Case Study:

Industry Experience from PACMP Pilot Program in Japan

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For CMC Strategy Japan 2020
December 8, 2020

Overview

- PACMP Pilot Program in Japan
- Chugai experience for the PACMP Pilot Program
- Lessons learned from the Pilot program
    - Expectation for ICH Q12 implementation (step 5)

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Introduction

- ICH Q12 reached Step 2 in Nov 2017.
- “PACMP Pilot Program in Japan” started in Apr 2018 in Japan.
    - MHLW notification No.0309-1：March 9, 2018
    - *“Trial” of PACMP to increase predictability and transparency for post-approval CMC changes*

Current Prerequisite to use PACMP Pilot Program in Japan

MHLW notification No.0309-1, March 9, 2018

1. Post-approval CMC Changes of medicinal product
   (excluding *in vitro* diagnostic agents and change(s) in MF)
2. Medicinal product for which CTD was submitted.
3. GMP Inspection of the change with the PACMP is to be performed only by PMDA.
4. Manufacturer(s) runs PQS following ICH Q10 and the result of the MAH's verification for the operational status of PQS is available.
5. If the change concerns a medicinal product for which the Description Adjustment Notification was submitted, PMDA has completed the checks on the matters in the Description Adjustment Notification and has removed the underlining which was drawn under the Approved Matters.
6. Changes not requiring Clinical study or non-clinical study data for assessing the impact of the change

Submission at Initial filing is out-of scope

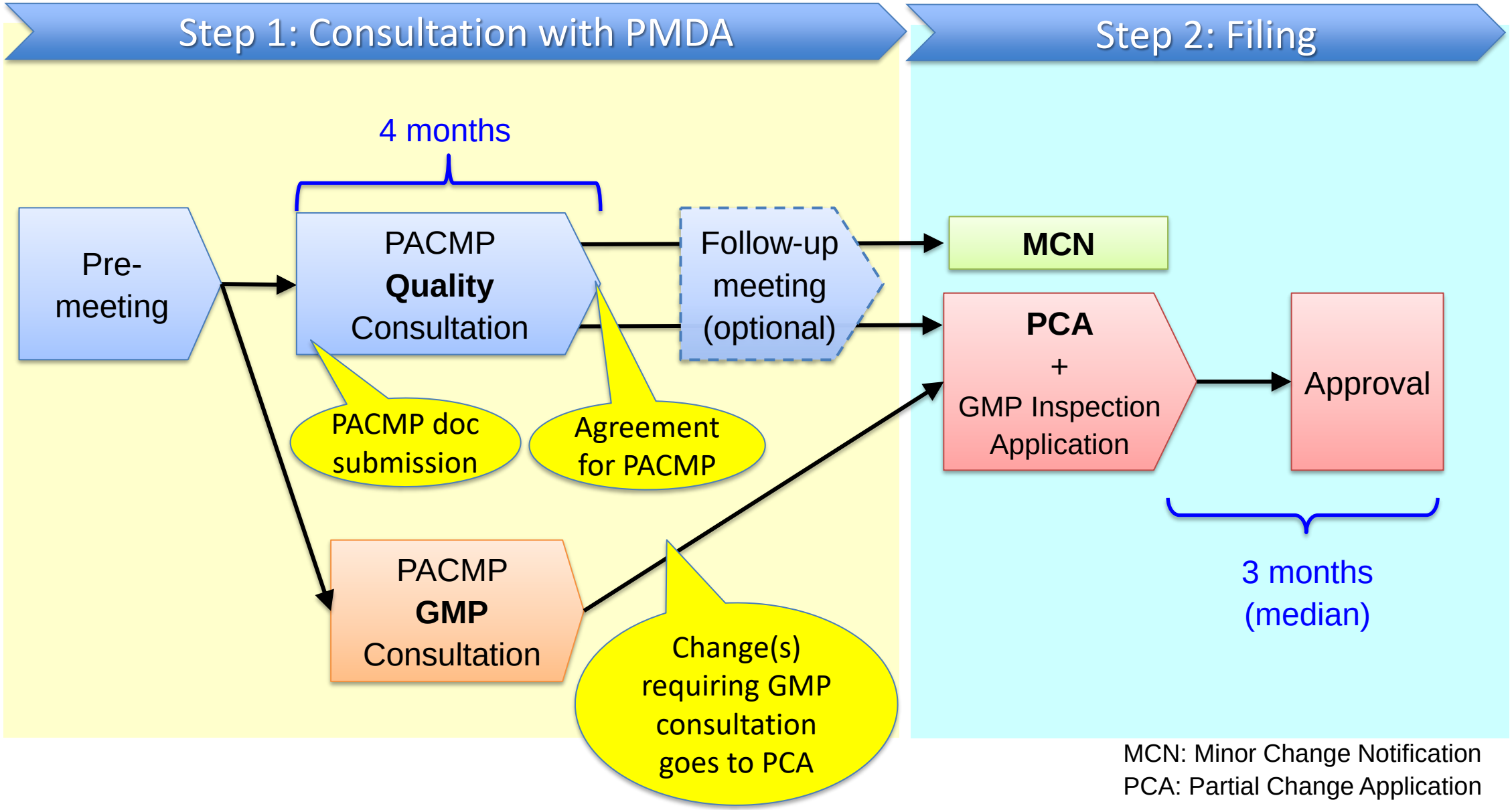
PMDA notification No.0207001 for 2020 April to 2021 March

- One change associated with a single product, as a general rule
- Each PMDA review dept can accept one consultation per month at maximum. → *Lottery system*

Broader Protocol of PACMP is out-of scope

Uncertainty of timeline predictability for MAH

Steps in PACMP Pilot Program of Japan



MCN: Minor Change Notification
PCA: Partial Change Application

Pre-meeting in the Pilot Program

Step 1: Consultation with PMDA

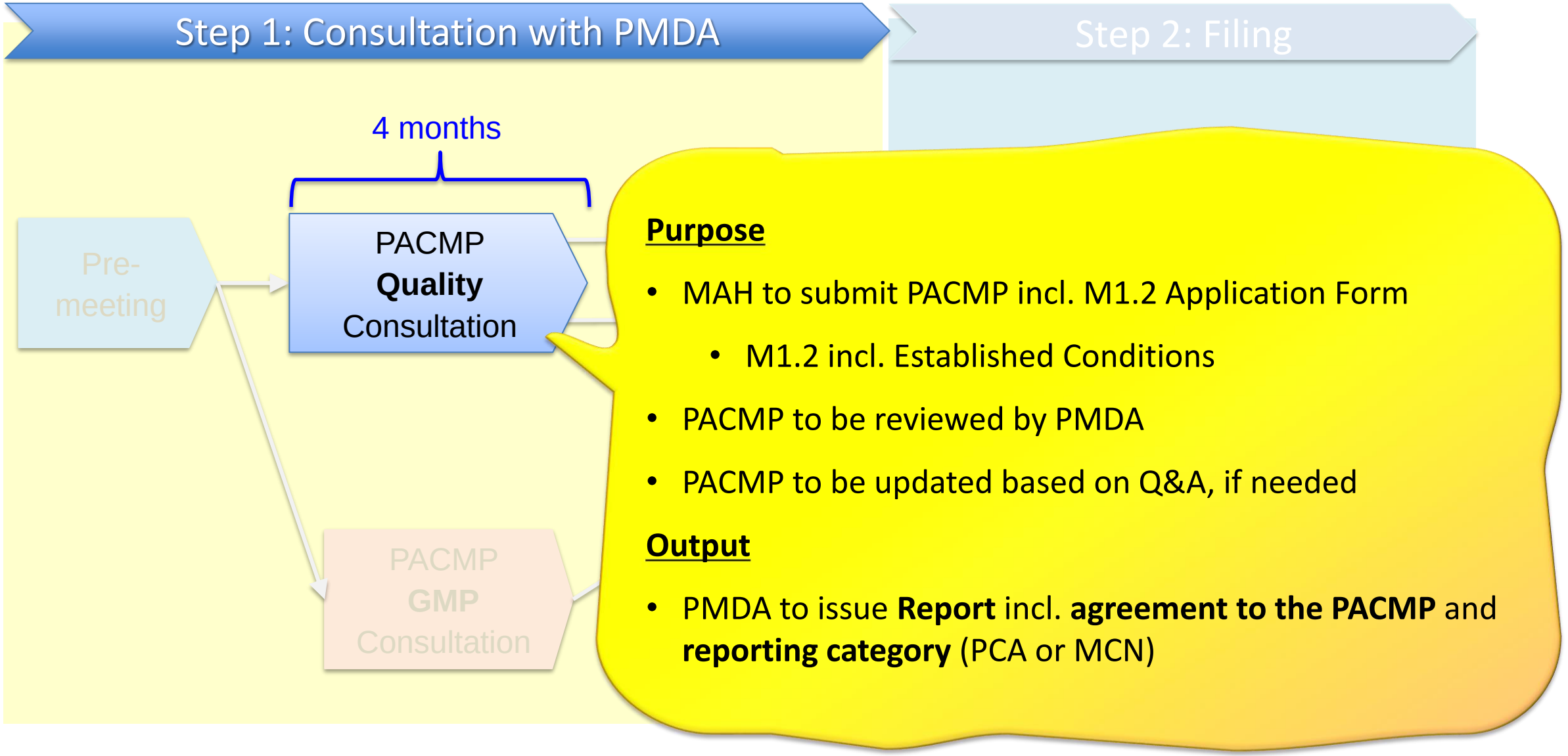
Step 2: Filing

Pre-meeting

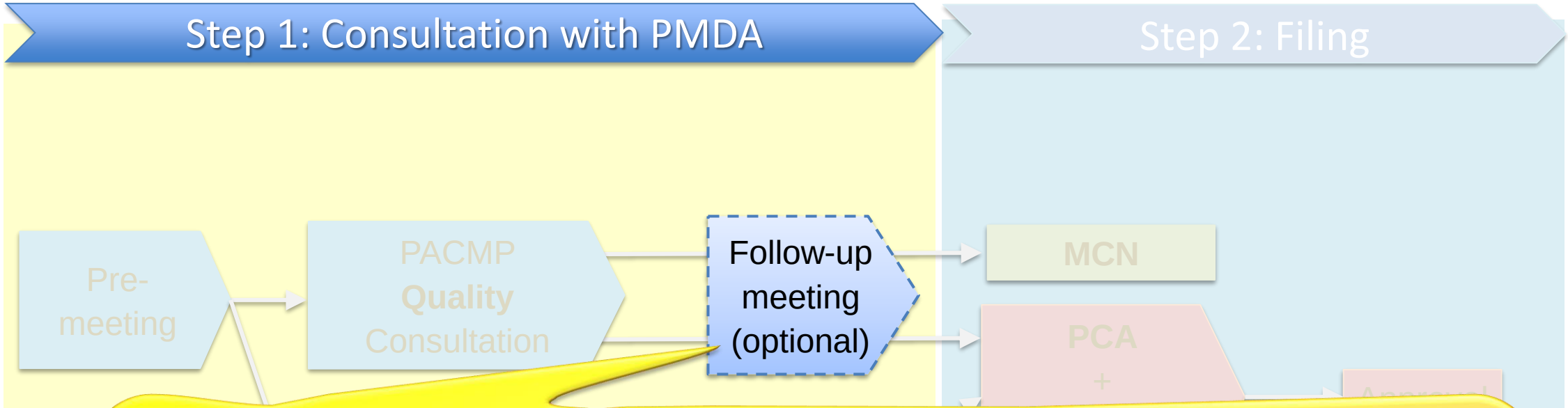
Purpose

- Communicate for preparation of PACMP Quality/GMP consultation
- PMDA to assess for necessity of PACMP GMP consultation
- Confirm timeline up to MCN/PCA
- PMDA to advice for documents of PACMP consultation

PACMP Quality Consultation in the Pilot Program



Follow-up Meeting (Optional) in the Pilot Program



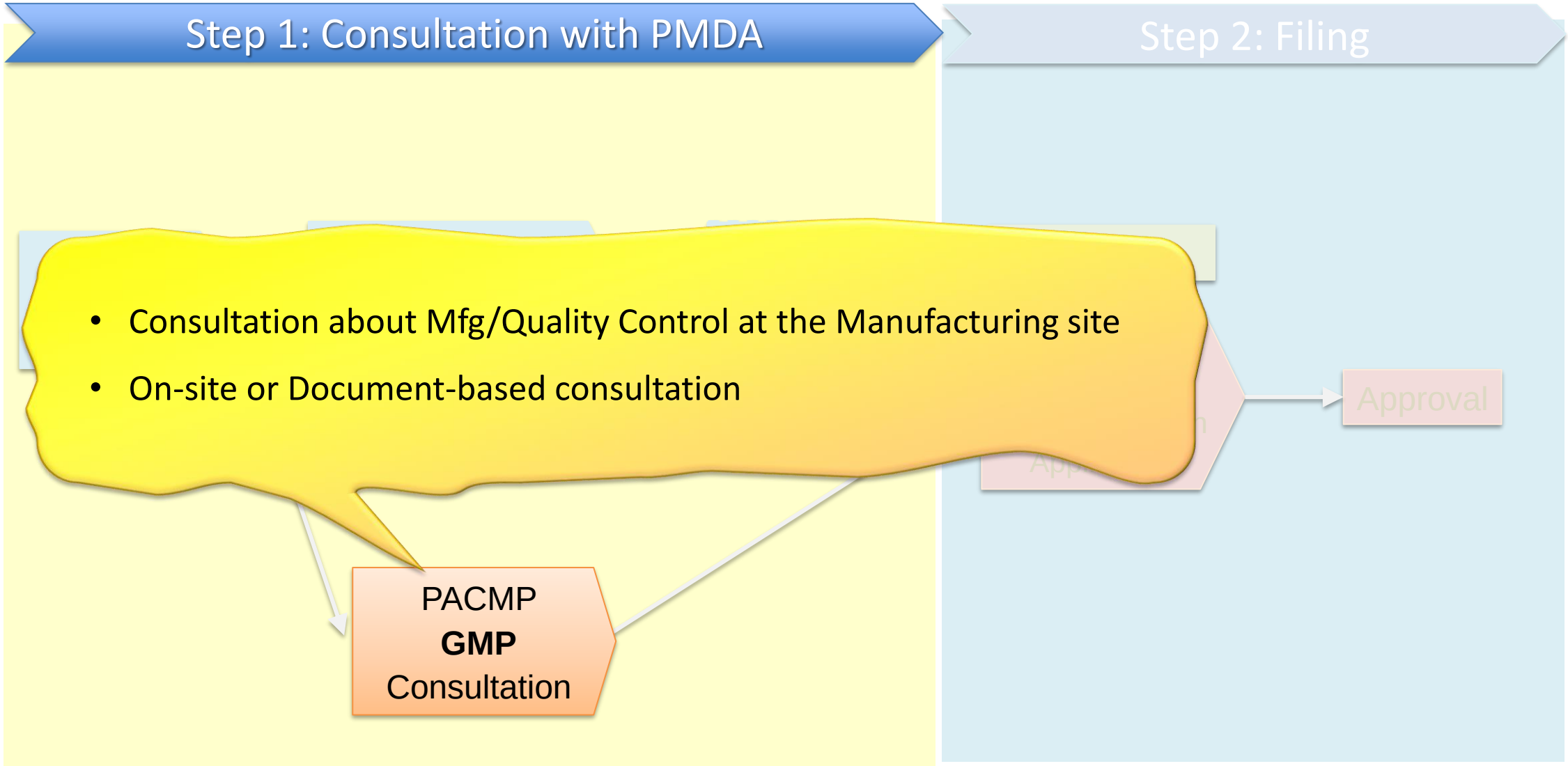
- If **Minor Modifications** to the Quality Consultation results are needed …
- Two type of F/U meeting available:

  1) Meeting <u>With</u> Report
     - If PACMP needs to be modified, the updated PACMP to be confirmed and agreed between PMDA and MAH.
     - PMDA to re-issue Report with agreement.

  2) Meeting <u>Without</u> report

     e.g. Information sharing about timeline changes, etc.

PACMP GMP Consultation in the Pilot Program



PCA/MCN Submission in the Pilot Program

Step 1: Consultation with PMDA

- Based on the agreed PACMP and PMDA report, MAH to do MCN or PCA
- Submission documents:
  - M1.2 Application Form
  - **PMDA Report** (incl. the agreed PACMP) from PACMP consultation
  - **MAH Statement** for No deviation against the agreed PACMP

PACMP
GMP
Consultation

Step 2: Filing

MCN

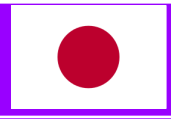
PCA
+
GMP Inspection Application

Approval

3 months
(median)

No review for data

Differences of PACMP System between US/EU and Japan

Step	Items		
		CP(US), PACMP (EU)	PACMP Pilot Program
Step 1	Allowable Timing of PACMP Submission	At Initial Filing and Post-approval	Post-approval ONLY
	PACMP Submission Acceptability by H. Authority	All application to be accepted	One application/one PMDA review dept /one month
	Type of PACMP	• One or more change(s) with single product • Broader Protocols	One change (and relevant change(s)) with single product
	Proposed Reporting Category	Need for Regulatory Inspection to preclude downgrade of Reporting category	Need of PACMP GMP consultation to go PCA
Step 2	Filing Documents	With data package (e.g. Comparability assessment results)	• M1.2 Application Form (incl. Established Conditions) • Statement for No deviation against PACMP (w/o data) → **Without data → No M2.3 & M3**

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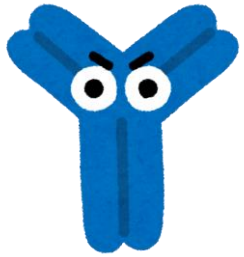
PACMP Pilot Program in Japan: Chugai Experience

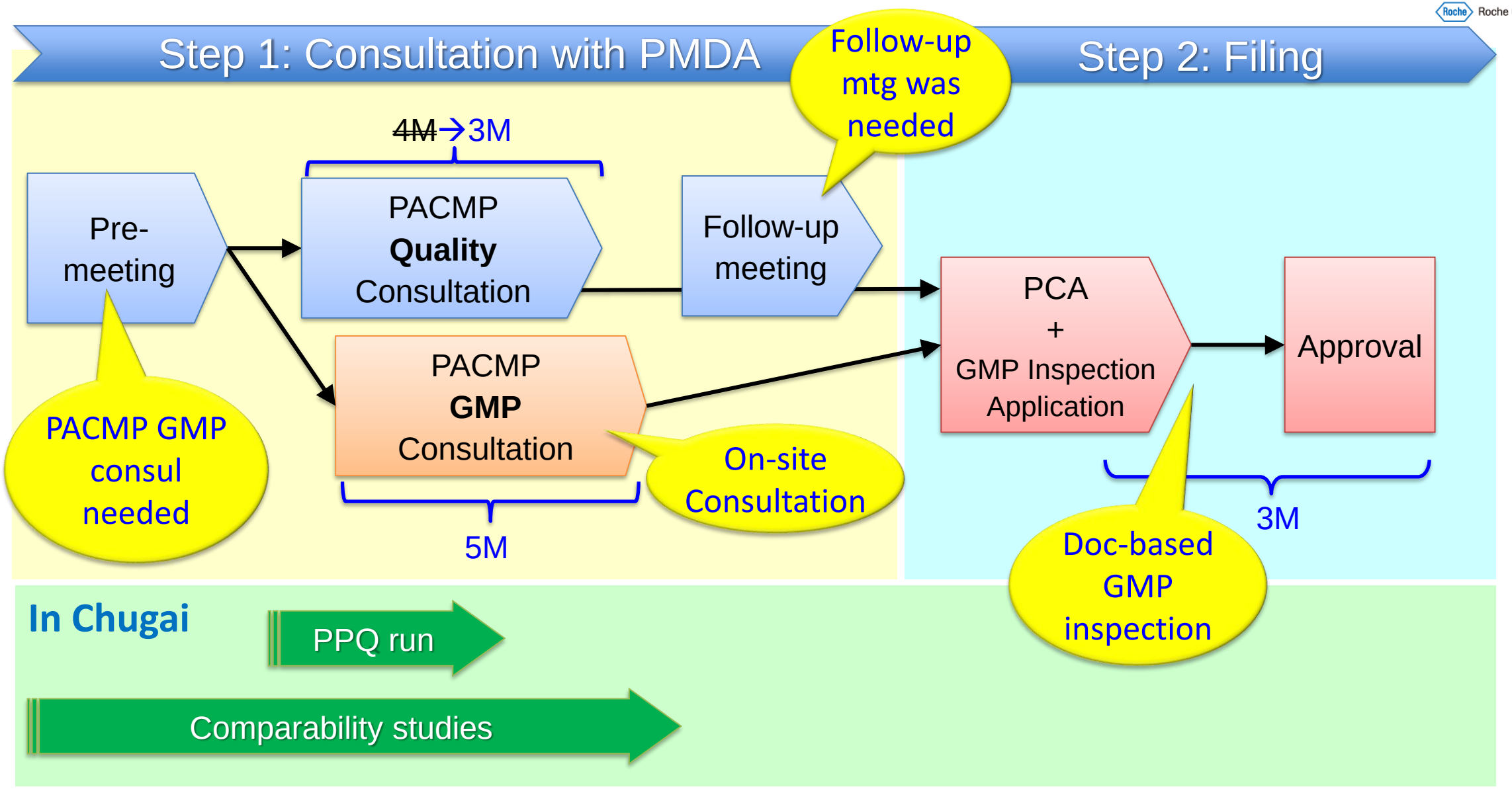
Following post-approval CMC changes were applied to PACMP pilot program in Japan.



- Product: Monoclonal antibody
- Changes:
  - Addition of New manufacturing facility for the Drug Substance
    (The facility had not been inspected by any health authorities.)
    - Scale-up of the production culture (and corresponding DSP scale-up)
    - Minor process changes - Adaptation to the manufacturing facility/equipment
    - Scale-up of the container for the Drug Substance

(No change for DS release specification)

PACMP Pilot Program in Japan – Chugai Case



Pre-meeting: Chugai Case

CHUGAI
Roche Group

- Documents submitted to PMDA before the meeting
  - Complied with PMDA Notification, No.0302070

#	Required Information
1	Summary of **Proposed Changes**
2	Summary of **Planned Documents** to be submitted for Quality/GMP Consultation
3	**Target timing** of Quality/GMP Consultation and PCA/MCN submission
4	Summary of **MCN** submitted after initial approval or latest PCA
5	Confirmation results by MAH for Manufacturer's **PQS**
6	**Application form** for **GMP inspection**

Meeting outputs

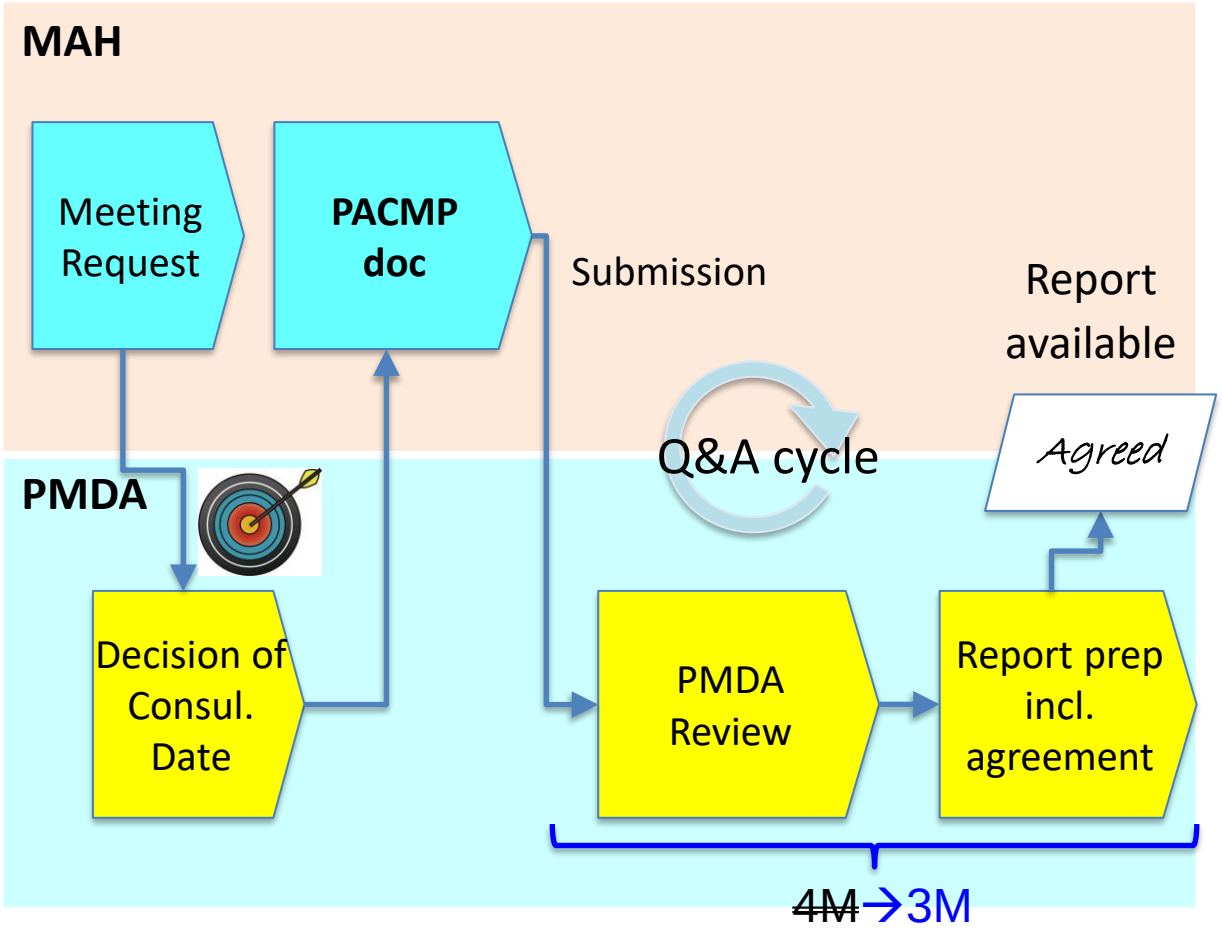
- PMDA advised on document structure/contents for PACMP Quality consultation
- Confirmed necessity of PACMP GMP consultation due to New mfg facility
- Confirmed timeline for PACMP Quality/GMP consultation and PCA

PACMP Quality Consultation: Chugai Case

- Chugai submitted **PACMP** doc.
- PMDA review → Q&A cycle
- PACMP was updated based on Q&A.

- **Output**: PMDA agreed the updated PACMP, issued the **Report with agreement**.
  →Reporting category was assigned as PCA.
- Total period: 3M

< Process Flow >



PACMP Quality Consultation: Chugai Case (cont.)

- Documents submitted to PMDA (= PACMP package in Japan)
  - Complied with PMDA Notification, No.0302070, and ICH Q12 (Step 2)

#	Required Information by PMDA
1	Description of **Proposed Changes**, including a **Rationale**
2	**Comparison Table before and after the changes** (including comparison table of **Module 1.2 Application Form**)
3	**Proposed Studies** and **Acceptance Criteria** to assess the impact of the changes (incl. **Comparability Protocol**)
4	Suitability of the approved **Control Strategy**, or any changes needed to the control strategy
5	Any other conditions to be met
6	**Supportive Data from previous experience** with same product
7	**Proposed Reporting Category** (PCA), and necessity of GMP inspection
8	Regulatory history and copies of previous Module 1.2 from initial approval

PACMP Elements in ICH Q12

Red indicates Japan-specific requirements for PACMP.

Proposed Studies in the PACMP: Chugai Case

- Comparability Studies (complied with ICH Q5E)
  - **CoA test items**: Release spec for DS and in-process spec.
  - **Quantitative assessment**: DS CoA test items and extended characterization
    - - Comparability Criteria based on pre-change manufacturing history
  - **Qualitative assessment**: Extended characterization
    - - Post-change DS are compared with Pre-change DS.
  - **Stability studies (Degradation)**: DS degradation studies with pre-change DS

- Other Studies (e.g. Site-dependent studies)

The proposed study plan was accepted by PMDA

Follow-up Meeting: Chugai Case

- Chugai proposed Follow-up Meeting because…
  - **Necessity to modify M1.2 Application Form** in the agreed PACMP:

    A few PPs were changed from Non-CPP to CPP based on the study results.

    → The CPPs were added in M1.2.
  - **Comparability assessment results**:

    Some data did not meet Comparability Criteria but were considered to be justifiable.
- **Follow-up meeting <u>with</u> Report** was conducted.
- Chugai submitted:

  1) **Updated PACMP** incl. updated M1.2

  2) **Comparability data** and **conclusion**

- **Output**: PMDA agreed the updated PACMP, issued **Report with agreement**.

PCA Submission: Chugai Case

- Documents submitted to PMDA
  - Complied with MHLW notification No.0309-1, March 9, 2018

Submitted Documents
Module 1.2 Application Form incl. Comparison Table
PMDA Report issued in Follow-up meeting (incl. **the agreed PACMP**)
MAH Statement for **No deviation** against the agreed PACMP
GMP inspection application

No necessity of M2.3/M3 (No Comparability Assessment Results)

- Approval after PMDA review (3M)

PACMP GMP Consul. and GMP Inspection: Chugai Case

- **PACMP GMP Consul.** in Step 1
  - Documents required by PMDA were similar with those for general GMP inspection.
  - GMP consul. was conducted **On-site**. (≒GMP inspection before PCA submission)
  - On-site consultation timing: After PPQ report available

    →PPQ data were confirmed during the on-site consultation.
  - **Output**: PMDA agreed to proceed Step 2 (GMP inspection application), issued Report with the agreement.

- **GMP Inspection** in Step 2
  - **Document-based** inspection
  - Follow-up from PACMP GMP Consultation

Note: The on-site GMP consultation results cannot be utilized for issuing GMP certificate by MHLW.

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Lessons Learned from PACMP Pilot Program in Japan

- **PACMP pilot program** in Japan - an efficient regulatory tool that provides predictability for post-approval CMC change(s).
  - Review period: 3M (Standard PCA: 12M)
  - Transparency between PMDA and industry is one of important key to enhance the program.

- **Pre-meeting** provides clear roadmap from PACMP consultations to PCA
- **PACMP Quality consul**: Total period was 3M (PACMP standard: 4M)
- **Follow-up meeting** in case of necessity to modify the agreed PACMP doc.
- **PACMP GMP consul**. (≒GMP inspection before PCA)
- **PCA**: No need of M2.3/M3 submission.

Expectations for ICH Q12 Implementation (Step 5) from Industry View

- To PACMP program in Japan
    - Apply to Initial Filing
    - Apply to Broader Protocol
    - Remove Lottery system (for timeline predictability in industry side)
    - Keep PCA system without M2.3/M3
    - Expand the scope (e.g. Regenerative Medical Products)
- PACMP Mock-up doc availability should be useful for industry.

- To PACMP in overseas
    - **If…** GMP inspection in the Step 1 like PMDA GMP consultation is available, PACMP would have more ability to use a lower reporting category.

Summary

- PACMP Pilot Program in Japan
  - It is a Trial still now – Some prerequisites.
- Chugai experience for the PACMP Pilot Program
  - PACMP is a efficient regulatory tool that provides predictability for post-approval CMC changes.
- Lessons learned from the Pilot Program
  - Expectation for ICH Q12 implementation (step 5) from industry view

Special Thanks to

API Process Development

Hiroyuki Kajiwara
Mitsuhiro Hitotsuyanagi
Akihiko Saito

Drug Substance Manufacturing

Yoshihisa Kishiguchi
Norio Suzuki

Analytical

Kim Minsoo
Satoshi Tainaka
Yousuke Ikeda
Kenji Ishida
Yuuko Nakamura
Atsuko Isobe
Nobuyuki Tanaka
Tohru Shimuta

Site QA

Chiaki Yamada
Kayo Tanahashi
Susumu Abe
Ikue Taguchi

Corporate QA

Masashi Tsukazaki

Regulatory Intelligence and Management

Takayoshi Furuyama

Project management

Hiroaki Nagashima
Satoshi Yasukawa

CMC Regulatory

Tokumasa Ando
Chiemi Sato

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