ICH Q12

Challenges to Pharmaceutical Lifecycle Management

ICHの実装に向けて

JAPAN PHARMACEUTICAL MANUFACTURING ASSOCIATION

QUALITY COMMITTEE, ICH PROJECT

ICH Q12

TOMONORI NAKAGAWA

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed its directors, officers, volunteers, members, chapters, councils, affiliates, or any organization with which the presenter is employed or affiliated.

TOPICS

Background of developing ICH Q12 guideline

Highlights of ICH Q12 Guideline

- Outline of important section of the guideline

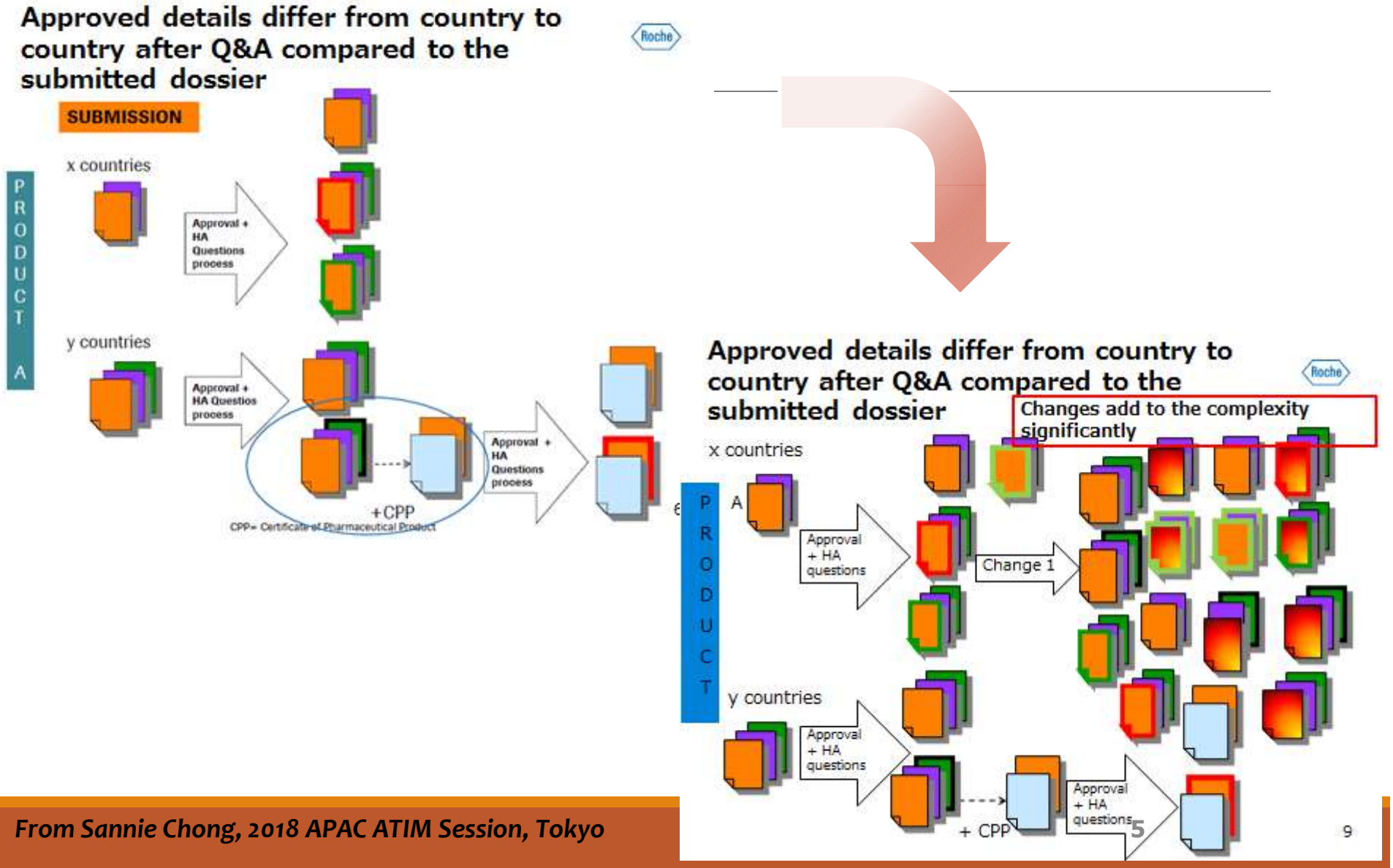
Introducing ICH Q12 guidelines

Implementation of PACMP

Work Continues

Background of developing ICH Q12 guideline

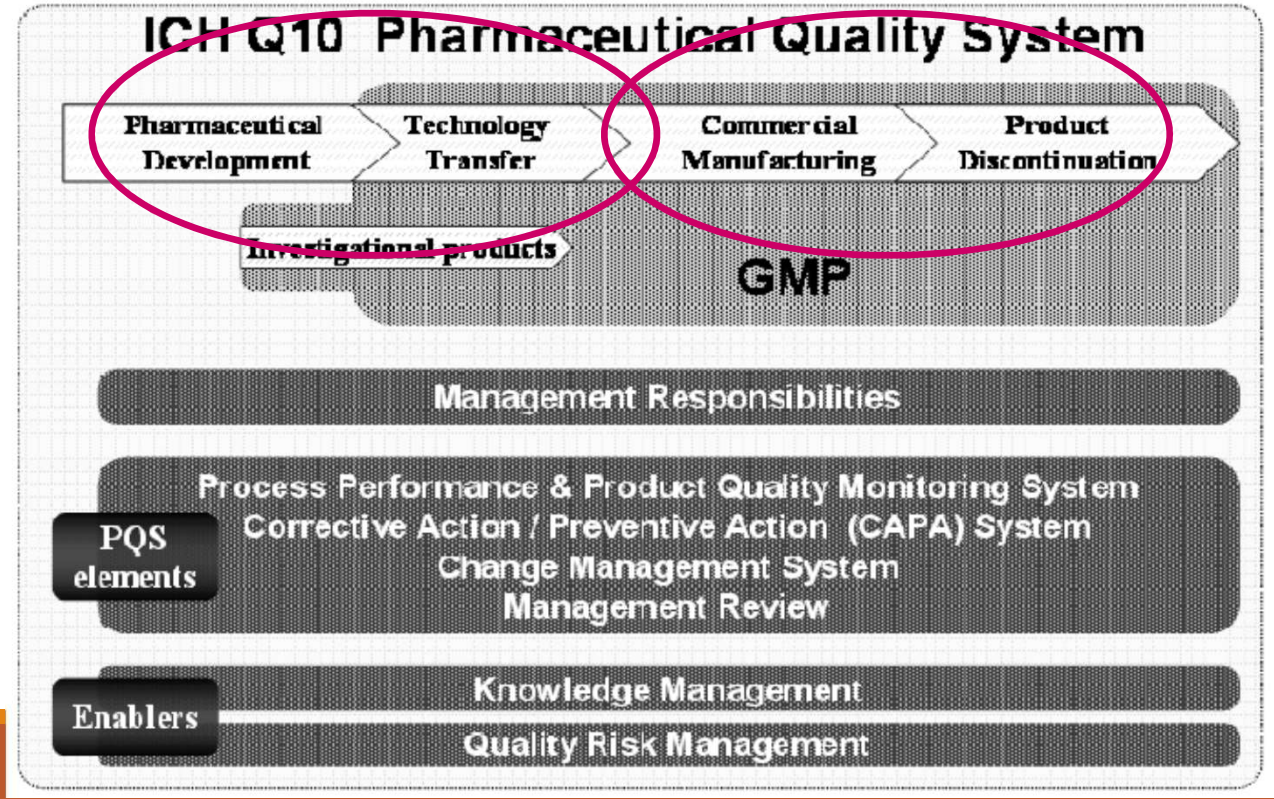
Complicated Product Lifecycle



From Sannie Chong, 2018 APAC ATIM Session, Tokyo

Expectations to “Product Lifecycle”

- Modernization of global regulation allowed develop of pharmaceutical products by multi-regional clinical study and the use of mutual data made possible global development of the product.
- Realization of “operational flexible” as proposed in ICH Q12 using QbD submission using the contents in ICH Q8-Q11
- Continuous improvement and operation using appearance of new technology



Post-approval Change Category

impact product quality	Japan	US	EU
High	Prior approval for changes	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	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	**SOP** (Under GMP change control)	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

Securing Supply Chain of Pharmaceutical Products

Throughout product lifecycle, it is more likely to outsource the pharmaceutical products to CMOs that have achieved low product quality risk

With complex pharmaceutical supply chain, it has become more important to secure the traceability of the product and clarify the responsibility of distributing the product

The demand to secure the traceability of the product have expanded from API to excipients

Issues to be Resolved

Regulatory Dossier
- Level of detail, Definition of ”Regulatory Commitment”

Pharmaceutical Quality System（PQS）aspects
- a harmonized risk-based change management system, Knowledge management

Post-Approval Change Management Plans and Protocols (PACMP)

（Reference）
- **Concept Paper**
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q12/Q12_Final_Concept_Paper_July_2014.pdf
- **Business Plan**
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q12/Q12_Final_Buisness_Plan_July_2014.pdf

Work in Progress

- June 2014, new topic was selected at Minneapolis
- Sept. 2014, approval of concept paper and business plan
- Nov. 2014, 1st EWG face-to-face meeting in Lisbon
- 9 face-to-face meetings including interim meetings
- Nov. 2017, approval of Step 2 document in Geneva
- June 2019, EWG face-to-face meeting after public consultation in Amsterdam
- Nov. 2019, last EWG face-to-face meeting in Singapore, adaptation of Step 4
- March 2020, Endorsement of ICH Q12 IWG for the Training Materials

Highlights of ICH Q12 Guideline

Purpose of ICH Q12

ICH Q12 **harmonized the change management** throughout the pharmaceutical product lifecycle as it was described in ICH Q8, Q9, Q10, and Q11

ICH Q12 guideline is established to have transparency between industry and regulators on changes made to **Chemistry, Manufacturing and Control (CMC)** and **Pharmaceutical Quality System (PQS)** and secure the stable supply of the product and mutual reliability

Step 4 document - Core Guideline-

1. Introduction
   - Objectives, Scope, Regulatory Tools and Enablers
2. Categorisation of Changes
3. Established Conditions
4. Post-approval Change Management Protocol
5. Product Lifecycle Management
6. Pharmaceutical Quality System and Change Management
7. Relationship Between Regulatory Assessment and Inspection
8. Structured Approaches for Frequent CMC Post-Approval
9. Stability Data Approaches to Support the Evaluation of CMC Changes

- Appendices

Step 4 document - Annex-

Annex I – Illustrative Examples

- Identification of Established Conditions for the Manufacturing Process - Chemical Medicinal Product
- Identification of Established Conditions for the Manufacturing Process - Biological Medicinal Product
- Identification of Established Conditions for Analytical Procedures
- PACMP Example 1
- PACMP Example 2
- Product Lifecycle Management Document - Illustrative Example

Annex II - Structured Approach to Analytical Procedure Changes

ICH Q12 Overview

- **Objective**

- … Harmonize change management… in a more transparent and efficient manner… across ICH regions
- … Facilitate risk-based regulatory oversight…
- Emphasize… control strategy as a key component of the… dossier
- Support continual improvement and facilitate introduction of innovation
- Enhance use of regulatory tools for prospective change management… enabling strategic management of post-approval changes…

Scope

- Applies to pharmaceutical drug substances and pharmaceutical drug products, including marketed chemical, and biotechnological/biological products.
- Applies to **drug-device combination products that meet the definition of a pharmaceutical or biotechnological/biological product**
- Changes needed to comply with revisions to Pharmacopoeial monographs are not in scope of this guideline

ICH Q12 Regulatory Tools and Enablers

Harmonised regulatory tools and enablers with associated guiding principles, will enhance the management of post-approval changes and transparency between industry and regulatory authorities, leading to innovation and continual improvement

- **Categorisation of Post-Approval CMC Changes（CH 2）** Categorisation of Post-Approval CMC Changes is a framework that encompasses a risk-based categorisation for the type of communication expected of the Marketing Authorisation Holder (MAH) with the regulatory authority regarding CMC changes

- **Established Conditions (EC) (CH 3）** The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the necessary elements to assure product quality and identify the elements that require a regulatory submission, if changed
  - This guideline describes how ECs are identified as well as what information can be designated as supportive information that would not require a regulatory submission, if changed.

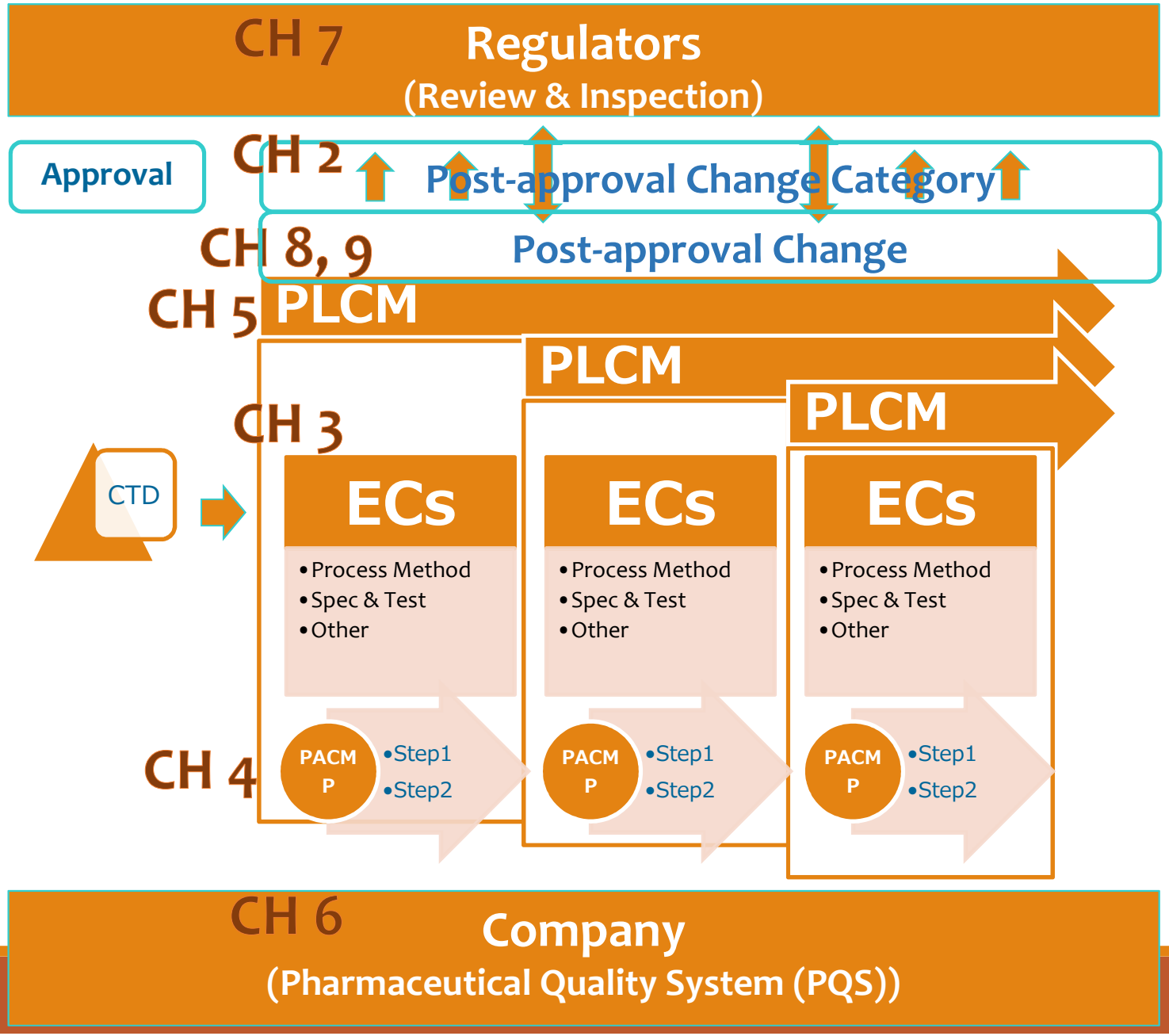
ICH Q12 Regulatory Tools and Enablers

- **Post-Approval Change Management Protocol (PACMP)(CH 4)** a regulatory tool that provides predictability regarding the information required to support a CMC change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority.
- **Product Lifecycle Management (PLCM)(CH 5)** document serves as a central repository for the ECs and the associated reporting category for changes made to ECs
  - The document also captures how a product will be managed during the commercial phase of the lifecycle including relevant post-approval CMC commitments and PACMPs.
- **An effective Pharmaceutical Quality System (PQS) as described in ICH Q10 and compliance with regional GMPs (CH 6)** are necessary for implementation of this guideline.
  - CMC change control management throughout supply chain is a must have as a part of effective change management

ICH Q12 Regulatory Tools and Enablers

- **Relationship Between Regulatory Assessment and Inspection(CH 7)** outlines the complementary roles of regulatory assessment and inspection, and how communication between assessors and inspectors facilitates the use of the tools included herein
- **Structured Approaches for Frequent CMC Post-Approval Changes (CH 8)** describes a strategy for a structured approach applicable to frequent CMC changes, and a discussion of data expectations, to enable the use of immediate or other post-implementation notification. Simplified approach to accomplish certain CMC changes for products whose marketing authorization did not involve identification of ECs and reporting categories
- **Stability Data Approaches to Support the Evaluation of CMC Changes (CH 9)** provides additional science- and risk-based approaches that are relevant to strategies for confirmatory stability studies to enable more timely implementation of CMC changes and the data needed to support the submission to the regulatory authority

Use of ICH Q12 Tools in Product Lifecycle

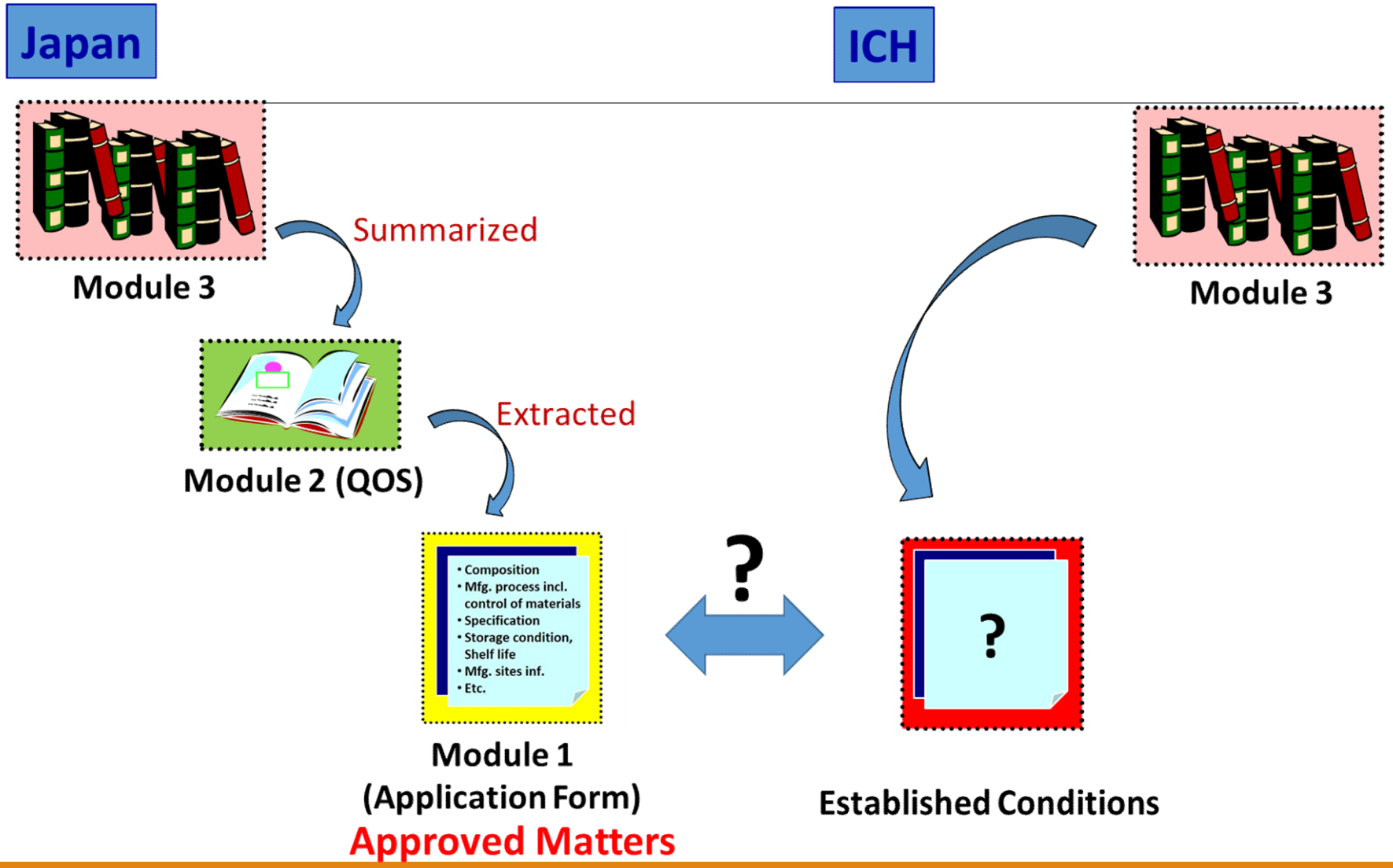


Identification of ECs

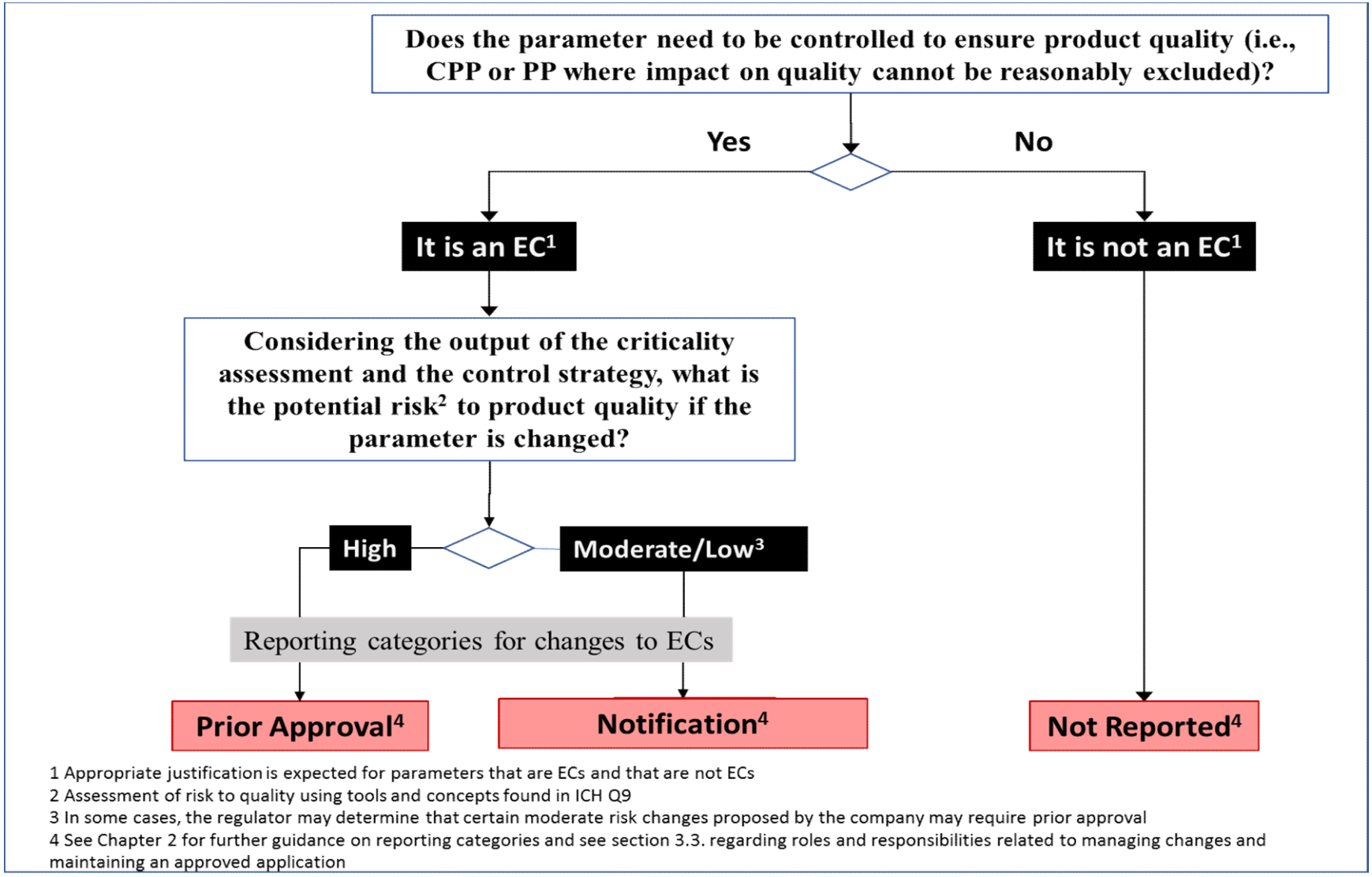
- The scope of EC depends on the company's developing method and potential risk reside in the product quality
- This guideline discusses the outline of the approaches available to determine the EC for manufacturing process and analytical method
- Other EC (performance of container closure) could be determined using similar approaches, however, it requires scientific justification to the regulator and need to be approved
- For better understanding of what is important and not important to determine the EC for securing product quality, a brief description of the manufacturing process need to be submitted

- **The use of this guideline need to be linked to CTD module 3**

Approved Matters and Established Conditions

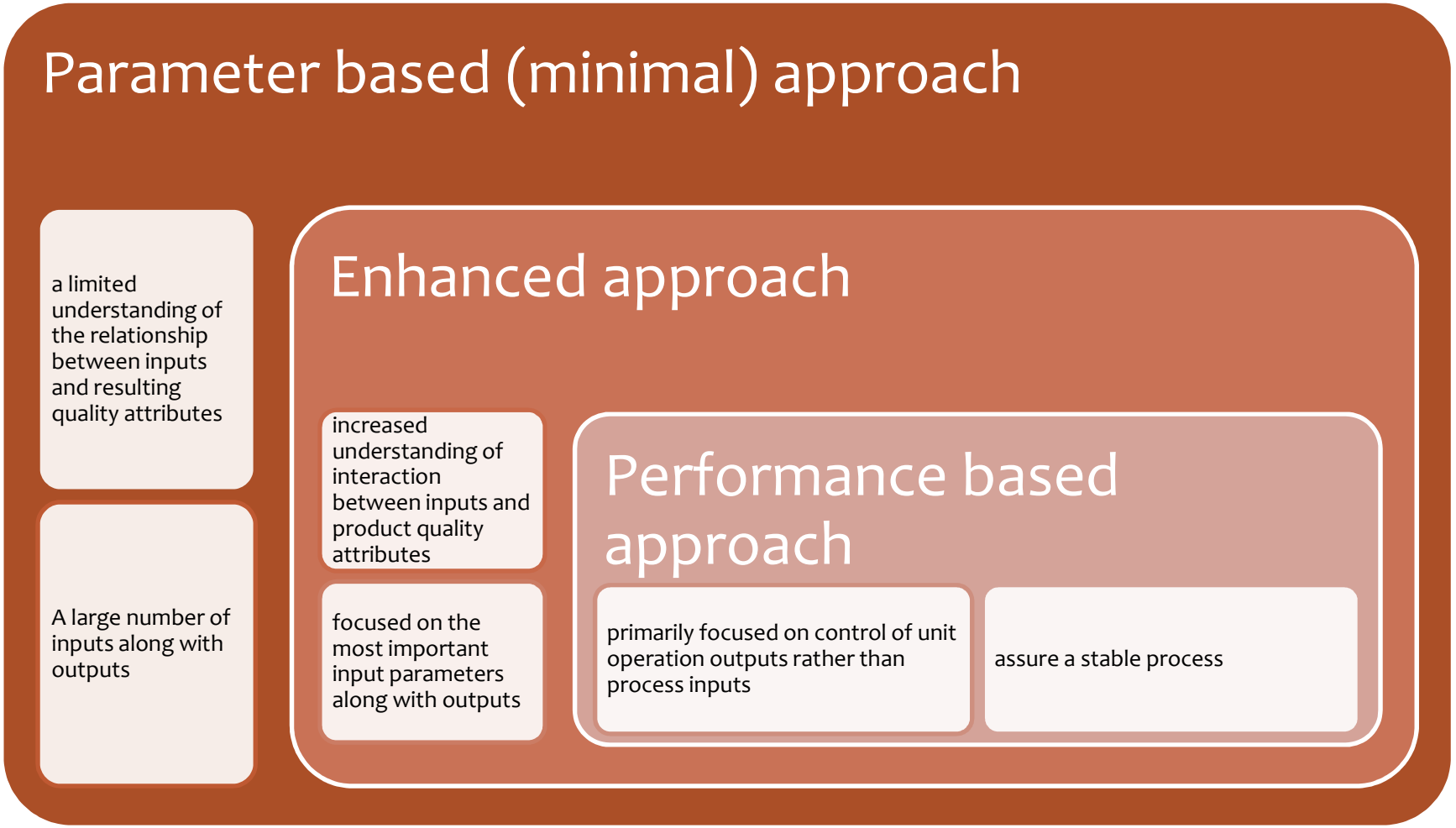


Identification of ECs for Manufacturing Process Parameters



1 Appropriate justification is expected for parameters that are ECs and that are not ECs
2 Assessment of risk to quality using tools and concepts found in ICH Q9
3 In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
4 See Chapter 2 for further guidance on reporting categories and see section 3.3. regarding roles and responsibilities related to managing changes and maintaining an approved application

ECs for the manufacturing Processes



Established Condition

CTD SECTION	SECTION TITLE	ESTABLISHED CONDITIONS – General List with notes
3.2.P.3	Manufacture	
3.2.P.3.1	Manufacturer(s)	Drug Product Manufacturing (including: testing, primary packaging, device assembly for drug product-device combination products) sites
3.2.P.3.2	Batch Formula	Drug Product Batch Formula (Qualitative and Quantitative)
3.2.P.3.3	Description of manufacturing process and process controls	Individual unit operations and their sequence in the manufacturing process For levels/details of ECs for inputs (process parameters and material attributes) and outputs of individual unit operations, reference is made to Chapter 3.2.3.1 – Identification of ECs for the Manufacturing Processes
3.2.P.3.4	Controls of Critical Steps and Intermediates	Specifications (e.g., test, elements of analytical procedure and acceptance criteria) for critical steps and intermediates including storage conditions of critical intermediates
3.2.P.3.5	Process validation and/or evaluation	Supportive information
3.2.P.4	Control of Excipients	
3.2.P.4.1	Specifications	Excipient Specification For each Quality Attribute on the specification • Test Method • Acceptance Criteria Or, if applicable, Reference to pharmacopoeial monograph
3.2.P.4.2	Analytical Procedures	Reference to pharmacopoeial monograph and if none exists, refer to Chapter 3.2.3.2 – Identification of ECs for Analytical Procedures
3.3.P.4.3	Validation of analytical procedures	Supportive information

Identification of ECs for the Manufacturing Processes

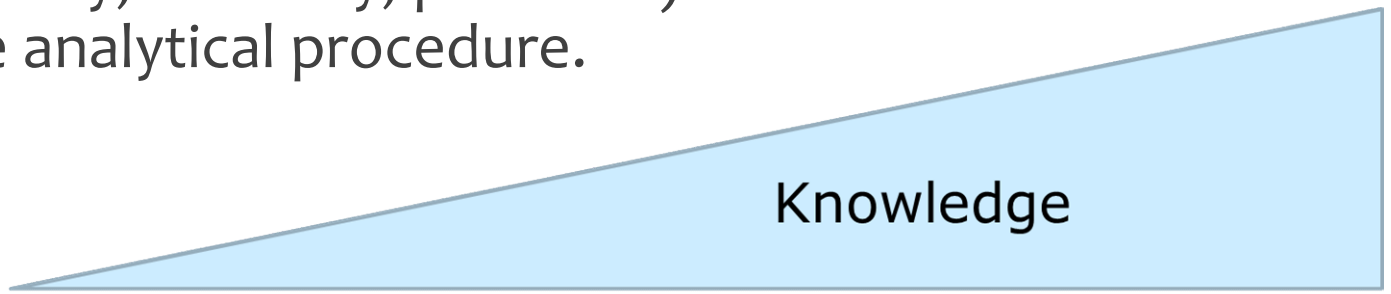
Powder Blending Unit Operation

	Parameter	Acceptable ranges and reporting categories (White boxes are ECs and grey ones are not-ECs.)			Comments/Justification
		Parameter Based Approach	**Enhanced Approach**	**Performance Based Approach**	Refer to section 3.2.P.2. for detailed justification and experimental data
Input Materials	API PSD	20-50um **(PA)**	5-200um **(NM)**	5-200um **(NM)**	API moisture and Pharmacopoeial specifications for excipients 1-3 are ECs in all cases. Excipient specifications managed in line with the Pharmacopoeia. Equipment type is an EC in all cases. **Enhanced Approach** API Moisture has limited impact on quality demonstrated within the ranges explored. Particle size distribution (PSD) of API demonstrated no impact on dissolution or absorption. DoE studies showed no significant impact on blend uniformity for 5-200um PSD of API. This allows reduction in reporting type for API moisture or PSD. Understanding of variability of blending on product performance allows reduction in reporting type. Knowledge of the impact of scale on blending may allow downgrading of the reporting category (See 3.2.P.2). Homogeneity (blend uniformity <5%RSD) is required for assurance of quality in the next manufacturing step. Experimental studies identified the range of blend speeds and times utilised without significant impact on blend uniformity as confirmed by successful process demonstration. Blending parameters being defined as ECs means homogeneity is not
	API Moisture	<1.0% **(NM)**	<1.0% **(NL)**	<1.0% **(NL)**	
	Excipients #1-3 Specification	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial	
Equipment and Parameters	Equipment type	Diffusion blender (V-blender) **(PA)**	Diffusion blender (V-blender) **(NM)**	Diffusion blender (V-blender) **(NM)**	
	Scale >10x	200kg **(NM)**	200kg **(NL)**	200-600kg **(NL)**	
	Blend Speed	20rpm CPP **(NM)**	10-20rpm KPP **(NL)**	**15 rpm (NR)**	

ECs for Analytical Procedures

Where the relationship between method parameters and method performance has not been fully studied at the time of submission, ECs will incorporate the details of operational parameters including system suitability.

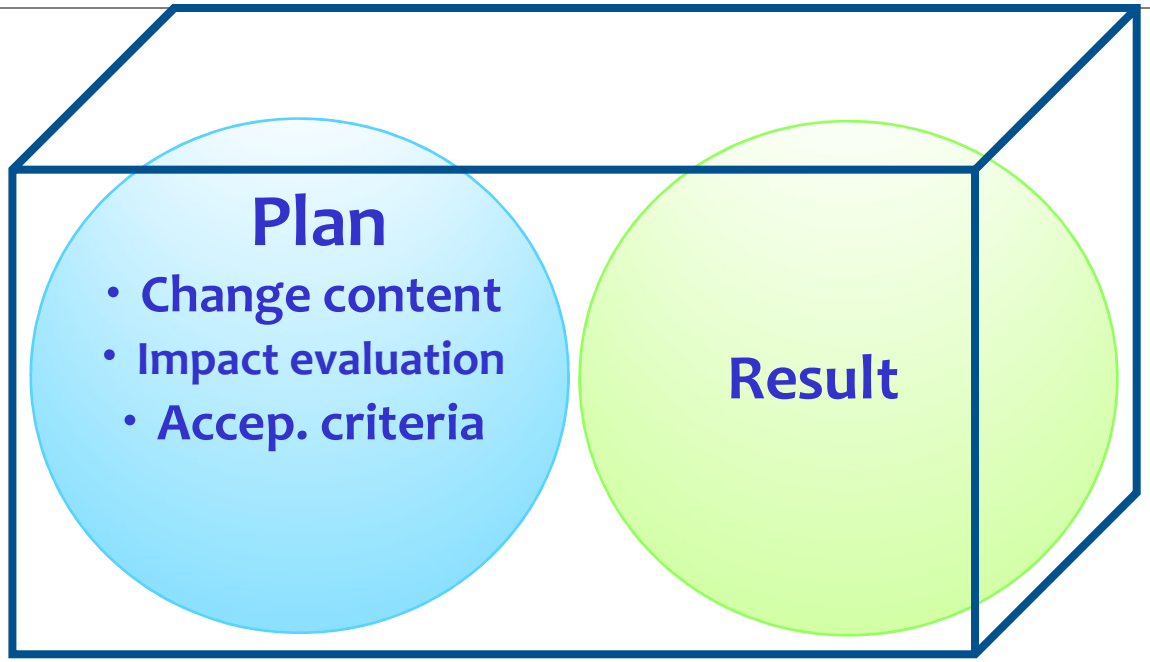
When there is an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, ECs are focused on method-specific performance criteria (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure.



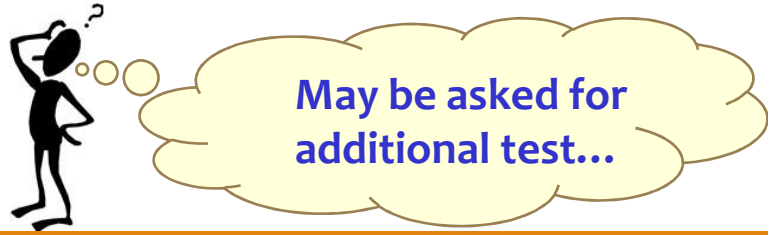
- Detailed Analytical Procedure
- System Suitability Test
- Specification

- High-level method description
- Method-specific performance criteria
- Specification

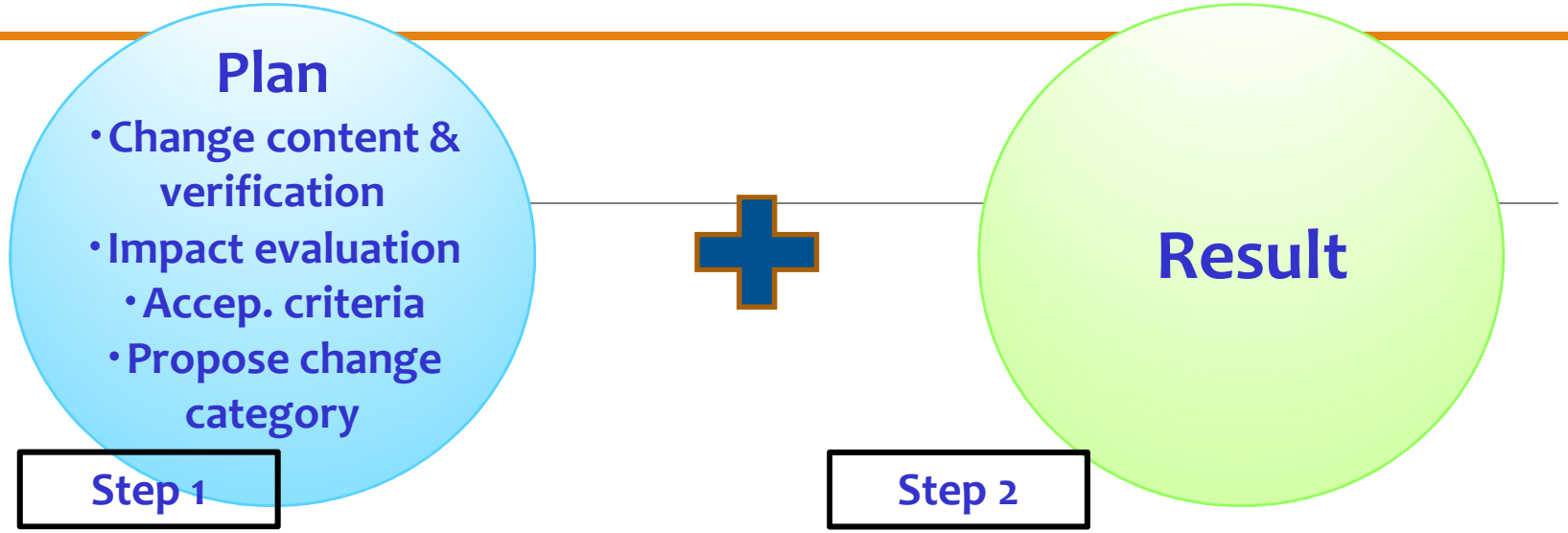
Normal Partial Post-approval Change



Submit test plan and the result for the review



Use of PACMP



Step 1

Submit
Post-Approval Change Management Protocol (PACMP)
→Content agree between industry and the regulator

Step 2

- Perform testing and verification according to PACMP
- If obtained result fulfills acceptance criteria in the protocol, follow the change category listed in the protocol to implement the change (may be a case where this need to be agreed with regulators)
- If necessary, submit the result of Step 2 to the regulator

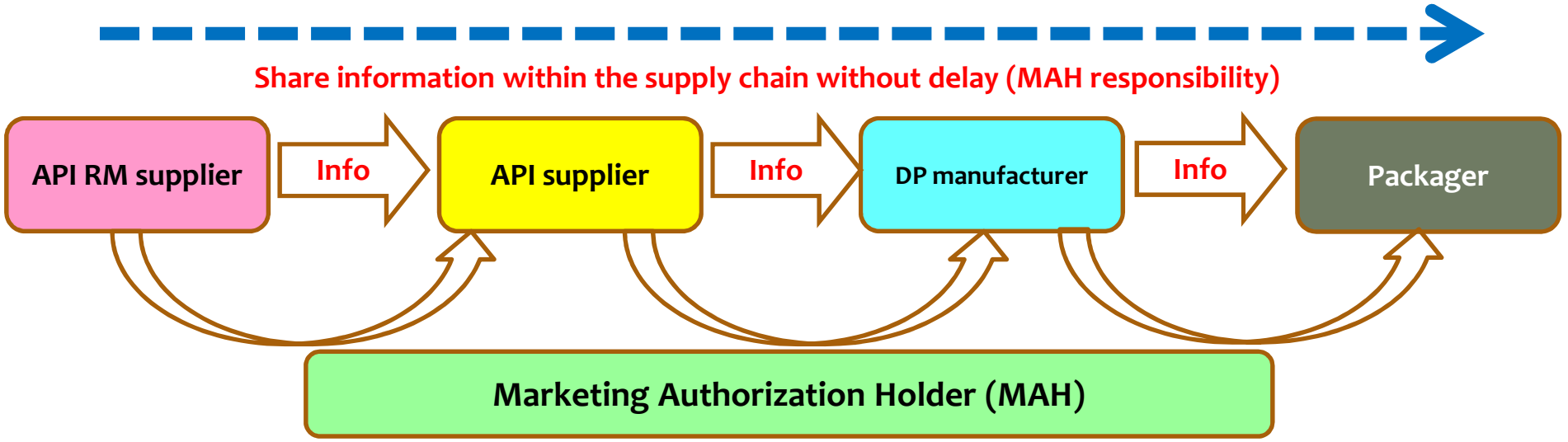
Product Lifecycle Management (PLCM) document

- A summary that transparently conveys to the regulatory authority how the MAH plans to manage post-approval CMC changes.
- Encourage prospective lifecycle management planning by the MAH and facilitate regulatory assessment and inspection.
- The PLCM document can be based on regional recommendations.
- Elements of PLCM document
    - Summary of Product Control Strategy
    - ECs
    - Reporting Categories for making changes to approved ECs
    - PACMPs
    - Post-approval CMC Commitments

Responsibilities of MAH

All stakeholders in the supply chain of the product have responsibility and expected to pass on the quality and regulatory information to the next interested party in the supply chain without delay

When the manufacturer defines ECs, MAH have a responsibility to share such information to all manufacturer in the supply chain depending on the impact of the work they perform.



Implementation of PACMP

Thorough Implementation of Pharmaceutical Approved Matter

（平成28年6月1日付け薬生審査発0601第3号・薬生監麻発0601第2号、厚生労働省医薬・生活衛生局審査管理課長、監視指導・麻薬対策課長連名通知）

1． Thorough check between Approved Matter and manufacturing practice

- Non-production associated person from the manufacturer periodically check the production operation is no different from the approved matter

2． Securing adequate organization to implement change control

- The MAH adequately place personnel for Pharmaceutical Officer and Quality Assurance Manager to conduct and monitor the requirements in Pharmaceuticals and Medical Device Law
- Collect information from the pharmaceutical manufacturer on changes to the manufacturing process and conduct necessary procedure as in Pharmaceuticals and Medical Device Law in the organized manner without delay.

3． Thorough prevention

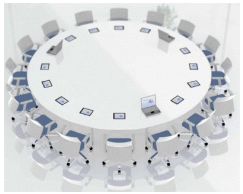
- In case there is excursion between in the actual manufacturing and approved matter and/or from other requirement in Pharmaceuticals and Medical Device Law, report agency without delay.
- Conduct cause investigation to resolve non-conformance and conduct immediate preventive measure and thoroughly execute such measures

Major Activities to Resolve Current Issues

December 2017

ICH Q12

May 2015



PMDA ICH Q12 WG

December 2014

AMED

AMED Research Group

September 2016

MHLW/PMDA-FPMAJ Task Force

AMED: Japan Agency for Medical Research and Development
MHLW: Minister of Health Labour and Welfare
FPMAJ: The Federation of Pharmaceutical Manufacturers' Associations of JAPAN

Handling, etc., of changes in the approved matters relating to the quality of drugs

平成30年３月９日付け薬生薬審発0309第１号、薬生監麻発0309第１号
厚生労働省医薬・生活衛生局医薬品審査管理課長、監視・指導麻薬対策課長連名通知

It is aimed at thoroughly ensuring adequate changes in approved matters accompanying changes in the manufacturing methods, etc., of drugs, and promoting the smooth changes in the manufacturing methods, etc.

The following six items were written together:

1. **Trial use of a system of changing approved matters**, using PACMP
2. **Rationalization of descriptions in the column for standards and test methods**
3. Post-inspection procedures relating to consistency between the approved matters and the actual manufacturing status
4. Descriptions on applications made with flexible disks, etc.
5. Approved matters that may be changed later, when making revisions because of other reasons
6. Procedures to extend the validity period of biological preparations, etc.

Health Sciences Council（Pharmaceuticals and Medical Device System WG）

http://www.mhlw.go.jp/stf/shingi/shingi-kousei_430263.html

Discussions for post-5 years implementation after the Law revision*

For the enhancement of the safety measures and revision of the marketing of pharmaceutical products, the 2013 revised two law supplement include proposed discussion topics to be implemented 5 years after endorsement of the law

* : 2013 partial revision of Pharmaceutical and Medical Device Law, 2013 partial revision of Pharmacist Law

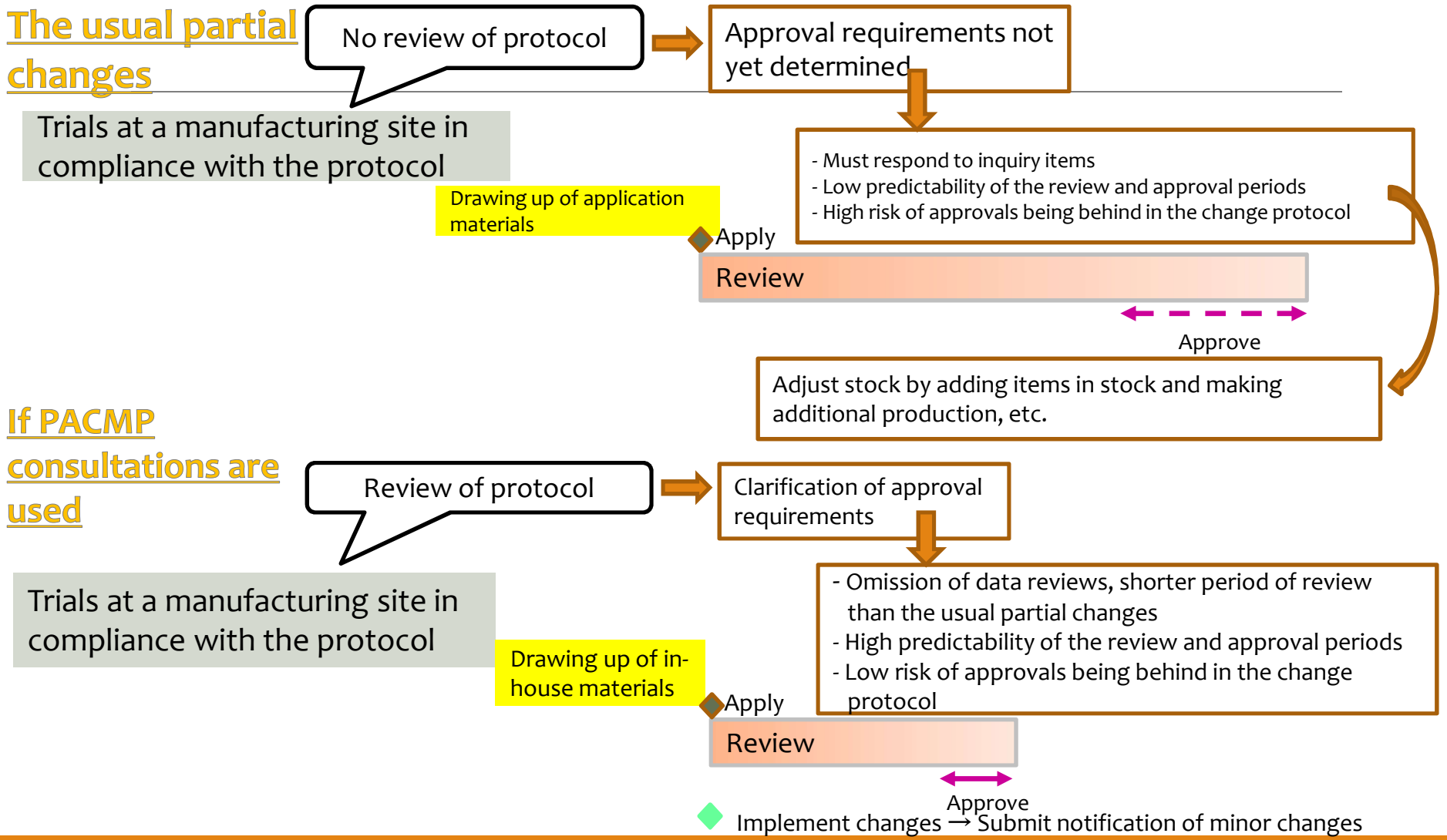
Theme ①: Fulfillment of Faster access and safety measures for innovative pharmaceutical and medical device

Theme ②: Fulfillment of manufacturing, distribution, and marketing scheme for pharmaceutical products and medical device

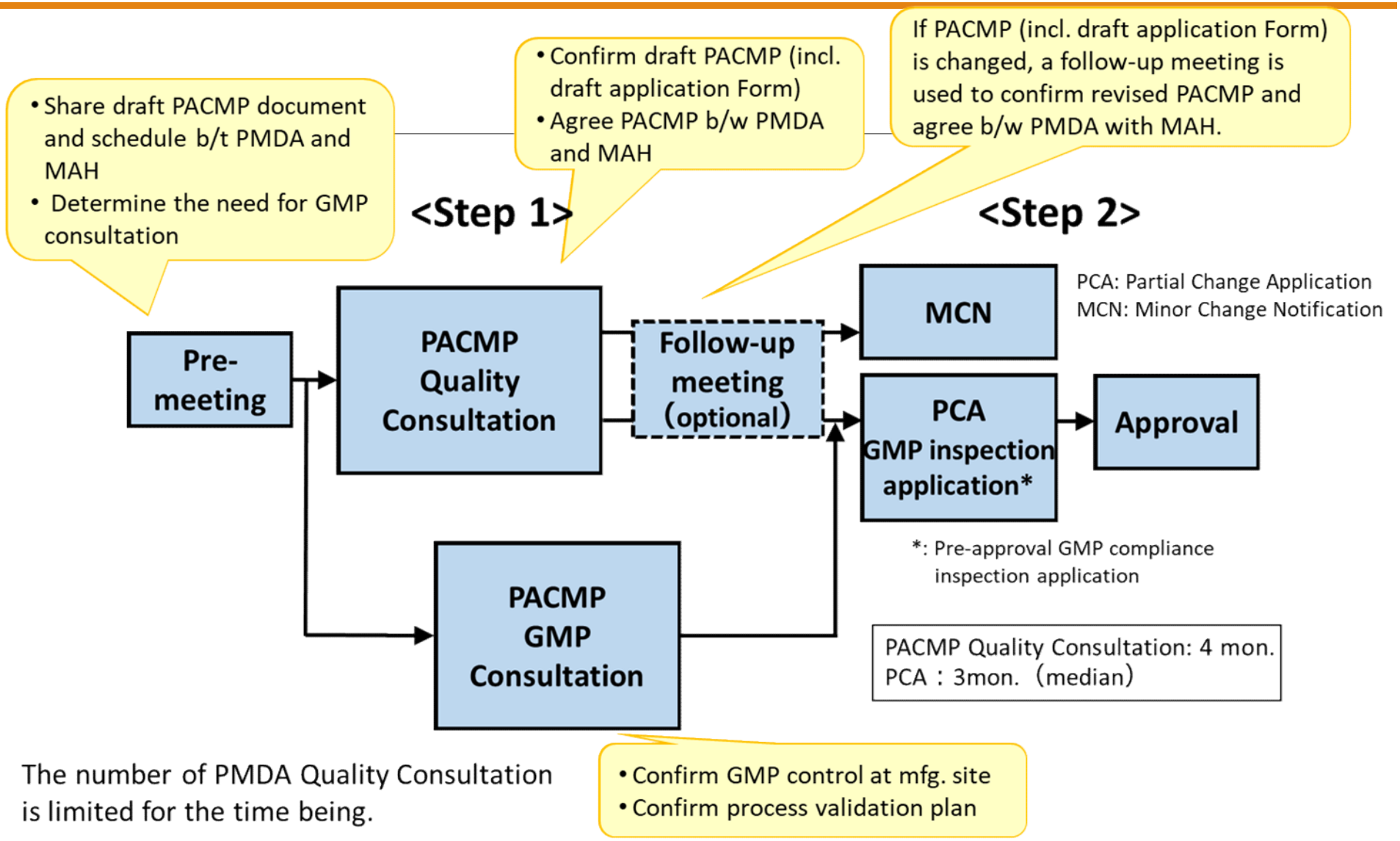
Theme ③: Conditions for Pharmacy and Pharmacist, obtaining safe pharmaceutical products

公表資料に基づき作成

Usefulness of this consultation system



Overview of PACMP pilot program in Japan



The number of PMDA Quality Consultation is limited for the time being.

Work continues…

Other Issues to Introduce Q12 in Japan

Implementation of effective Pharmaceutical Quality System (PQS)

Documentation and handling of EC and PCLM

Revision of content in Approved Matter
（【Manufacturing Process】【Spec & test method】）

Handling of PLCM

→ **New notifications in Japan**

Post-Approval Change Management Protocol（PACMP）

Further elaboration of the regulatory process

→ **Improvement after trial**

Issues to be considered in the future

- Expansion of application to items in which **the local government has the right to implement GMP inspections**
- Expansion of application to matters that were registered with a drug master file (MF)
- Expansion of application to items whose new drug application has been submitted
- Expansion of application to **a broader protocol**
- Improvement of management operations

Product Lifecycle Management document in Japan