Introduction of post-approval change management protocol (PACMP) mock-up in Japan preparation

by AMED PACMP working group

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Objective

Japan Agency for Medical Research and Development (AMED) PACMP working group has actively created a post-approval change management protocol (PACMP) mock-up in Japan.

- **This has been refered to actual oversee cases and in line with the ICH Q12 in Japan.**
- **In this presentation, we will introduce some contents along with our discussion and challenges through this example.**

Contents

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Differences between Japan, the United States, and Europe in terms of approval items and change control

	Japan	US/EU
Items to be approved	M1. 2 (Application Form) Items Only	Up to M3
Change category	Be included in Application form (Manufacturing method: partial change application, Minor change)	Major, Moderate, Minor changes included in the categories according to the guidelines.
Development of CTD after approval	None	Maintenance of M3 (Reflection of Changes)
Mechanism to apply for and approve a change plan in advance	None	Europe: PACMP US: Comparability Protocol
Relate to changes Annual Report	None	With

Q12

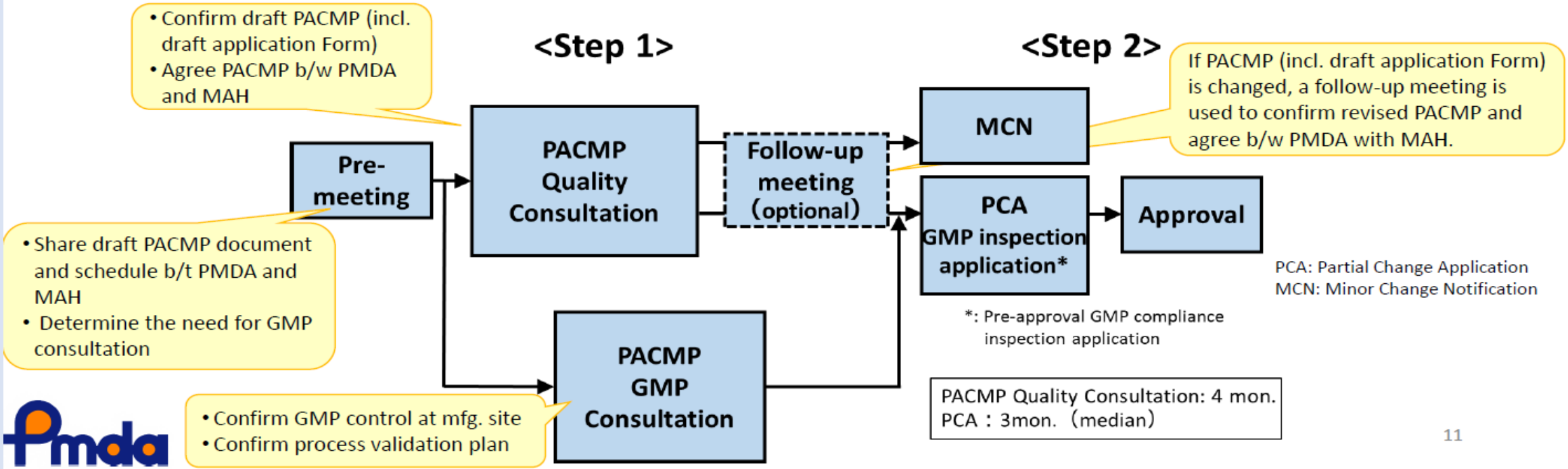
ECs

PACMP

(In both Japan and overseas, there is no system for quantitatively evaluating a company's quality system.)

Preparation for ICH Guideline Implementation
~ Introduction of PACMP pilot program in Japan ~

- ICH Q12 will introduce PACMP (Post-Approval Change Management Protocol), a mechanism enables planning and implementation of future CMC changes in an efficient and predictable manner.
- MHLW/PMDA started the pilot program for future implementation since April 1, 2018 (before ICH Q12 reaches Step4/5).



Nobumasa Nakashima, *Symposium for the draft ICH E8 (R1)*, July 25, 2019.

PACMP/CP systems

	Japan Note)	United States	Europe
PACMP/CP in Original registration submission	• Unavailable	• Include into 3.2.R of NDA/BLA	• Include into 3.2.R of MAA
PACMP/CP in Post-approval CMC variation	• Separately request a PMDA consultation. Submit a briefing document including the protocol	• Include into 3.2.R of PAS	• Include into 3.2.R of Type II variation
Agreement of PACMP/CP with Agency	• Protocol is agreed with PMDA through the PMDA consultation process	• Regulatory review and approval is required	• Regulatory review and approval is required
Downgrading of category for subsequent variation	• PCA to an expedited PCA or MCN	• PAS to CBE-30, CBE-0 or Annual Report	• Type II to Type IB, Type IA_{IN} or Type IA
Change(s) where GMP inspection is anticipated	• In scope	• Out of scope	• Not applicable
Other	• Products where no Application form conformity issue wasn't found or was already closed through a PCA approval		

NOTE) The Japanese system is in a trial phase.

PCA: Partial Change Application, MCN: Minor Notification

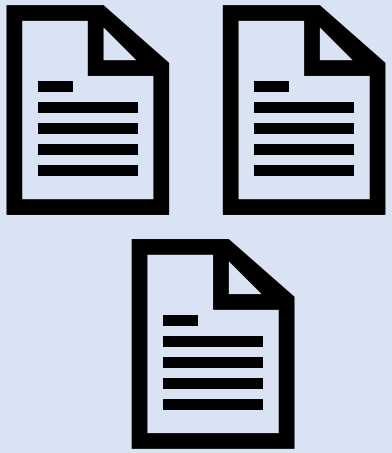
Hatsuki Asahara, 20th Symposium of the Quality Forum, September 11, 2018.

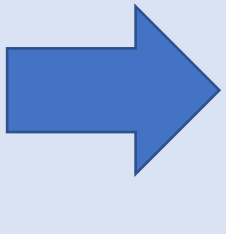
How to prepare PACMP document

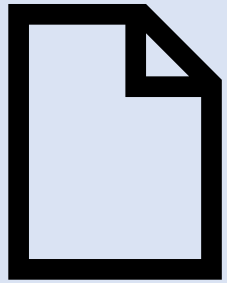
Europe: PACMP
US: Comparability Protocol

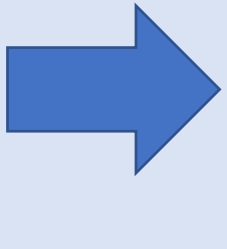
Select a theme

PACMP
For Japan

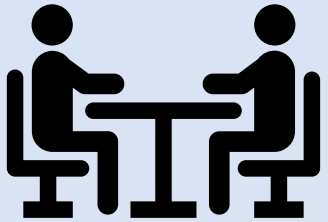








ICH Q12
Application form



Case Studies:Post-Approval Change Management Plans (PACMP)

	Active ingredient	Types of changes	Change category	Number of pages
Bio Pharmaceuticals	Antibody	Adding a new manufacturing site for drug substance with scale-up	EU:Type II ⇒ Type IB US:PAS ⇒ PAS	40
	Antibody	Adding a new manufacturing site for drug product	EU:Type II ⇒ Type IB US:PAS ⇒ PAS	35
	Fusion protein	Adding a new purification column resin	EU:MAA New: Type II ⇒ Type IB	11
	Recombinant proteins	Adding a new production line to the drug product manufacturing process	EU:Type II ⇒ Type IB	16
	Vaccine	Renewal of the WCB	EU:Type II ⇒ non-reportable US: PAS ⇒ Annual report (planned)	34
	Vaccine	Adding a new manufacturing site and testing facility	EU:Type II ⇒ Type IB	35
	Vaccine	Batch size change	EU:Type II ⇒ Type IB	21
Chemicals		Potential manufacturing change to the starting material of the drug substance	US:BLA New:PAS ⇒ Annual Report	3
		Changes to testing method (Rapid Test for Microorganisms in Water for Manufacturing)	US:PAS ⇒ CBE-0	60

Selected Theme

Monoclonal antibody drug
Adding a new manufacturing site for a drug substance with scale-up

- **Manufacturing site X (Manufacturing Process A:5000L)**
- **Manufacturing site Y (Manufacturing Process B:20000L)**
  - **No change of manufacturing process and manufacturing site of drug product**

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Precautions for the mock-up

Challenges at the time of preparation

What level should be presented ?

-Assessment of the impact of the change on the quality of the drug substance (risk assessment summary)

What level should be presented ?

-Comparability study plan

1) Manufacturing process performance

2) Characterization and specification

3) Stability Presentation

Precautions in creating this mockup

- This mock-up showed as an example in the post-approval change control protocol (PACMP: Post-Approval Change Management Protocol) shown in ICH Q12.
- This mock-up does not intend to propose new regulatory requirements or to reduce existing regulatory requirements.
- This mock-up does not cover all the contents, but is just as an example, and the evaluation items depending on the changes and quality characteristics of the drug.
- This mockup is an example of PACMP description after approval, but it can also be used as an example of PACMP at the time of initial application for a new drug
- It is only for Japan and not intended to use in the US or EU.

Introduction of the representative section

2. Changes in manufacturing processes

Manufacturing process of the drug substance	Manufacturing process A	Manufacturing process B	Overview of Changes
Step 1 Thawing of vials and seed culture	Shaking flask, single-use bioreactor	Shake flask	Seed culture is carried out only in shake flasks
Step 2 Extended culture	Bioreactor (300L, 1000L)	Bioreactor (50L, 500L,5000L)	Scale change
Step 3 Production culture	Bioreactor(5000L) Antifoam is not used	Bioreactor (20000L) Antifoam addition	Scale change Antifoam addition
Step 4 Harvest	Filter area (15 m^2)	Filter area (45 m^2)	Scale change

Fig. 2 Comparison of Changes Between the Manufacturing process A and manufacturing process B Cell Culture and Harvest Processes

2.2. → Comparison table before and after the change

The note1) note2) of the comparison table (draft) of the application for approval are shown in the attached sheet.

Notes

Notes: 1) Control tables of new and old products are shown in the attached sheet. In this mockup, the record of the old and new comparative tables (draft) is omitted.
You are.
Note 2) When applied at the time of new drug application, the form includes the time of application for approval and changes in this plan after approval.

Introduction of the representative section

3. Impact of process changes on drug substance (risk assessment summary)

Table 1 Changes and impact assessment Note1) for Process A and Process B

Process	Proposed changes	Manufacturing site X Manufacturing process A	Manufacturing site Y Manufacturing process B	Impact	Results of the prior study of validity of impact assessment	† Mitigations
Step X • • •	• → • • •	• • •	• • •	• • •	• • •	• • •
Step 3: Production culture	• → Scaling of Bioreactors for Extended Culture and Production Culture	5,000 L	20,000 L	Medium	Small scale tests were performed to confirm that differences between the steps of the expansion culture and production culture bioreactors did not affect the quality. In addition, pilot scale tests were carried out and verified. Preliminary review estimated that these changes did not affect the process or product from the results obtained in the study. However, from the past production results including other products, there is a possibility that scale change, etc. may affect the quality in actual production.	Perform production culture on the actual production scale and evaluate the effect on process performance and quality attributes.
	• → Antifoaming agents	Not used	Use	Medium	Tests were conducted on small-and pilot-scale to confirm that the defoaming agent concentration was sufficiently reduced in the purification process and that the use of the defoaming agent did not affect the quality. Based on the results obtained from the test and the previous manufacturing experience, including other products, it was estimated by prior review that this change would not affect the process or product.	Proper removal of during the production scale purification process will be demonstrated as part of the process validation

† No risk reduction study will be conducted for parameters with "low" impact assessment results.

Introduction of the representative section

4. Comparability study plan (Manufacturing process performance)

- → Cell culture step (steps 1-4)

☐ Comparability will be verified by the following items in the cell culture process.

Table 2. Acceptance criteria for process performance of cell culture process

Step	Process performance	Acceptance Criteria
Steps 1 to 2	Cell survival rate	Xx % or more
	・・	・・
Step 3	Cell survival rate	Xx % or more
	・・	・・
	Production volume	Xx mg/mL or more
Step 4	Bioburden (in-process control test)	Xx CFU/mL or less
	・・	・・

- → Purification step (steps 5-12)

☐ Comparability will be verified by the following items in the purification process.

Table 3 Criteria for process performance of the purification process

Step	Process performance	Acceptance Criteria
Step x	Yield	Xx % or more
	・・・	・・・
・・・	・・・	・・・
Step y	Yield	Xx % or more
	Bioburden (in-process control test)	Xx CFU/mL or less
	HCP (in-process control test)	Xx ng/mg or less
	・・・	

Introduction of the representative section

4. Comparability study plan (Characterization and specification)

Table 5 Test Items and Proposed Comparability Acceptance Criteria between Manufacturing Process A (5000L) and Manufacturing Process B (20000L) (according to the specifications and test methods of the drug substance)

Test item	Test method	Proposed Comparability Acceptance Criteria 1	Proposed Comparability Acceptance Criteria 2
Description	Visual inspection	Be a liquid of XX	---
Identification test	Peptide map	Equivalent to the reference material	---
Carbohydrate profile	Liquid Chromatography	Equivalent to the reference material	---
pH	pH determination	XX-XX	Being within the 95% confidence interval of the measured value of the batch of Manufacturing Process A
Charged isoform	Cation Chromatography	Equivalent to the reference material	---
Aggregate	Size exclusion Chromatography	Aggregates ≦ XX%	Being within the 95% confidence interval of the measured value of the batch of Manufacturing Process A
Fragmentation	iCE	Purity ≧ X%	Being within the 95% confidence interval of the measured value of the batch of Manufacturing Process A
Host cell Derived protein	ELISA	≤ XX ng/mg	Being within the 95% confidence interval of the measured value of the batch of Manufacturing Process A
Endotoxin	Endotoxin Test method	≤ XX EU/mg	---
Microbial limit	Viable count	≤ XX CFU/XX mL	---
Relative potency	Biological activity test	XX-XX%	Being within the 95% confidence interval of the measured value of the batch of Manufacturing Process A
Protein content	UV/VIS	XX - XX mg/mL	Being within the 95% confidence interval of the measured value of the batch of Manufacturing Process A

Introduction of the representative section

4. Comparability study plan (Stability)

Table 6. Stability study plan of drug substance after manufacturing process change

Test	Conditional	Time-point	Test Lot Count
Accelerated test	2～8℃	1, 3, or 6 months	3 lots
Stress Testing	25℃	1 month	1 lot

Introduction of the representative section

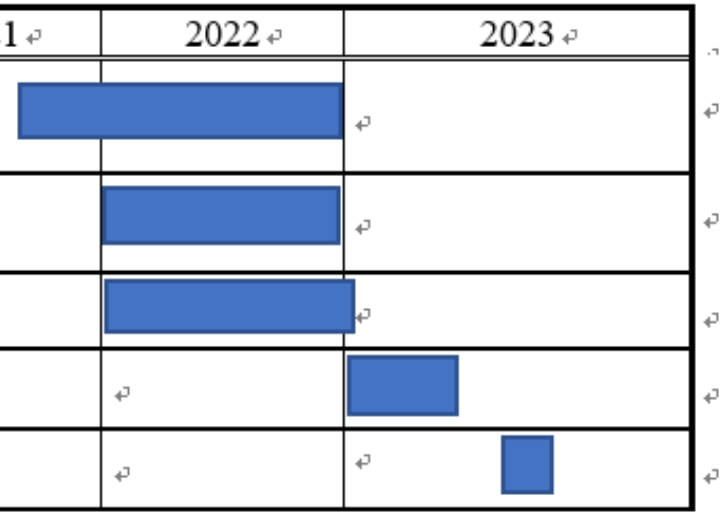
5. Process Validation

3-batches for process validation (PPQs) is planned to be manufactured and evaluated on a commercial scale at Manufacturing Process B (Manufacturing site Y).

Introduction of the representative section

6. Project timeline overview

	2021	2022	2023
Manufacture and evaluation of batches for validation of production scale processes			
Comparability study using the drug substance			
Accelerated and Stress Testing of Drug Substances			
GMP inspection			
Notification of change (Step 2)			



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Result and discussion

- **Preparation of PACMP example was started for implementation of ICHQ12 in Japan.**

- **It was recognised through the preparation,**
  - **The data will be required according to the changes.**
  - **The evaluation items will depend on the changes and quality attributes.**

- **It would be further discussed by any points that are considered to be potential issues for implementation in Japan.**

The review after preparation
(point view of the content)

Though the example was prepared inline with ICH Q12, were there any major differences from Europe and the U.S. ?

- **We were able to prepare based on ICH Q12**
- **We were also able to show reflected the contents in terms of Application Form in Japan.**
- **Through this preparation, it was confirmed that there were no major gaps from Europe and U.S.**

The review after preparation
(perspective from the current pilot program)

What are concerns with this pilot program in Japan?

- **Downgrading the variation category and/or shortened review period**
- **PACMP in original registration submission**

The review after preparation
(perspective from after ICH Q12 implementation)

What are expectations for future implementation in Japan?
ICHQ12 and PMD Act revision

- **Expected to be shortened to 30 days (e.g.CBE30, Type1B) in the future.**
- **Expected to be with the original registration submission as same as US/EU**
- **Expected to be reducing the gap between Japan and US/EU depending on the operation of ECs**

Based on the above, we would like to further collaboration between the regulatory authorities and the industry in the future

Conclusion

- **AMED PACMP WG is aiming at creating reference document through the creation of the example for ICHQ12 in Japan**
- **It will also be used as an example of PACMP at initial application for a new drug of implementation in Japan**
- **We would like to continue to consider proposals for solutions**

Messages from AMED Bio PACMP WG

We prepared PACMP example considering the use of new drugs in post-approval changes based on ICH Q12.

We hope there will be as many people as possible to utilize it.

Thank you !!