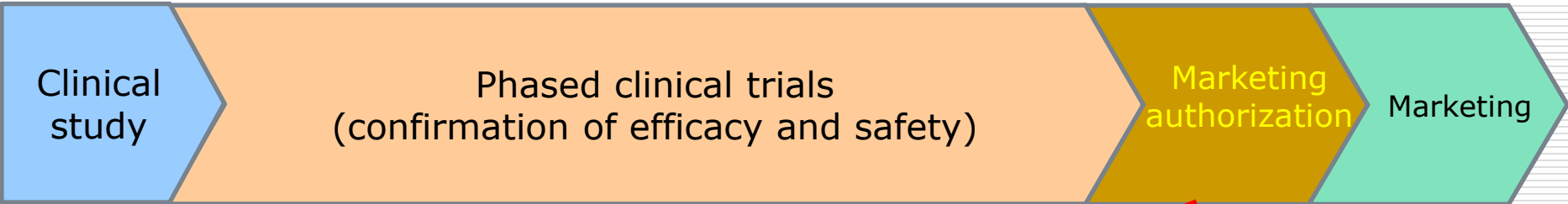
Classification	Class I	Class II	Class III	Class IV
	Extremely low risk	Low risk	Medium risk	High risk
Example	X-Ray film 	MRI 	Dialyzer, Artificial bone 	Pacemaker, Artificial heart valve 
Category	General MDs	Controlled MDs	Specially controlled MDs	
Review regulation	Self-declaration	Third party certification	Minister's approval (PMDA's review)	
Post-market safety vigilance/surveillance	<p>PMDA and MHLW</p> <p>Re-examination or Use-results survey for Brand New MDs, Re-evaluation, AE reporting, Researches, etc.</p>			

Regenerative Medicines

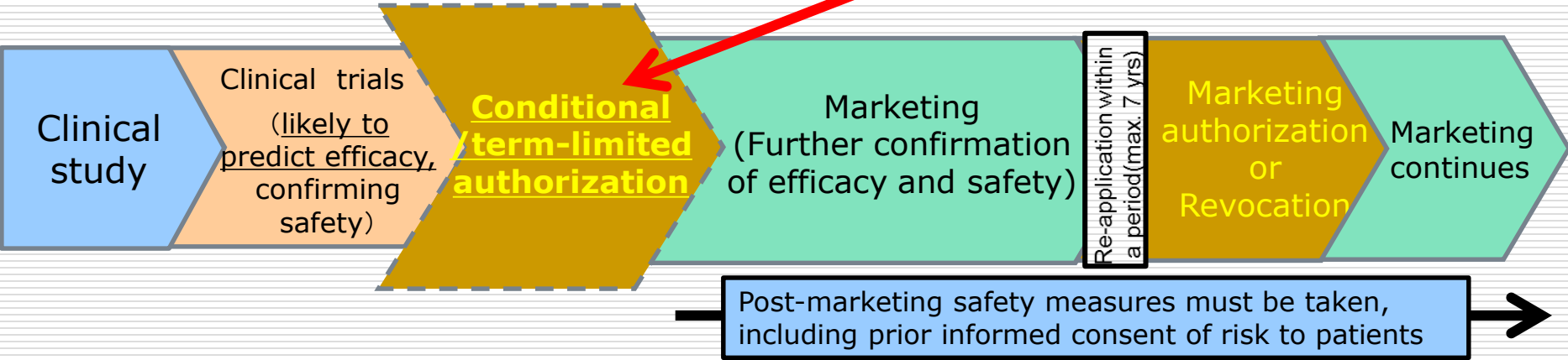
- **New Regulations** for Regenerative Medicines
 - Approval system for earlier commercialization of regenerative medicine products:
 - Introduction of Tentative Approval with conditional / term-limited authorization.
 - This is because regenerative medicines generally have characteristics that the qualities are not homogeneous.
 - Efficacy and safety will be further confirmed after tentative approval.

Expedited approval system under PMD Act

Traditional approval process



New scheme for regenerative medicines



SAKIGAKE Designation System

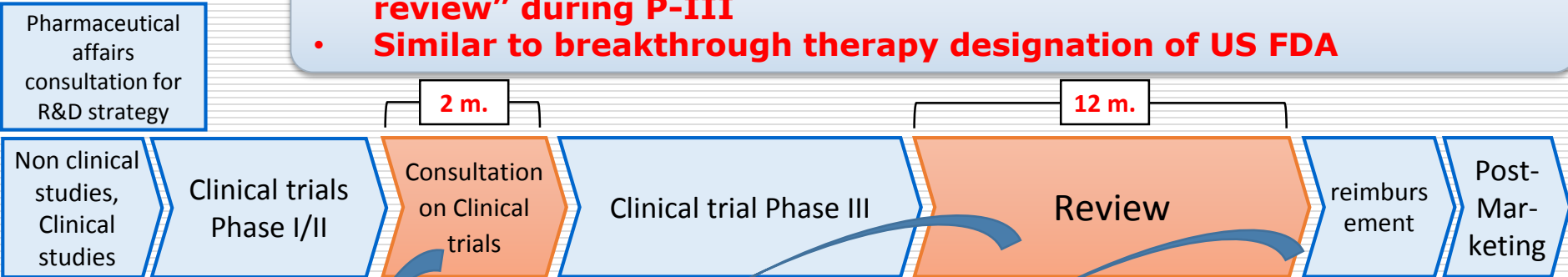
- ❑ SAKIGAKE is a system to put into practice innovative medicines/medical devices/ regenerative medicines initially developed in Japan.
- ❑ Designation Criteria
Medical products for diseases in dire need of innovative therapy and satisfies the following two conditions:
 1. **Having developed firstly in Japan and anticipating an application** for approvals (desirable to have PMDA consultation from the beginning of R&D)
 2. **Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected** based on the data of mechanism of action from non-clinical study and early phase of clinical trials (phase I to II)

Not limited to life-threatening and regenerative medicine

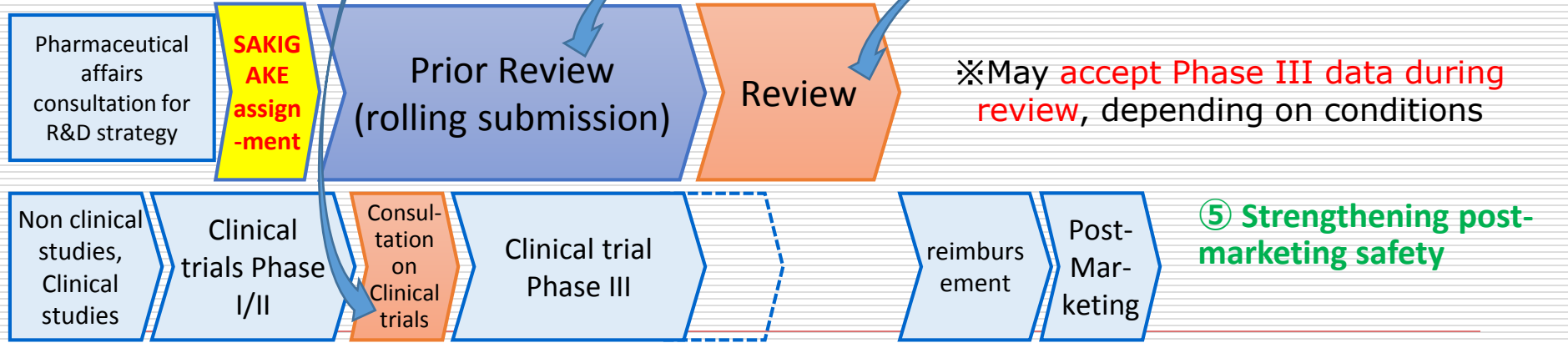
General Timeframe of SAKIGAKE

【Standard】

- Shorten review time, using rolling submission of data as “prior review” during P-III
- Similar to breakthrough therapy designation of US FDA



【SAKIGAKE】



The Japanese Pharmacopoeia (JP)

- JP was first published on June 25, 1886 and implemented on July 1, 1887
 - *JP has a 129 year history*
- JP is the official, public and transparent standard set for ensuring Quality of Pharmaceuticals, prepared by the JP secretariat in PMDA and published by the Ministry of Health, Labour and Welfare (MHLW) **as a Ministerial Notification.**
- JP has been **revised periodically.**
- **JP 17 will be published in February, 2016.**



Overview of the 17th JP

- Improving quality by positive introduction of **latest science and technology**
 - Introduce the new sections in JP by referring to European Pharmacopoeia (EP)
- Promoting **internationalization** of JP
 - Introduce the philosophy of ICH guidelines into JP as well as EP and United States Pharmacopeia (USP)

New sections

□ Seizo Yoken:

- Referring to “Production” section in EP.
- Statements under the heading Seizo Yoken draw attention to particular aspects of the manufacturing process.
- They relate to source materials; to the manufacturing process itself and its validation and control; to in-process testing etc..



We expect that “Seizo Yoken” section can facilitate to carry biotech products and products developed by QbD in JP

New sections (continued)

- Itoteki Konnyu Yugai Busshitsu:
 - Referring to “Potential Adulteration” section in EP.
 - Information of fraudulent activities and cases of adulteration.
 - A method for the detection of potential adulterants and relevant limits are included in this section of monographs.



The JP can take account of cases of adulteration such as Over Sulfated Chondroitin Sulfate (OSCS) in Heparin Sodium quickly and appropriately.

Introduction of ICH guidelines into JP

- The philosophy of **ICH Q6A/B** was introduced into the general information in JP.
- **ICH Q9** was introduced into the general information in JP.
- **ICH Q3C** was introduced into Residual Solvents Test in JP.



We expect that there will no longer be difference of control strategy between New Drugs and Drugs in JP in the near future.

PMDA International Strategic Plan 2015

Vision I : To contribute to the world through regulatory innovation

Vision II: To maximize the common health benefits to other countries/regions

Strategy 2: Promotion of international regulatory harmonization and global cooperation

1. Expediting the global utilization of the Japanese Pharmacopoeia (JP)

- ① Further expedite harmonization of the JP, the United States Pharmacopeia (USP) and the European Pharmacopoeia (EP) through the activities of the Pharmacopoeial Discussion Group (PDG)
- ② Contribute to improving quality of pharmaceuticals that are globally distributed, by proactively incorporating in the JP the concept of quality assurance based on cutting-edge science, and by promoting JP as one of the reference pharmacopoeia in other countries/regions

Vision III: To share the wisdom with other countries/regions

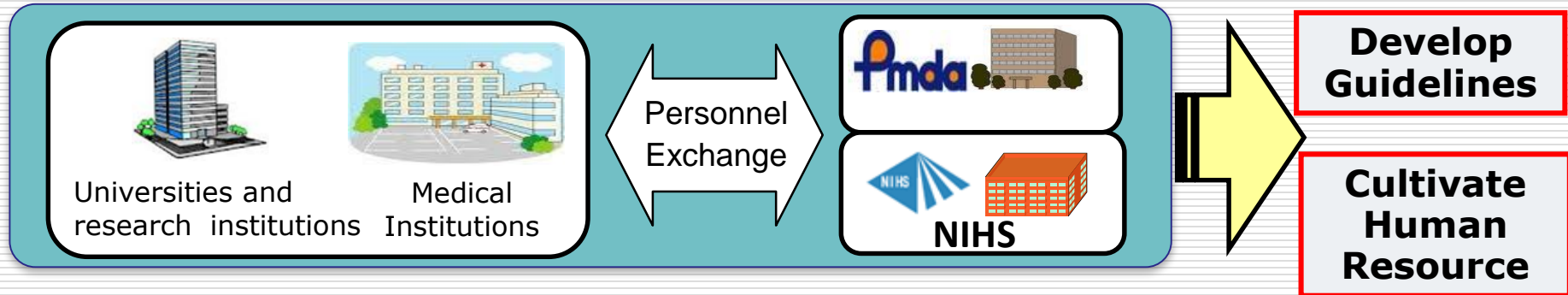
<http://www.pmda.go.jp/english/int-activities/outline/0017.html>



Collaboration with external organizations

- The EMA-FDA pilot program of QbD
 - PMDA participates in the program as an observer
- MHLW-sponsored Health Science studies
 - Sakura Bloom Tablets P2 Mock
 - CTD P.2 section for a drug product that had been developed by using the QbD methodology presented in ICH Q8,Q9,Q10 and Q11.
 - <http://www.nihs.go.jp/drug/DrugDiv-J.html>
 - Discussion of Analytical QbD
 - A mock will be posted for public review and comment soon.
- Joint MHLW/EMA reflection paper
 - Reflection paper on the development of block copolymer micelle medicinal products
 - <http://www.pmda.go.jp/files/000157408.pdf>

Current Works in CMC area



MHLW Nanomedicine Study Group (included Industries):

- Drafting a guideline for development of **Liposome Drug Products**
 - The draft guideline written in Japanese will be posted for public review and comment soon.
- Drafting a reflection paper for Drug Products carrying small interference RNA (**siRNA**).

QbD Applications in Japan


- Number of Approved Products with QbD

2008	2009	2010	2011	2012	2013	2014
3	3	2	11	11	12	27



Nowadays most applications usually apply QbD approaches.

Changes

- At the beginning of ICH Q-trio implementation
 - Applicants try to set **Design Space** for their flexibility.
- 
- Now
 - Applicants tend not to state the Design Space even if they have developed the Design Space.

Why?

- One of possibilities is
 - The Q&A at FDA-EMA QbD pilot program mentions Design Space **Verification**.



- Design Space allows for less flexibility compared to their effort such as Design Space Verification Activities or valid explanation of Design Space.

Current situation

- Industry's interest is moving to
 - Real Time Release Testing
 - Continuous Manufacturing
 - Lifecycle Management
 - Regulatory Commitment (Established Conditions)
 - Post-Approval Change Management Plans/Protocols

ICH Informal Quality Discussion Group (IQDG) in Minneapolis, 2014

- IQDG Quality Workshop
 - The 2003 Quality Vision expectation was achieved



However, more efforts are needed to fully address challenges and strengthen product lifecycle management

ICH Q12 : Pharmaceutical Product Lifecycle Management

ICH Q12

□ Objectives include:

- Provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle
- Optimization of industry and regulatory resources
- Support innovation and continual improvement and help to assure drug product supply

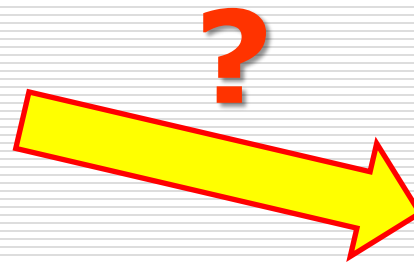
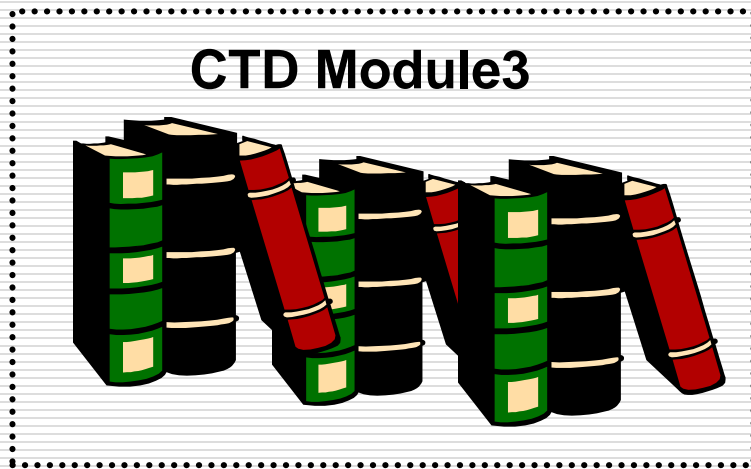
Issues to be addressed

- Established Conditions
- Post-Approval Change Management Protocols (PACMPs)

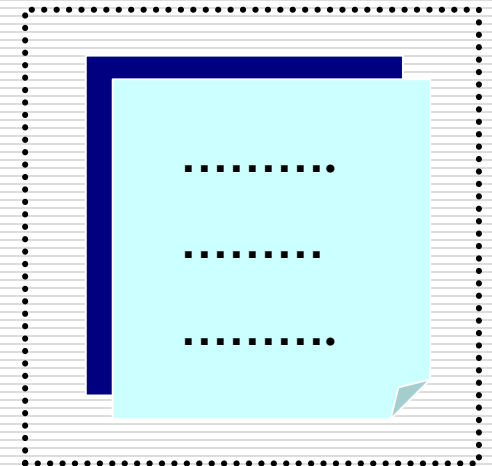
Established Conditions (1)

- Established Conditions for Manufacture and Control are binding information or elements concerning the manufacture and control of a pharmaceutical product, including description of the product, elements of the manufacturing process, facilities and certain equipment, specifications and other elements of the associated control strategy(e.g. storage conditions or shelf-life), found in a submission, that assure process performance and desired quality of an approved/licensed product.

Established Conditions (2)



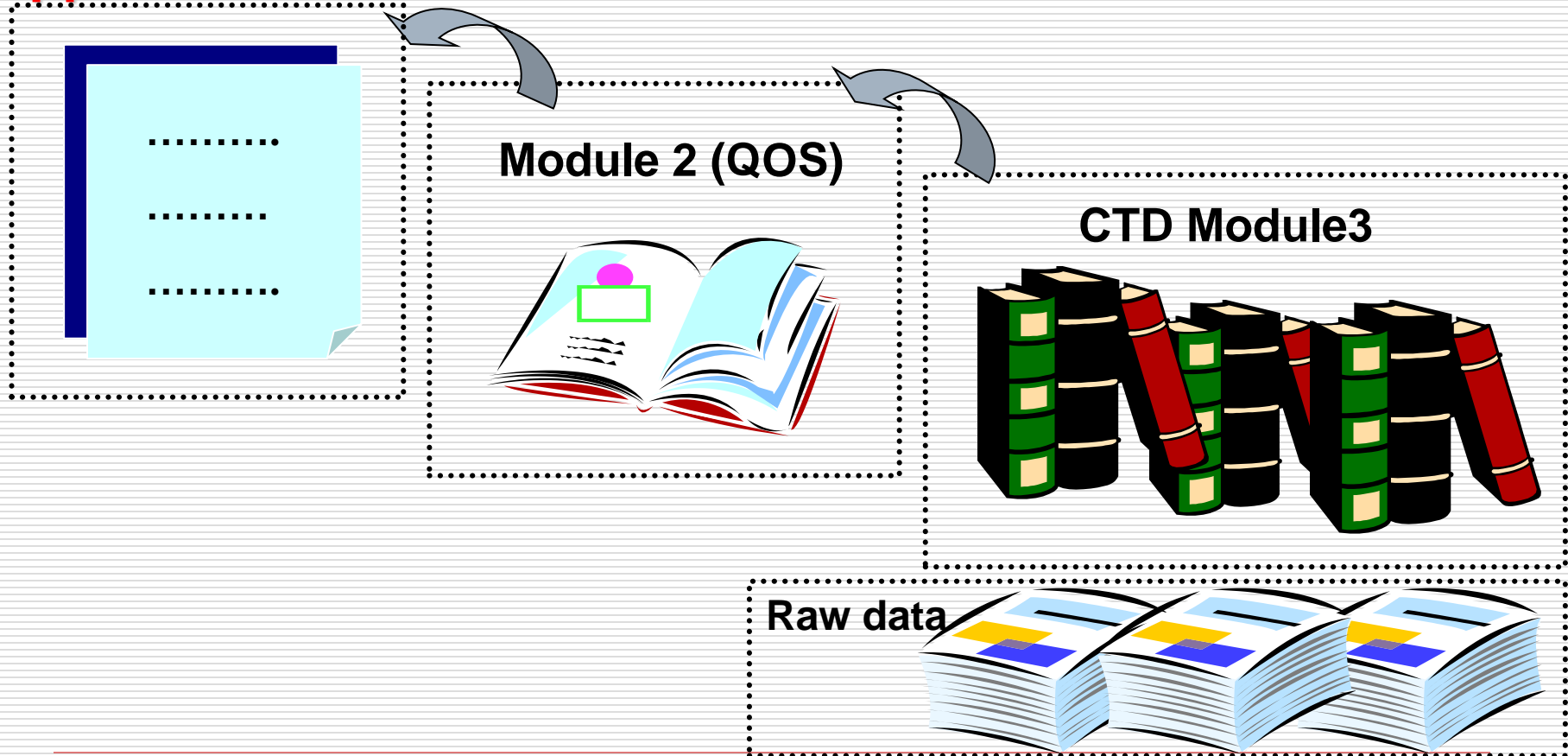
Established Conditions



- ① How to set Established Conditions from CTD Module3?
- ② How and where to describe Established Conditions in CTD?

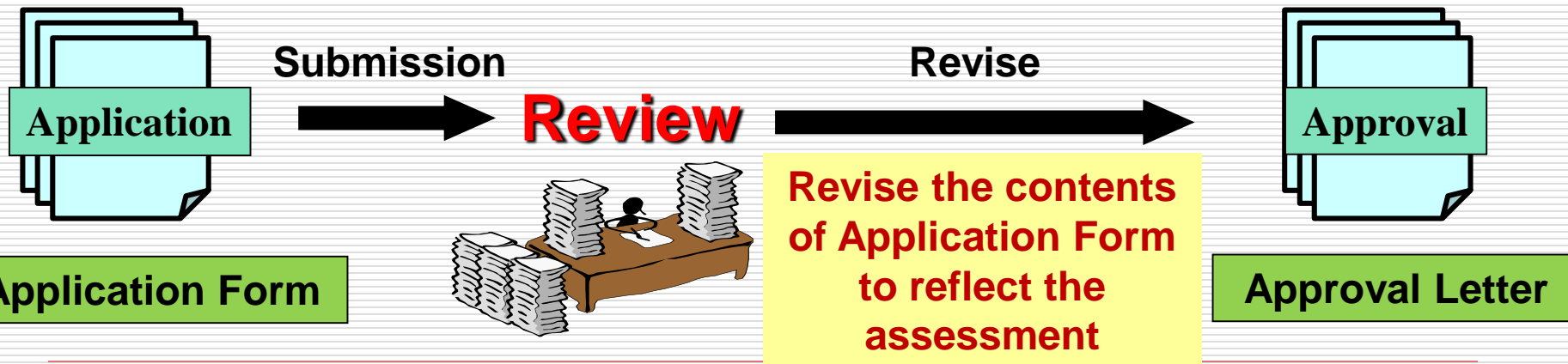
Relationship between **Application Form** and CTD Documents in Japan

Application Form



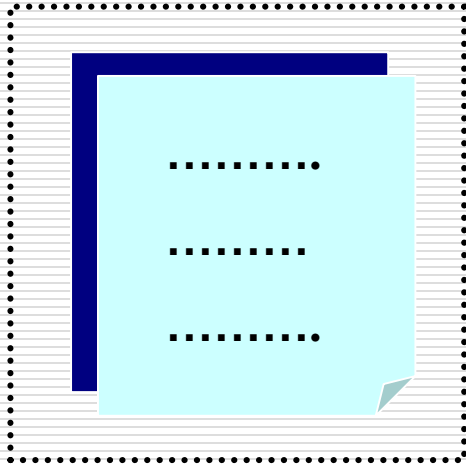
What is the Application Form?

- ❑ Contents provided in the **Application Form** by applicants are dealt with as “matters subject to approval.”
- ❑ Contents described in **Approval letter** are “legally binding” approval matters.

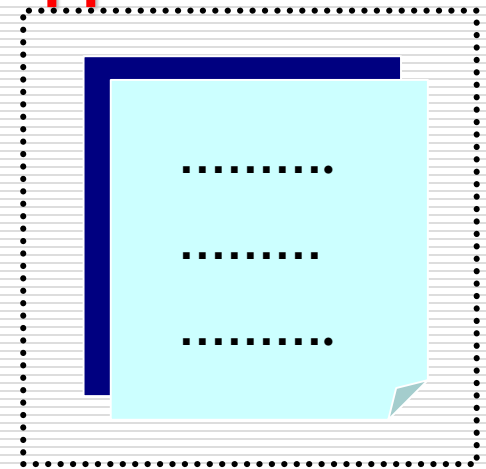


The main point at issue

Established Conditions



Application Form

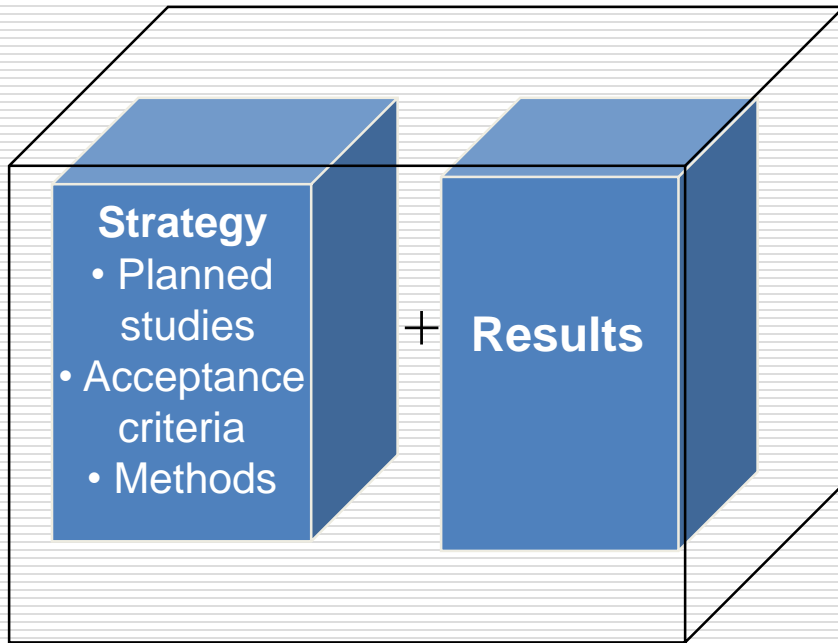


Post-Approval Change Management Protocols (PACMPs)

- ❑ A regulatory tool that enables prospective planning of future change(s) including the assessment of the impact of the proposed CMC change(s) to product quality.
- ❑ Describes specific change(s) a company would like to implement during lifecycle of a product and how these would be prepared and verified.
- ❑ May be submitted with the original marketing authorization or subsequently as a stand-alone submission.
- ❑ Companies may implement the change based on the established regional requirements without using a PACMP.

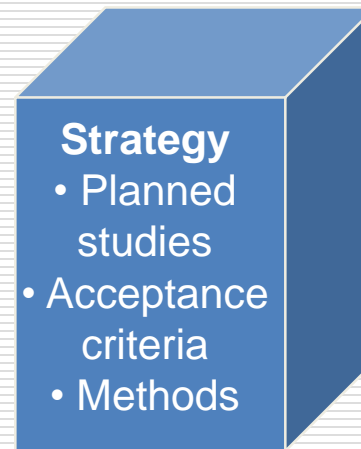
(EU) Principle of PACMP

Questions and answers on post approval change management protocols
(EMA/CHMP/CVMP/QWP/586330/2010)



Traditional

Evaluation of a proposed variation as a 'whole' (Strategy + Results)

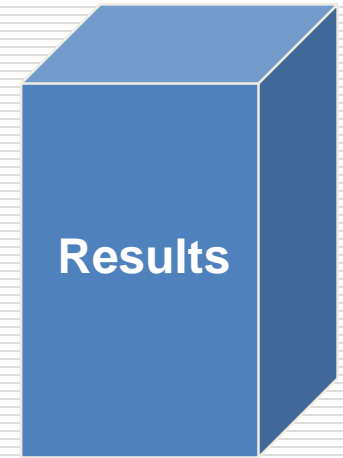


Early Step 1:

Submission of a Change Management Protocol



Type II Variation



Fast Step 2:

Reporting of implementation of a change in accordance with an approved protocol



Type IA or IB Variation

Post-authorization Procedure

Risk of Changes	Japan	US	EU
High	Partial change (Application for approval of variation)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	Minor change (Notification within 30 days after implementation or shipping)	Moderate change 1) Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2) Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low		Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

The main point at issue

- ❑ There is no system to accept only protocol in Japan.
- ❑ How to harmonize the concept of PACMP?



We are trying to introduce philosophy of PACMP in Japan.

Challenge for Patient and Industry!

Thank you for your attention

