Manufacturing, Quality control and Supply (MQS) Session

April 05, 2022
APAC conference
MQS-TF

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TF Team name

- We have been active in ATIM(Access to Innovative Medicine）-TF as our team's name.
- Our main field is manufacturing and quality control for products.
- We decide to change our team’s name that match the activity.

Manufacturing, Quality Control and Supply task force team(MQS-TF)

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Background

Team discussion about MQS session in 11th APAC

- Results from questionnaire and discussion with PMDA, we think that it is need to collect more information and investigation to produce a big achievement of discussion about GMP inspection at APAC conference
- We decide to change our session contents as follows
  - ☐ Survey results about GMP inspection
  - ☐ Introduction of discussion theme for next APAC; PACMP(Post-Approval Change Management Protocol)

MQS session operates a small session without discussion

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Questionnaire about GMP Inspection to APAC pharma associations

Questionnaire Period: Nov. 2021 – Feb. 2022
Target inspection: Pre-Approval inspection(PAI)
Number of response: 6 countries

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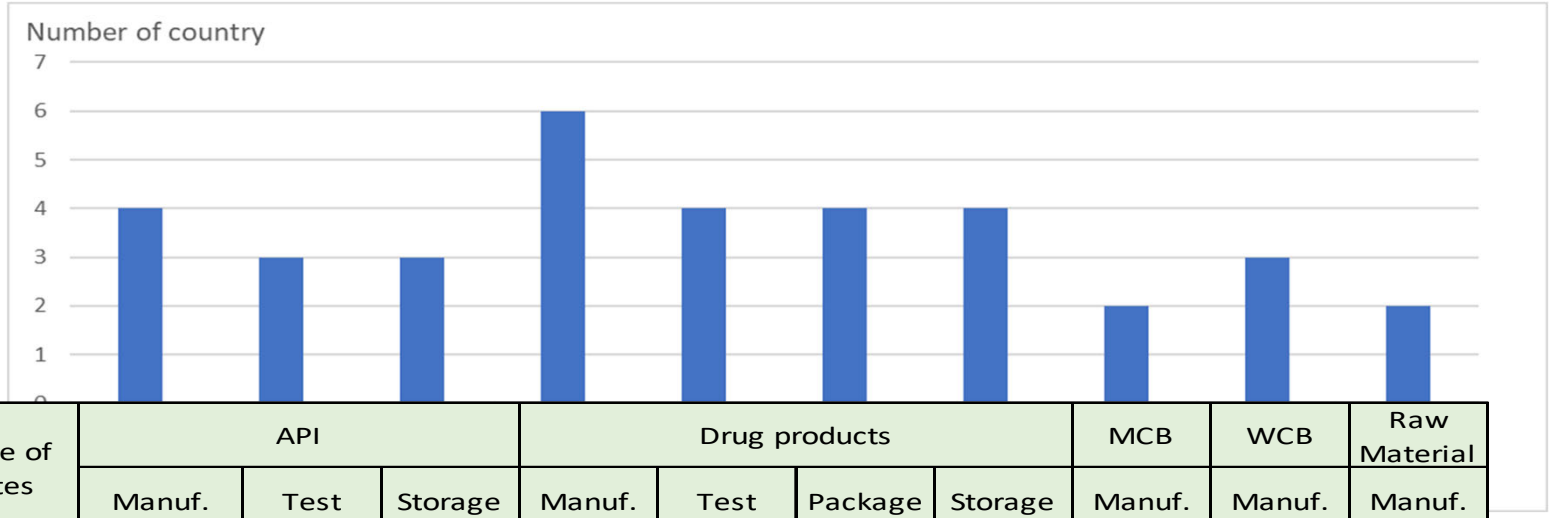
I. Overall GMP Pre-approval inspections (PAI)

1. Scope of PAI sites



Type of sites	API			Drug products				MCB	WCB	Raw Material
	Manuf.	Test	Storage	Manuf.	Test	Package	Storage	Manuf.	Manuf.	Manuf.
Japan	Y	Y	Y	Y	Y	Y	Y	N	Y	N
A country	N	N	N	Y	Y	N	Y	N	N	N
B country	Y	N	N	Y	N	Y	N	Y	Y	N
C country	N	N	N	Y	N	N	N	N	N	N
D country	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
E country	Y	Y	Y	Y	Y	Y	Y	N	N	Y

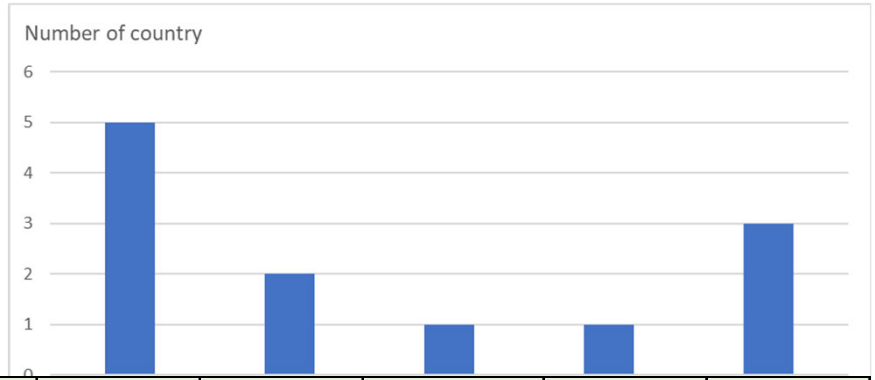
The scope of PAI sites is different in each country. The drug product manufacturing sites were subject to inspection in all countries, but there were variations in the scope of PAI sites among countries such as the packaging, test and storage of drug products, and the manufacture of API, MCB/WCB and raw materials.

I. Overall GMP Pre-approval inspections (PAI)

2. Timeline for Application and close of PAI

In many countries, the application for a PAI was required separately from the NDA, and the timing of the application for a PAI was before or at the same time as the application. However, compliance results were required in all countries prior to NDA approval.

3. Documents issued by authorities for PAI



Documents	Inspection reports	Inspection Results	Manufacturing License	GMP Certificates	Approval letter
Japan	**On-site only**	Y	N	N	N
A country	Y	N	N	Y	N
B country	N	N	N	N	N
C country	Y	N	N	Y	Y
D country	Y	N	N	N	Y
E country	Y	Y	Y	Y	Y

As the results of PAI, the inspection reports are issued by almost countries.

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II. PAI for overseas manufacturing sites(DP)

1. Inspection Method

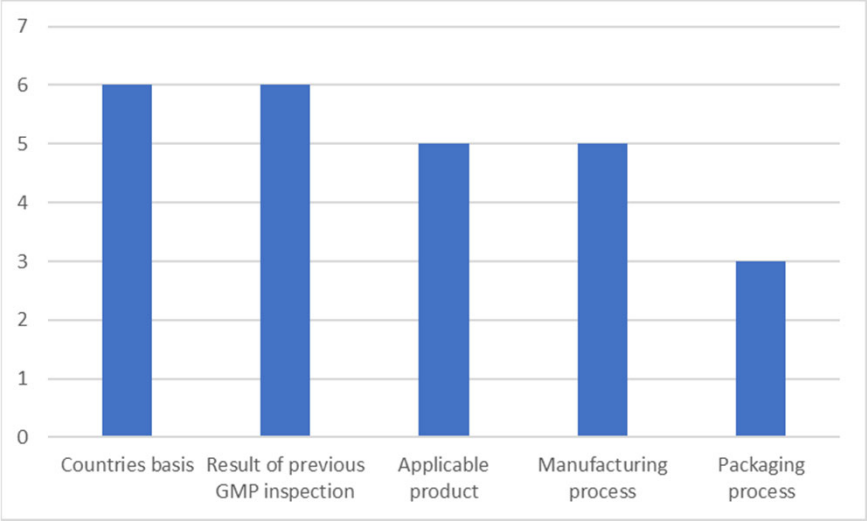
All countries adopt on-site and document-based inspections as an inspection method. Remote inspection is implemented under COVID-19 pandemic in some countries.

2. How to determine the inspection method

The selection of method is determined in all countries according to the risk assessment.

3. What risks are considered

The risk assessment was based on the countries of the manufacturing site, the characteristics of the product, the manufacturing process, the packaging process, the results of the previous GMP inspection. All countries are same approach of risk assessment.



4. What condition can PAI be waived

Some countries may omit PAI if GMP certificate is available from MRA signatory countries or PIC/S members

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II. PAI for overseas manufacturing sites(DP)

5. Documents required for PAI

Documents required	Japan	A country	B country	C country	D country	E country
GMP cert. or Inspeciton report	Y	Y	Y	N	Y	Y
Outline of product and site	Y	Y	Y	Y	Y	Y
Relating to manufacturing process	Y	Y	Y	N	Y	Y
・MBR	Y	N	Y	N	N	Y
・BR	Y	N	Y	N	N	Y
・IPC procedure	N	N	Y	N	Y	N
・Others	1)	2)	N	N	N	N
Relating to the test process	Y	N	Y	N	N	Y
・Test procedures	N	N	Y	N	N	N
・Specification	N	N	Y	N	N	N
・Test results	Y	N	Y	N	N	Y
・Others	N	N	3)	N	N	N
PQS	Y	Y	Y	N	Y	Y
Product quality review	Y	Y	Y	N	Y	N
process simulation test	Y	N	Y	N	Y	N
BSE/TSE	Y	Y	Y	N	Y	N
SMF	Y	Y	Y	Y	Y	N
SOPs	Y	Y	Y	N	Y	Y
・what SOP	4)	5)	6)	N	-	7)
Others	Y	Y	N	N	N	N
what others	8)	9)	N	N	N	10)

The required documents are different among countries for the PAI. As the SMF is required in all countries, a common format for the SMF may contribute to accelerate the PAI .

II. PAI for overseas manufacturing sites(DP)

6. What condition can some required documents be omitted

There were 3 countries that admit to be omitted a submission of some required documents if conditions were met.
However, the conditions for omission are different in each country.

V. Requests for improvement regarding PAI

- PAI can be waived if the country is PIC/S member.
- Submission exemption of some required documents from manufacturing site in PIC/S member's countries.
- Formal option for pre-consultation prior to submission of the inspection request.

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A Step of Challenge to Post-Approval Change Management Protocol (PACMP)

11th APAC
Manufacturing, Quality Control and Supply-TF
(MQS-TF)

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A Step of Challenge to PACMP

Contents

- TECHNICAL AND REGULATORY CONSIDERATINS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT (ICH Q12)
- POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)
  - Comparison of Change Categories Among Japan / US / EU
  - PACMP in Global
  - PACMP in Japan
- Expansion of PACMP utilization in Asia

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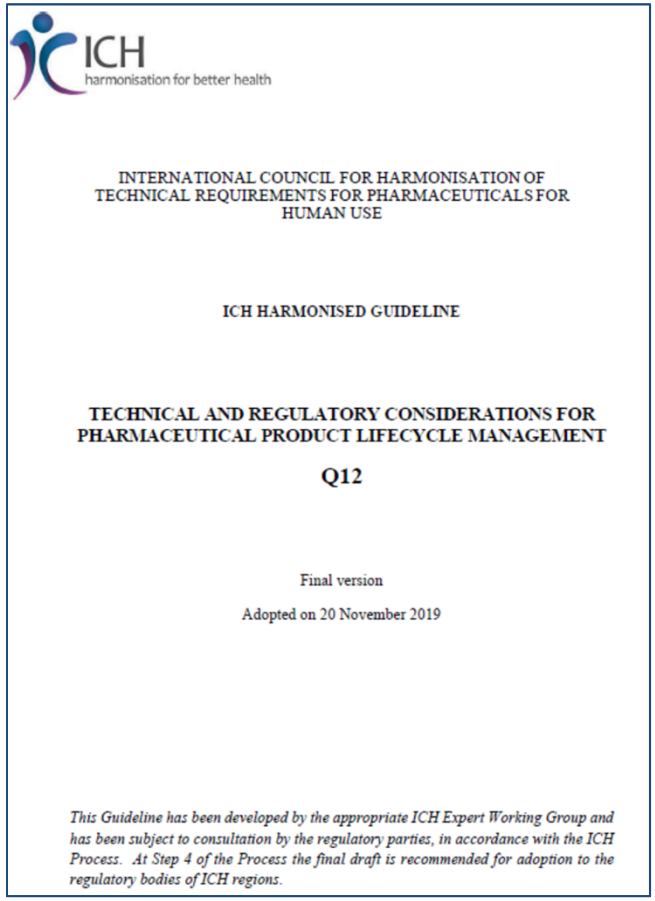
TECHNICAL AND REGULATORY CONSIDERATINS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

ICH Q12



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

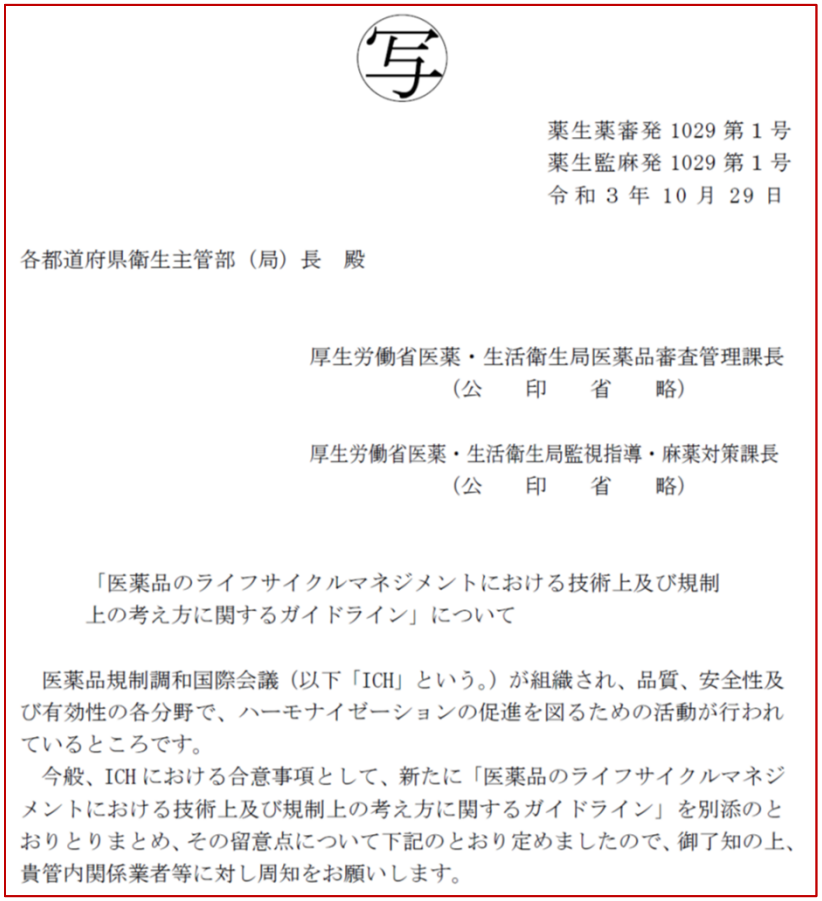
Q12

Final version

Adopted on 20 November 2019

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

1yr



写

薬生薬審発 1029 第 1 号
薬生監麻発 1029 第 1 号
令 和 3 年 10 月 29 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（公　印　省　略）

厚生労働省医薬・生活衛生局監視指導・麻薬対策課長
（公　印　省　略）

「医薬品のライフサイクルマネジメントにおける技術上及び規制上の考え方に関するガイドライン」について

医薬品規制調和国際会議（以下「ICH」という。）が組織され、品質、安全性及び有効性の各分野で、ハーモナイゼーションの促進を図るための活動が行われているところです。

今般、ICH における合意事項として、新たに「医薬品のライフサイクルマネジメントにおける技術上及び規制上の考え方に関するガイドライン」を別添のとおりとりまとめ、その留意点について下記のとおり定めましたので、御了知の上、貴管内関係業者等に対し周知をお願いします。

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TECHNICAL AND REGULATORY CONSIDERATINS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

ICH Q12

A new ICH guideline topic since 2014 to discuss the pharmaceutical product lifecycle.

The guideline discuss on the introduction to change categories and tools that are useful to manage the product throughout the lifecycle based on the contents in ICH Q8-Q11, for the effective and efficient review of the proposed changes to sustain the stable supply of product and introduce innovations.

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ICH Q12 Chapter 4

POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)

- A PACMP is a **regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change** as the approved protocol provides an agreement between the MAH and the regulatory authority
- A means of method to **make changes to the Established Condition (EC) under efficient and predicable approach** under the protocol and execution
- A PACMP can address one or more changes for a single product, or may address one or more changes to be applied to multiple products
- The PACMP may be submitted with the original MAA or subsequently as a stand-alone submission
- **The PLCM document can be located in CTD Module 3.2.R. (In some regions, the PLCM may be included in Module 1)**

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POST-APPROVAL CHANGE MANAGEMENT PROTOCOL (PACMP)

Step 1

- Submit Protocol
  - Change proposal based on scientific sound logic
  - Risk management activities
  - Proposed approach (study) and acceptance criteria to assess the change impact
  - Any other fulfilling condition (is available)
  - Proposed change category
  - Any other justification to support the change
- Need to be approved by regulatory agency

Step 2

- Execute the experiment and work as in the protocol
- Confirm that the result have fulfil the acceptance criteria and any other condition in the protocol and submit such results to the regulatory agency according to the protocol
- In some cases, some change category may not be necessary to obtain an approval from the regulatory agency

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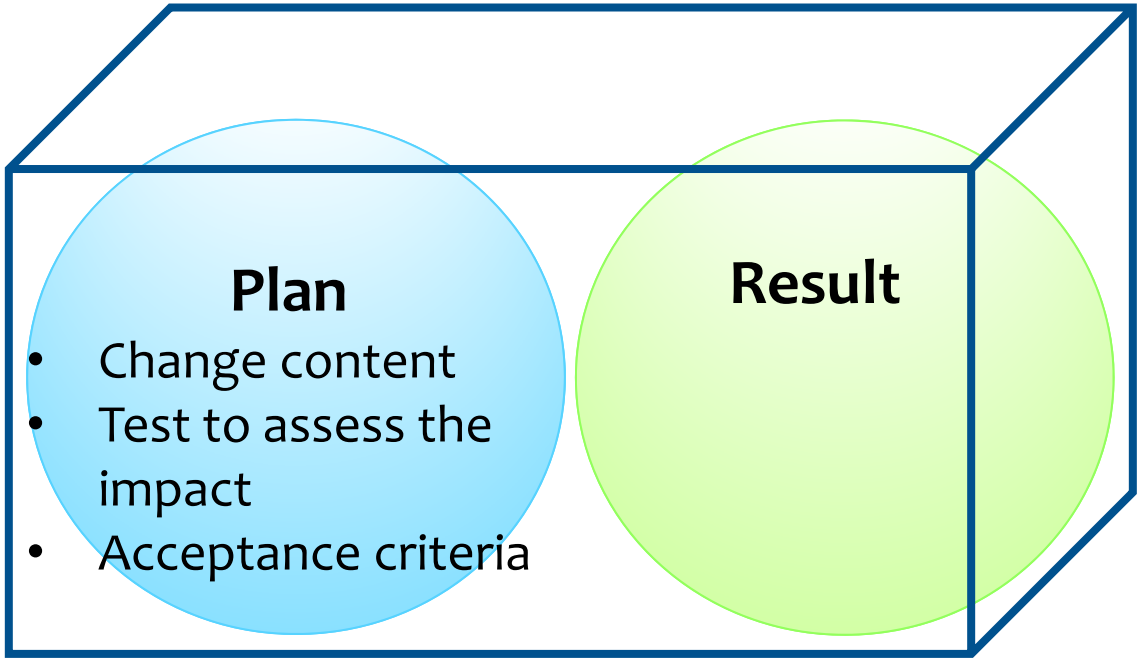
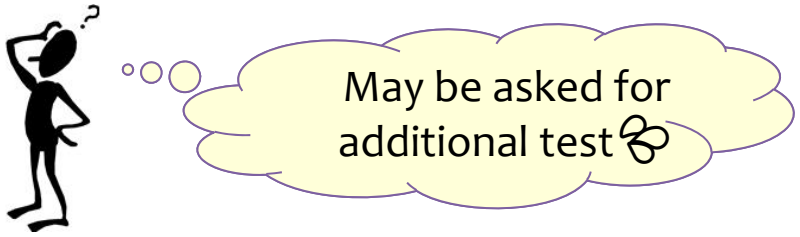
Ordinary Partial Change



Submit test plan and result as a package for the review



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When Using PACMP

Protocol

- Change content & justification
- Test and studies to assess the impact
- Acceptance criteria to fulfill
- Justification
- Other

Result

Step 1

Submit PACMP→content is assess and approved by regulatory agency

In Japan, as a step 1, "**Application for Change Protocol Review**" is created

Step 2

- Execute test and studies as in PACMP
- In case obtain results/data satisfied the acceptance criteria and other conditions in the protocol, MAH will submit such information to the regulatory agency and assess (depending on the change category, there may be a case additional approval is not necessary)

In Japan, step 2 process is "**Submission of implementing changes in accordance with change protocol**"

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Comparison of Change Categories Among Japan / US / EU

Current

○ In US and EU, in addition to the similar pre-approval review process as in Japan, a multiple change submission categories are established depending on the content of the change

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 2)Supplement-changes being effected (CBE)	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days) 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)

Revising Change Control Process Management to PACMP

Benefit of Introduction

* For the submission that may take a time to review, there is **a potential to shorten the review period**

* Since the change process starts with initial submission, there will be a flexibility to set the timing to implement the process change and replacement of the product with changed process, that **effectively contributes the supply chain management**

* When a company create a change protocol, it is necessary to collect enough information on the new method or new technology. Therefore, **a potential enhancement in the capability of using innovative technology and/or quality control**

※ May not applicable to all pharmaceutical products

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PACMP in Global

"Comparability protocols" have been in US regulations for decades

- US comparability protocol draft guidance in 2003 and 2016

PACMPs have been part of EU regulations since 2010

- EMA Q&A published in 2012

Japan performed a pilot program for PACMPs in 2018 and included in the regulation from 2021

- Step 1 is through a meeting rather than a variation

A few countries will accept PACMPs even though not specifically in regulations (e.g., Switzerland, South Africa)

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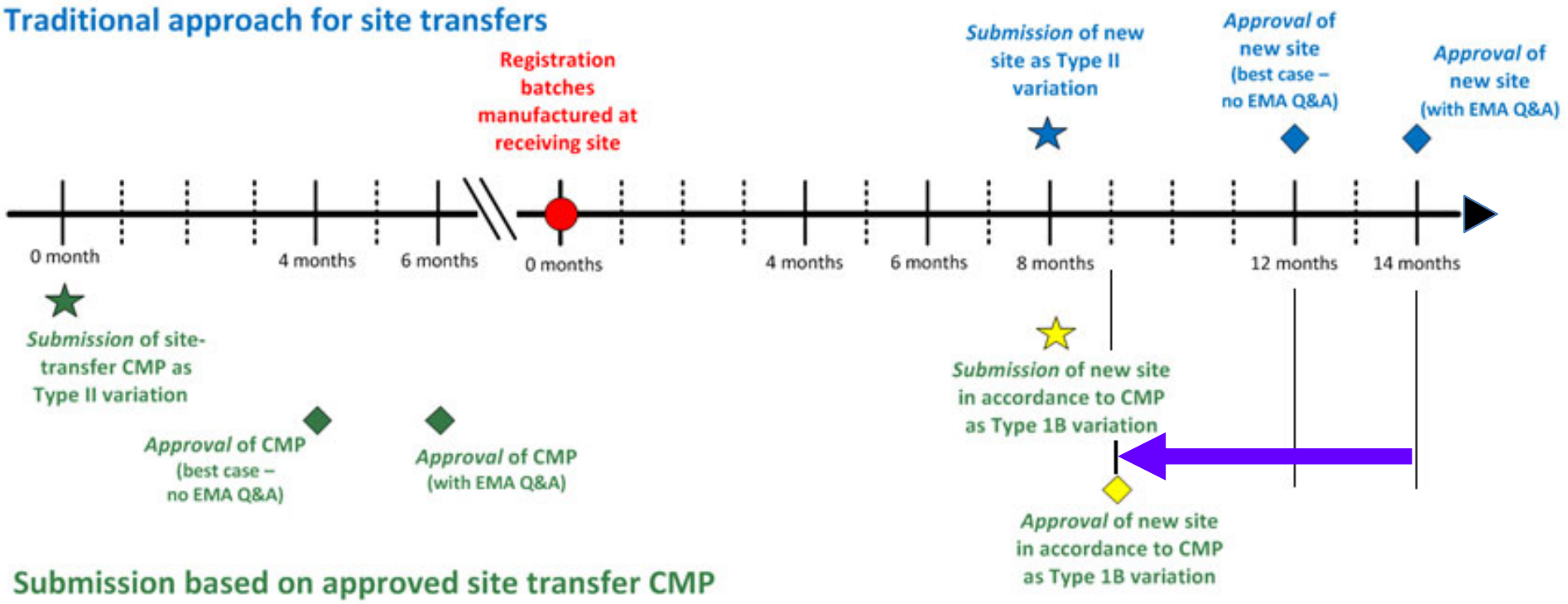
Example of PACMP in EU

- **PACMPs in the centralised procedure**(until December 2016)

SCOPE	TYPE II	MAA	Line extension
New site for manufacture and/or QC testing of the drug substance	Bio: 15	Bio: 1 Che: 5	
New site for manufacture and/or QC testing of the drug product	Bio: 27 Che: 3	Bio: 8 Che: 1	Bio: 2
Change to the manufacturing process of the drug substance	Bio: 14	Bio: 6 Che: 1	
Scale-up of the drug substance manufacturing process	Bio: 7	Bio: 2	
Change to the preparation of a cell bank		Bio: 2	
Change to the manufacturing process of the drug product	Bio: 3 Che: 4	Bio: 1 Che: 3	
Change to the container closure system of the drug substance or drug product	Bio: 1 Che: 1	Che: 1	
Other	Bio: 4	Bio: 2	Che: 2
TOTAL	**- Bio products: 95** MAA 22, Type II 71, Extension 2 **- Chemical: 21** MAA 10, Type II 9, Extension 2		

Example (EU): Biologics DS manufacturing site transfer - Benefit of PACMP Approach vs. „Traditional“ Approach*



- **3-5 months faster approval of the site change using a PACMP**

**Note: approval timelines for type II variation in this scheme include positive CHMP opinion and Commission Decision*

Benefit of PACMP

- **Realization of review of change and GMP inspection** in 2 steps of PACMP
- **A potential down grade of change category** in a predicable manner (exclude some products)
- **Clarify the conditions to implement change in a predicable and under transparency** (change implemented in accordance with agreed protocol)
- **Faster implementation of the change** by satisfying the PACMP condition for the faster release of pharmaceutical products to the patient
- **A potential tool to introduce break through technology** and early phase application, if there is an agreement

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Benefit of PACMP

Result

Protocol + Result

Regulator

- Predictable
- Adequate document to review
- Expectation known

Industry

- Transparent
- Adequate document to prepare
- Clear agreed goal

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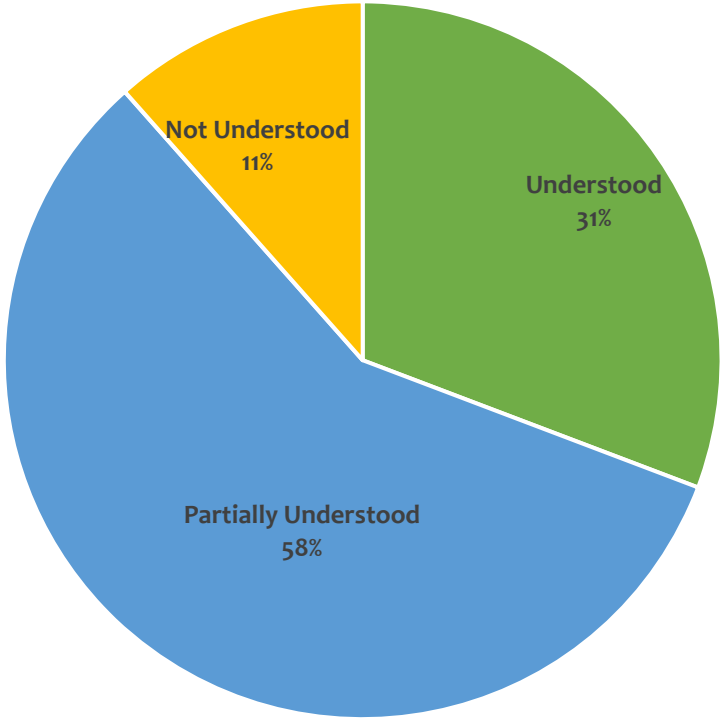
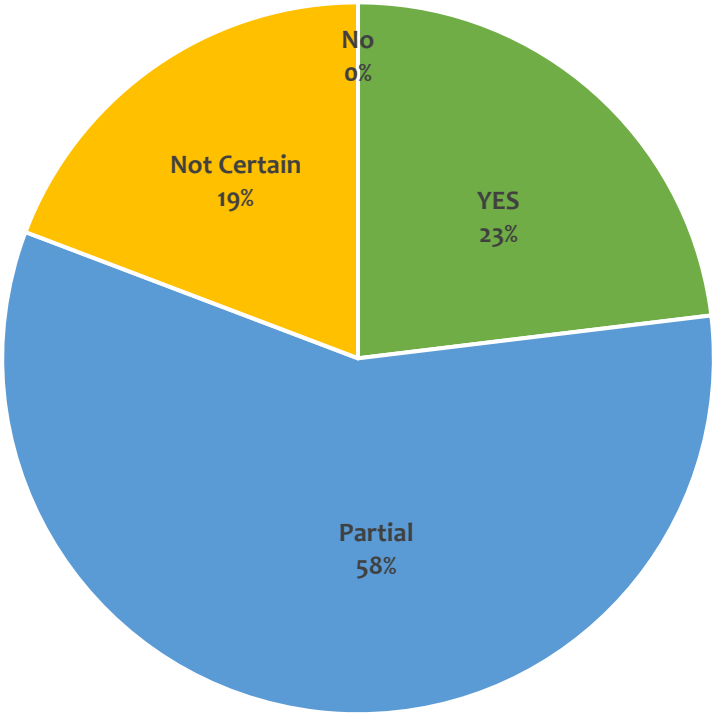
PACMP in JPMA

Q1 Do you know PACMP regulation?



Q2 Is there a benefit to use PACMP?



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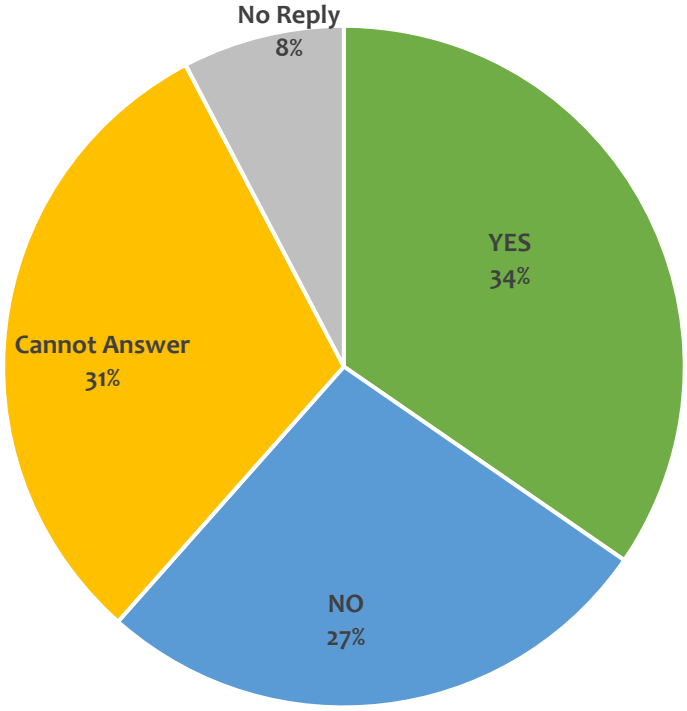
PACMP in JPMA

Q3 Have you used PACMP?

Q4 Do you want to use PACMP other than US / EU?



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Expansion of PACMP utilization in Asia

MQS would like to propose to discuss the benefit of PACMP to both industry and regulatory authority at 12th APAC meeting.
MQS TF would like your support and cooperation for the success of next year's session

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Thank you for your attention

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