CMC Topics and PMDA's activities

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Agenda

- Introduction of PMDA
- ICH Q12
- QbD assessment experience in Japan
- Example of QbD Application in Japan
- Continuous Manufacturing

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/en/index.html

Regulatory authorities for drugs and medical devices

PMDA

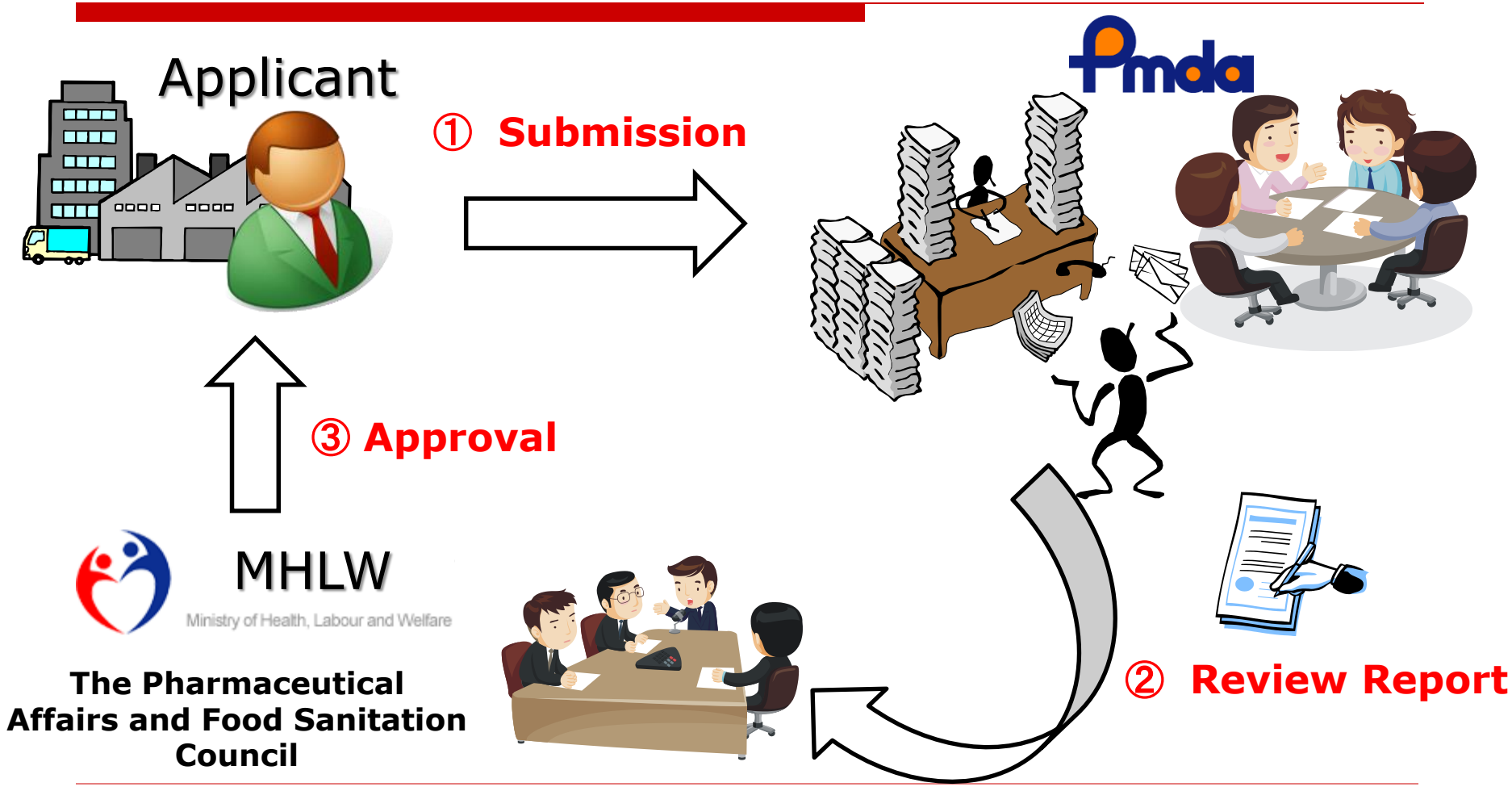
- Scientific review for drugs and medical devices
- Consultation on clinical trials etc.
- Inspection (GCP, GLP, GMP, QMS etc.)
- Supporting MHLW's activities

MHLW

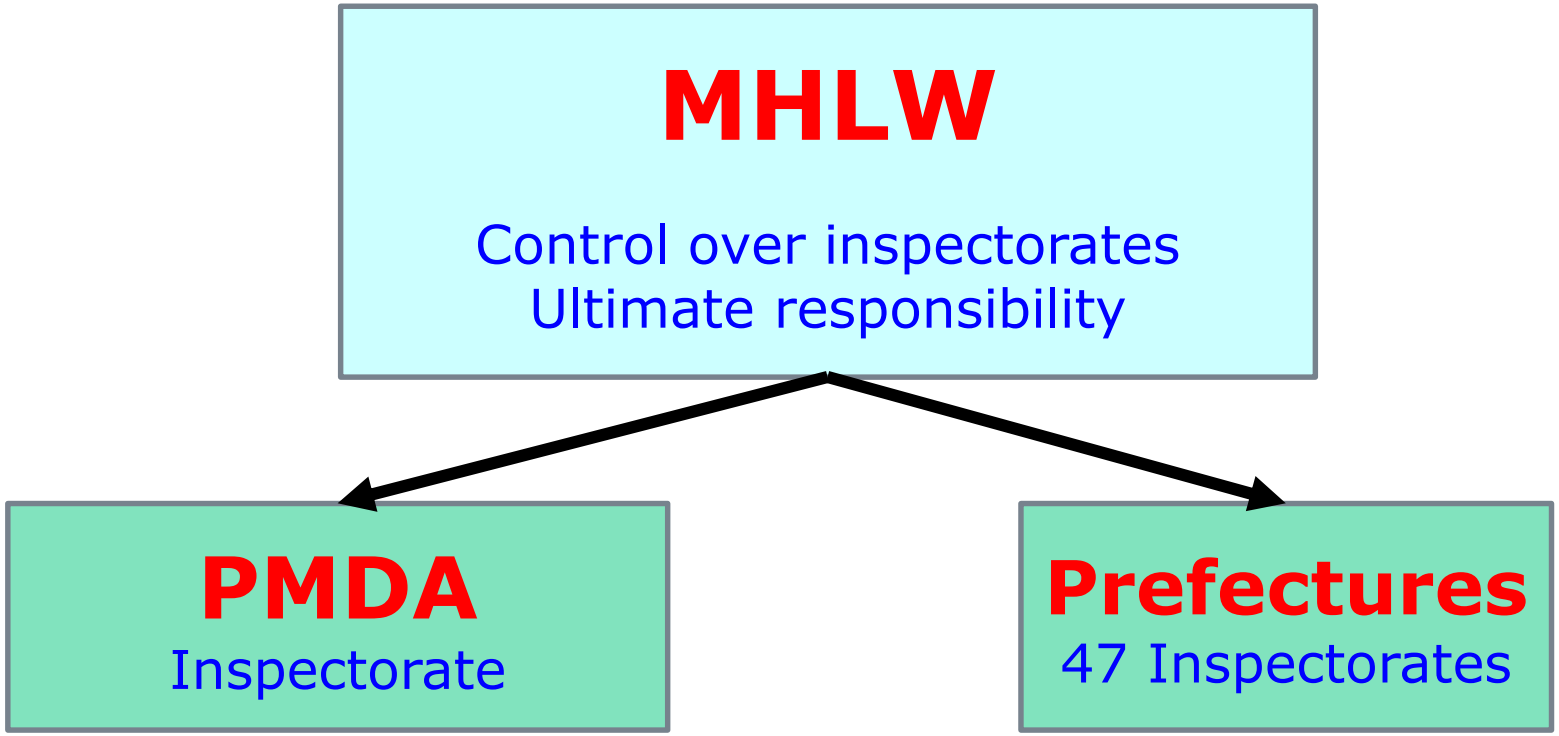
- Authorization of applications
- Publication of guidelines
- Supervision of PMDA activities

PMDA: Pharmaceuticals and Medical Devices Agency
MHLW: Ministry of Health, Labour and Welfare

Flowchart of Reviewing Process



GMP Inspection System



PMDA is partially vested with authority of MHLW

Prefectures are vested with part of MHLW's authority to exercise local autonomy.

GMP Inspections by PMDA and Prefectural Governments(47)

	Domestic Site	Foreign Site
New Drugs, Biological Products, Radio Pharmaceuticals	PMDA	PMDA
Other Drugs	Pref. Gov.	PMDA

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)

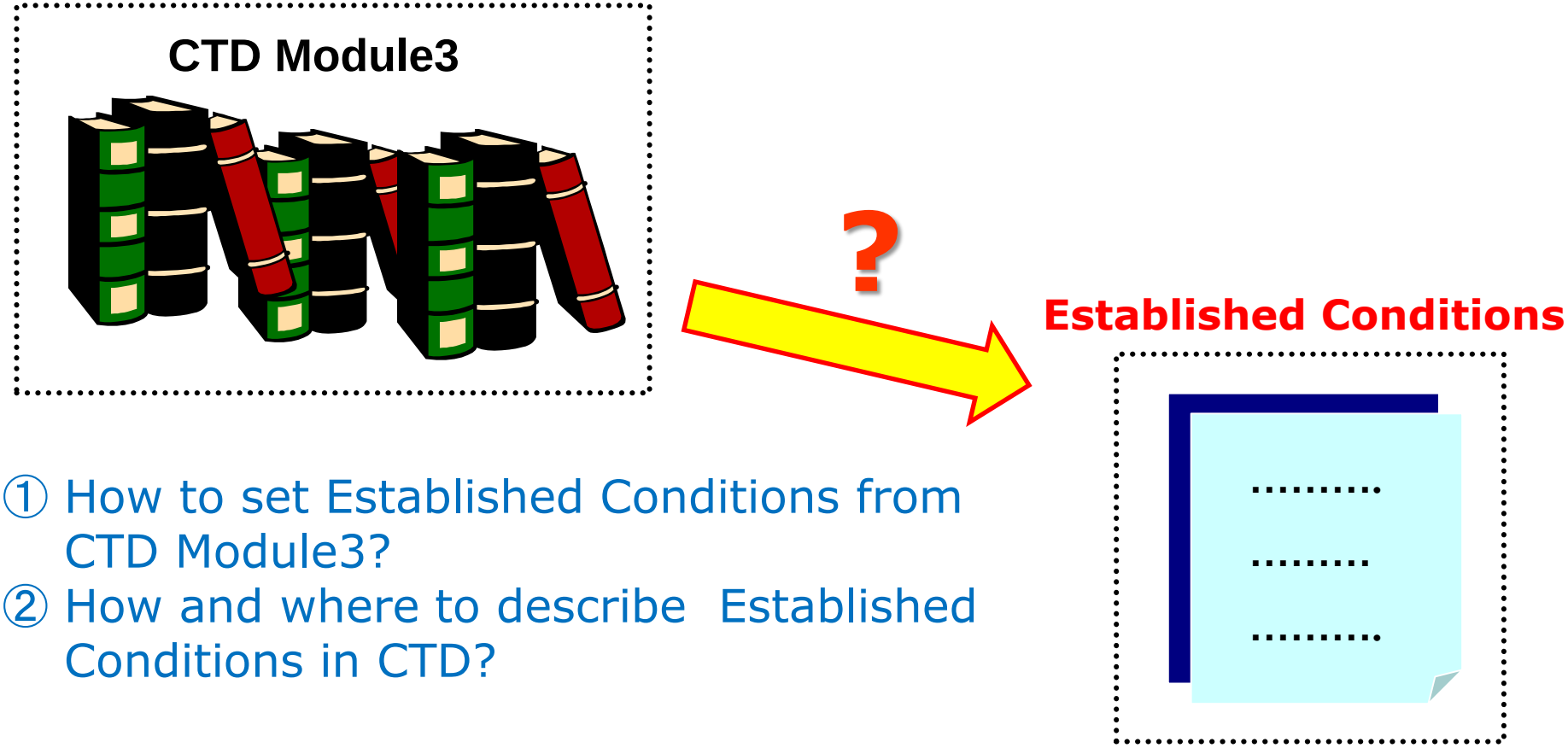
Definition of Established Conditions

- Legally binding information defined in an approved Marketing Authorization Application
- Any change to an Established Condition, as defined in an approved application, would initiate a post-approval regulatory submission

Discussion Points:

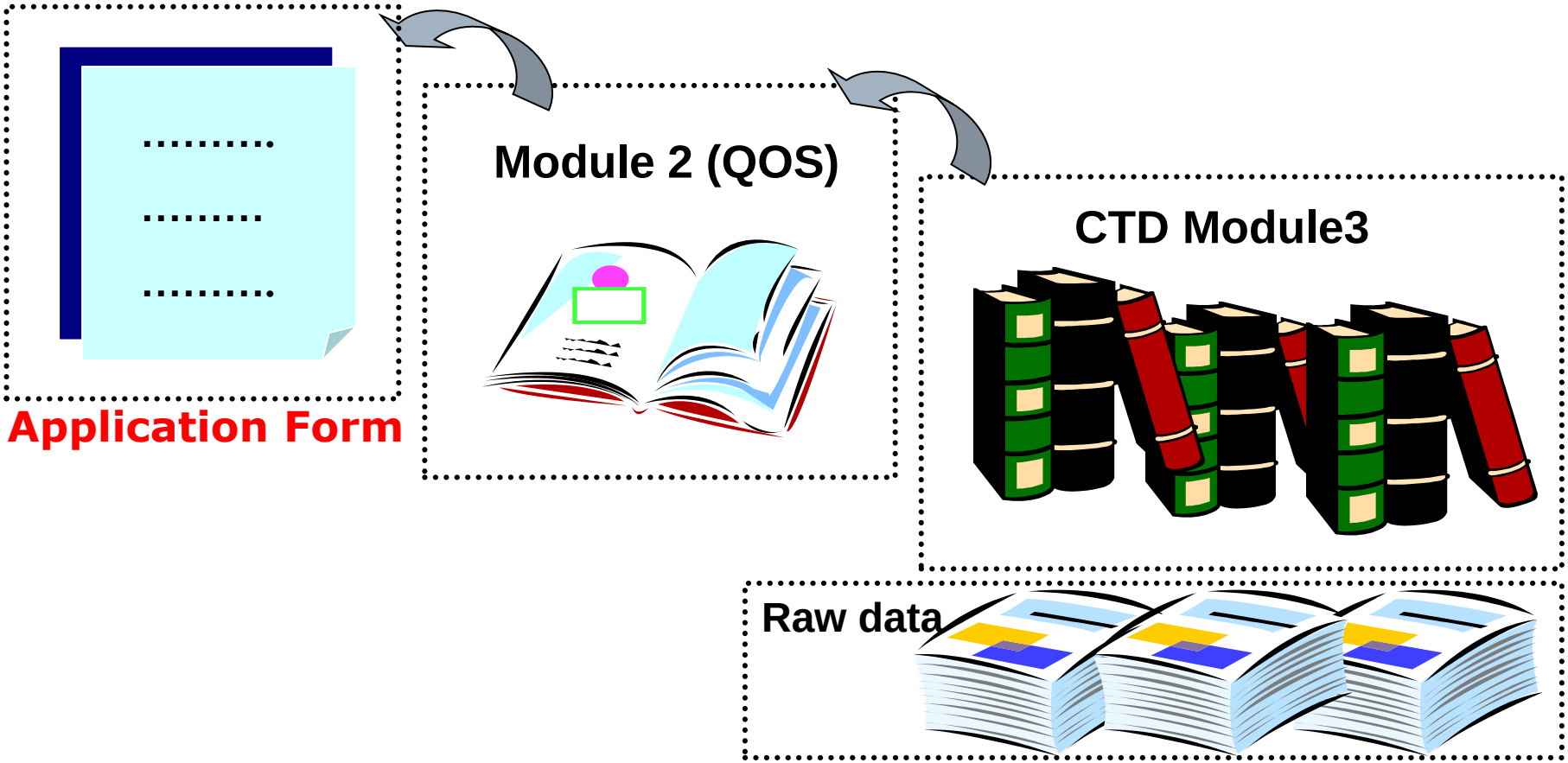
Any change to a non-Established Condition does not require regulatory interaction

Established Conditions



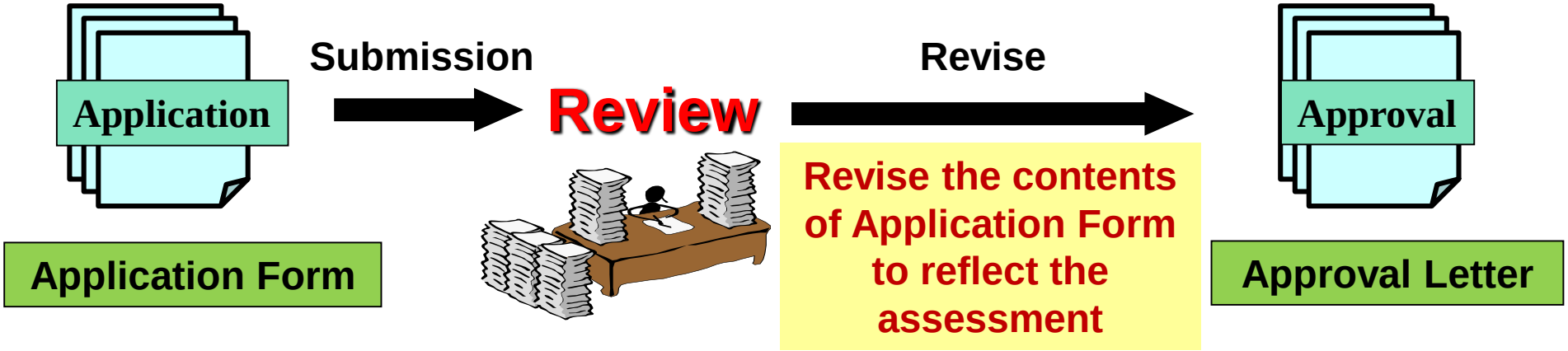
① How to set Established Conditions from CTD Module3?
② How and where to describe Established Conditions in CTD?

Relationship between Application Form and CTD Documents in Japan



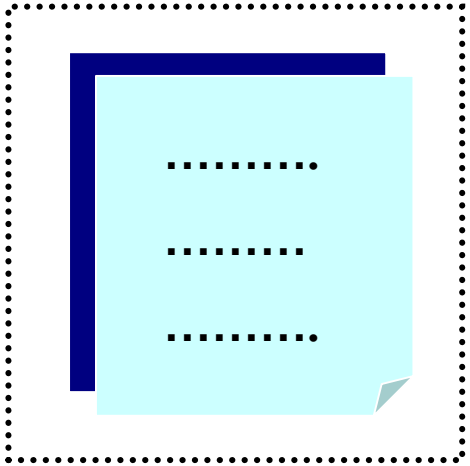
What is the Application Form?

- 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



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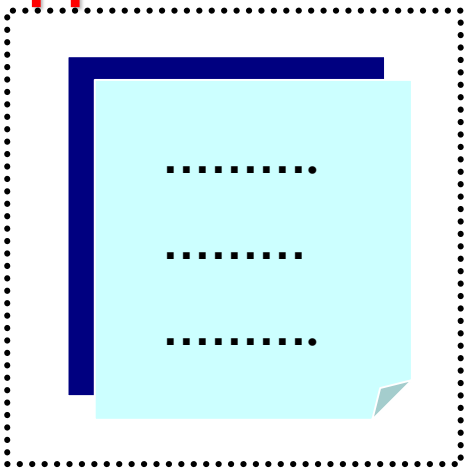
Application Form

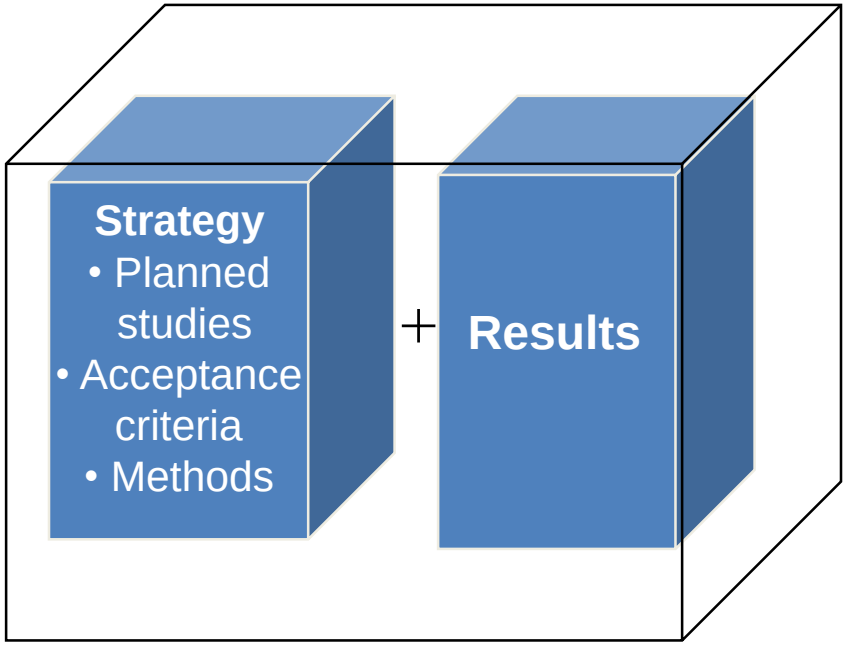


Post-Approval Change Management Protocols (PACMPs)

- 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.

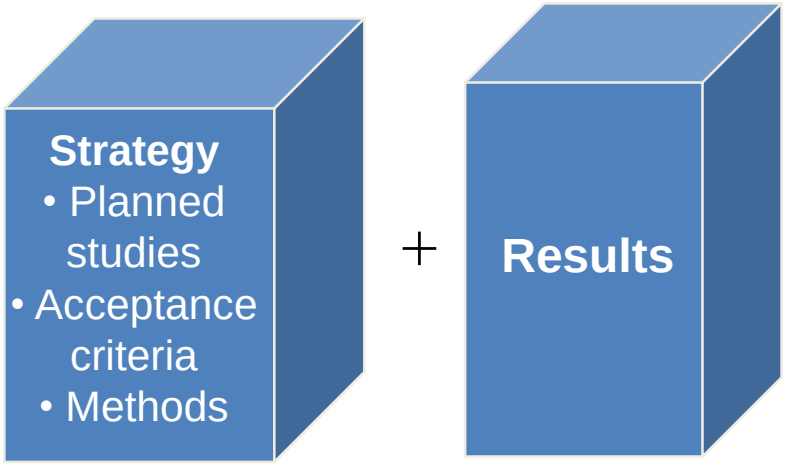
(EU) Principle of PACMP

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 protocol only in Japan like to EU.
- How to harmonize the concept of PACMP?

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We are trying to introduce philosophy of PACMP in Japan.

Our Challenge!

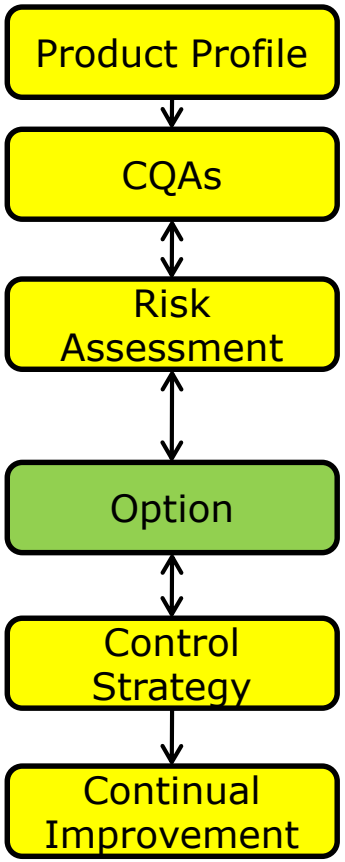
QbD assessment experience in Japan

- Number of Approved Products with QbD

2007	2008	2009	2010	2011	2012	2013	2014	2015
0	3	3	2	11	11	12	27	16

Nowadays most applications usually apply QbD approaches.

Example of QbD Approach



- Quality Target Product Profile (QTPP)
- Determine "potential" critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop Mathematical Models, Design Space or Real Time Release Testing (*optional and not required*)
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Acknowledgement : Adapted from ICH Q-IWG training materials

Why do you think QbD is the focus?

- Provides a higher level of quality assurance
- Facilitates regulatory assessment
  - Systematic development described in regulatory submissions will improve the regulatory assessment
  - Improves the efficiency of the assessment / inspection
- Enables science and risk based regulatory decisions
  - Provides more operational flexibility
  - Facilitates innovation
- Improves communication
  - Between Regulators and Industry
  - Between Assessors and Inspectors

Example of QbD Application in Japan

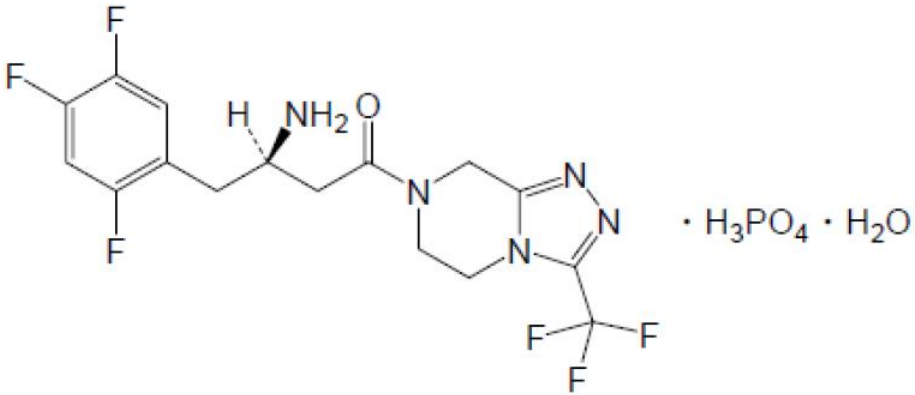
- MSD presented at the ISPE Annual meeting in 2014;
  - By introducing RTRT(Real Time Release Testing) to Januvia tablets which they market worldwide,
  - They were able to save up to 20 million US dollars in 5 years

Why?

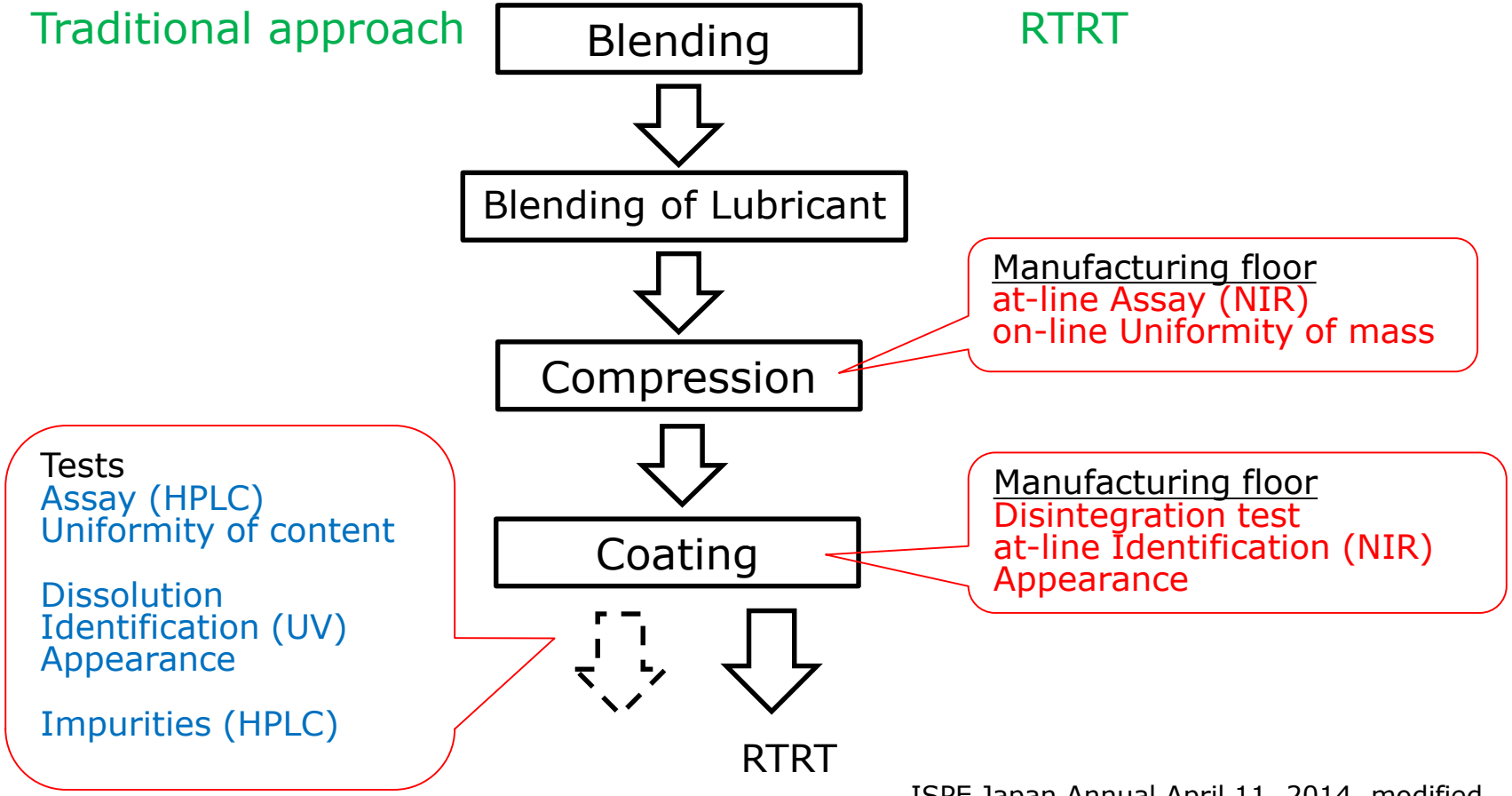
Example of Januvia® (1)

Januvia®

- Active Ingredient : Sitagliptin Phosphate Hydrate
- Approved : Oct. 2009
- Indication : Type 2 diabetes mellitus
- DPP-4 inhibitor



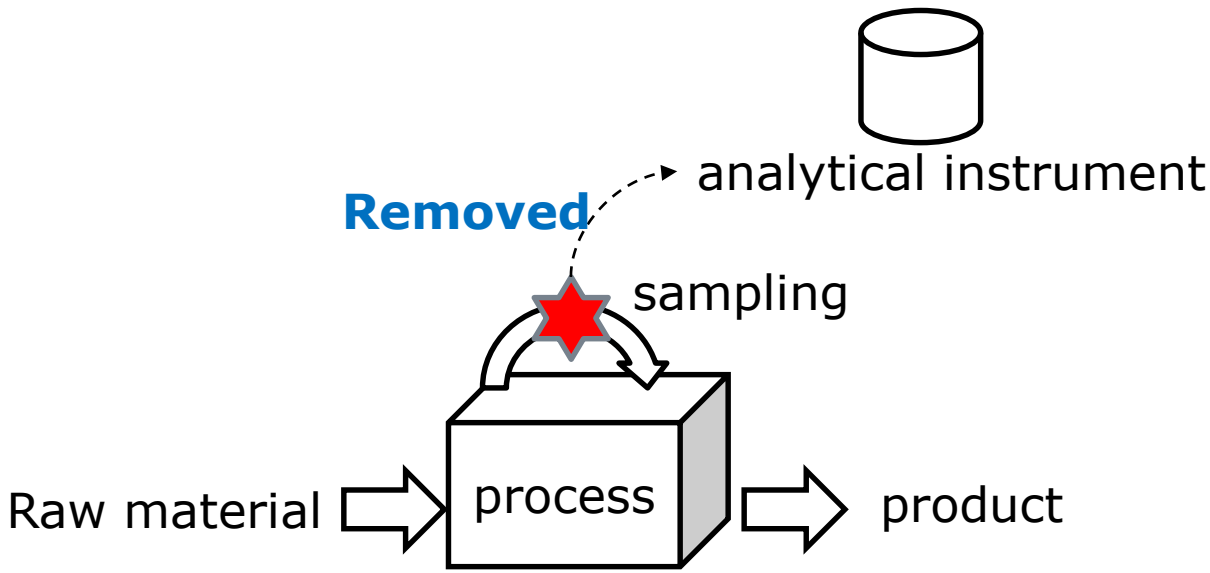
Example of Januvia® (2)



ISPE Japan Annual April 11, 2014, modified

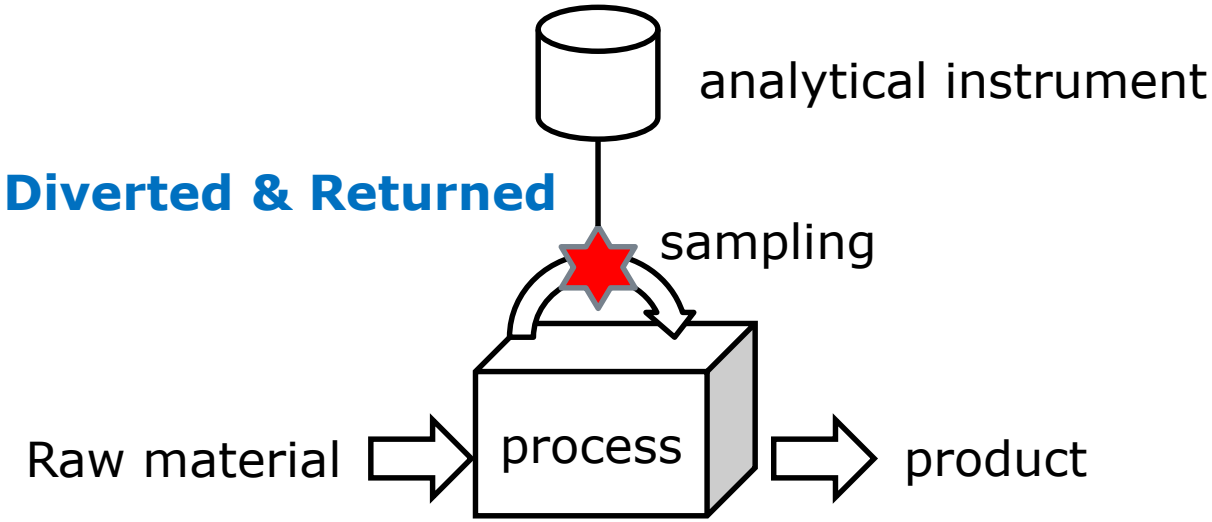
Example of Januvia® (3)

- at-line



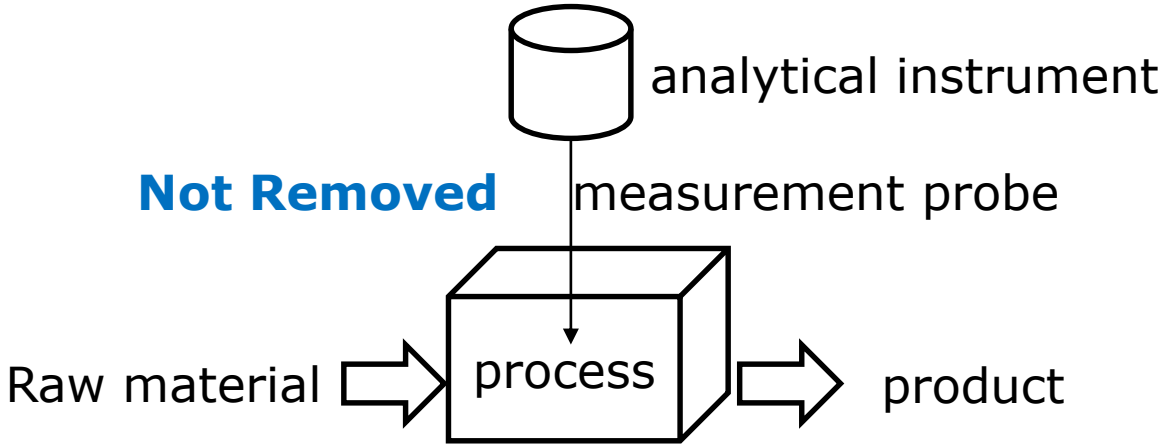
Example of Januvia® (4)

- on-line



Example of Januvia® (5)

- in-line



Example of Januvia® (6)

- They were able to save up to 20 million US dollars in 5 years

- Opportunities exist to **develop more flexible regulatory approaches**, for example, to facilitate:
  - risk-based regulatory decisions (reviews and inspections)
  - manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
  - reduction of post-approval submissions
  - real-time quality control, leading to a reduction of end-product release testing

Example of Lixiana® (1)

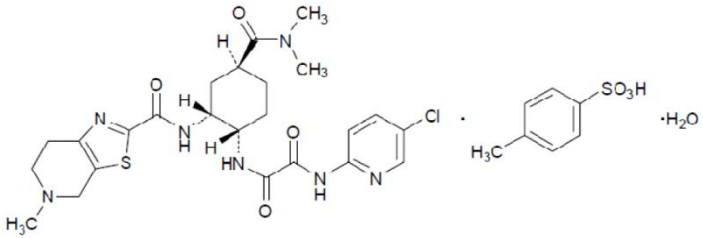
Report on the Deliberation Results

March 1, 2011

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name]	Edoxaban Tosilate Hydrate (JAN*)
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	March 29, 2010

[Chemical structure]



Some review reports are translated into English.
http://www.pmda.go.jp/english/service/drugs.html

Example of Lixiana® (2)

2.A.(3).4) Control of drug product

The proposed specifications for the drug product include description (appearance), identification (HPLC, ultraviolet-visible spectrophotometry [UV]), uniformity of dosage units (content uniformity), dissolution (paddle method, UV), and assay (HPLC). For [redacted], an alternative test or a real-time release test (RTRT) performed as [redacted] test are defined as follows as the release acceptance criteria for the drug product.

- Approved in April 2011
- RTRT : Uniformity of dosage units, Dissolution and Assay
- The first case that RTRT for Dissolution was approved in Japan

Example of Lixiana® (3)

2.B.(2) Design space to ensure dissolution

Regarding the design space for ensuring the dissolution, the applicant explained as follows: At the time of the regulatory submission, [redacted] had been determined as the factor affecting the dissolution, based on the [redacted] of the results from [redacted] to the commercial-scale production. After the submission, the concept of the control strategy on dissolution was changed from [redacted] to [redacted], and the dissolution-related risks were re-evaluated. As a result, a total of [redacted] factors, [redacted], were extracted as factors affecting dissolution. The subsequent systematic analysis of the above [redacted] factors based on the design of experiments provided an equation for calculating the dissolution rate that contains [redacted] as input variables. [redacted] was not included in the variables of the equation, which showed that [redacted] did not affect the dissolution within the range studied. With the above results taken into consideration, [redacted] were identified as factors that constitute the design space for ensuring the dissolution and then a design space for ensuring the dissolution was re-constructed.

Example of Lixiana® (4)

- Identification of factors affecting the dissolution
- The subsequent systematic analysis of the factors based on the DoE provided an equation for calculating the dissolution rate
- Is it possible to ensure the dissolution by the mathematical model in the same way as the Sakura Tablet*?

* Sakura Tablet was used in ICH Q-IWG Workshop.

http://www.nihs.go.jp/drug/section3/English%20Mock%20QOS%20P2%20R.pdf

Example of Lixiana® (5)

- What reviewers focused on
  - Is the dissolution method adequately set?
  - Is it enough to determine the factors affecting the dissolution?

- In this case, the concept of the control strategy was changed by applicant after NDA.
  - What is the reason why applicant needed to change the concept?
  - What influence will the changes have on the construction of the model?

Example of Lixiana® (6)

Continued

- Is the validation/verification of the model adequate?
  - The verification of the model throughout the lifecycle is essential.

- How reliable is the model?
  - To know the limits of the prediction model
  - To consider the uncertainty of models

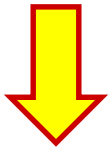
Example of Lixiana® (7)

Since the re-constructed design space for ensuring the dissolution of the drug product is configured based on the mathematical model, it is useful to ensure the performance of the model by confirming that the drug product with the appropriate dissolution rate is manufactured as expected. Therefore, PMDA considered that it was necessary to perform the dissolution test included in the specifications at release from the early post-marketing phase, and asked the applicant to confirm the performance of the equation for calculating the dissolution rate, by simultaneously carrying out the dissolution test on the commercial lots after approval, based on the production plan for the drug product as well.

- PMDA considered that this case is the highest impact model among the High-Impact Models in ICH Q-IWG Points to consider because the judgment for release is based on the indirect indicator.

Example of Lixiana® (8)

- To facilitate innovation, regulators and industry need to work in cooperation.



- PMDA assessed
  - The relationship between each of the extracted variables and dissolution had been investigated appropriately.
  - The maintenance program was established to ensure the model's continuity.

Example of Lixiana® (9)

- However, this case was the first one to ensure the dissolution by indirect indicators in Japan.
- Finally, PMDA required the applicant both to perform the dissolution test included in the specifications at release from the early post-marketing phase, and to confirm the performance of the equation for calculating the dissolution rate, by simultaneously carrying out the dissolution test on the commercial lots after approval, based on the production plan for the drug product as well.

One of our challenges and the best way to move forward!

Changes

- At the beginning of ICH Q-trio implementation
  - Applicants try to set Design Space for their flexibility.

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- 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 because of their effort such as Design Space Verification Activities and 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

A Background of CM – ICH(1)

- One of the Future ICH Topics proposed by FDA
  - Continuous Manufacturing of Pharmaceuticals
- Problem Statement:
  - Continuous manufacturing of pharmaceuticals is a rapidly growing approach for production of both active ingredients and finished products.
  - There is a lack of guidance for regulators and industry on how to implement and regulate continuous pharmaceutical manufacturing.

A Background of CM – ICH(2)

- Desired State:
  - Clear expectation of scientific and regulatory approaches for continuous manufacturing which will lower perceived barriers and encourage implementation of this emerging technology.
- Timelines:
  - Start in the Spring of 2018
  - The target completion is in the Fall of 2020

A Background of CM – MIT(1)

- International Symposium on Continuous Manufacturing of Pharmaceuticals
- MIT on May 20-21, 2014
- This meeting was brought about by FDA CDER Dr. Janet Woodcock to open up Novartis-MIT Center for Continuous Manufacturing vision to a wider industry view.
- 8 white papers were finally published after discussion at the symposium.

A Background of CM – MIT(2)

- 2nd International Symposium on Continuous Manufacturing of Pharmaceuticals
- September 26-27, 2016
- Attendee: more than 300 people
- Regulatory and Quality Session

  Chair: Dr. Moheb Nasr

  Industry: Dr. Markus Krumme

  US FDA: Dr. Larry Lee

  PMDA: Dr. Yoshihiro Matsuda

Approaches to CM at PMDA(1)

- Before ICH activity for CM, we have a lot to learn regarding CM.

- Collaboration with AMED sponsored Study Group.
- Communication between PMDA and Industries who are studying CM.
- Collaboration with other regulators.

(AMED: Japan Agency for Medical Research and Development)

Approaches to CM at PMDA(2)

- Professional Training together with GMP Inspectors.
  - External specialists/scientists give us lectures.
- Collaboration with a society, e.g. JSPME(Japan Society of pharmaceutical Machinery and Engineering).
  - PAT, Multivariate analysis etc.

Innovative Manufacturing Technology Working Group (IMT-WG)

- Has been established in PMDA since July, 2016.
- Purpose
  - To establish PMDA's perspective on the latest technologies of pharmaceutical quality control
  - To propose a new regulatory framework for the pharmaceutical quality control by the new technologies
  - To draft guidelines
- Members
  - Senior Scientist (for Quality); Dr. Yoshihiro Matsuda
  - From Office of New Drugs
  - From Office of Manufacturing/Quality and Compliance
  - From Office of Regulatory Science

IMT-WG Activity Plan (J-FY 2016*)

- To organize face-to-face meeting(s) with FDA and EMA
- To visit continuous manufacturing sites
- To discuss with stakeholders including industries and academia
- To collaborate with a national research project on pharmaceutical quality control
- To publish points-to-consider about CM

*; April, 2016 – March, 2017

Perspective on CM(1)

- Opportunities:
  - To avoid poor quality product with PAT etc.
    → Prevention of drug shortage problem
  - To avoid scale-up issues
    → Rapid development
  - To operate multiple scales and dosage manufacturing
    → Personalized medicine
  - To reduce inventory
    → Cost reductions

Perspective on CM(2)

- PMDA is positive towards CM
- Issues to solve
  - Definition of Batch/Lot
    - How to determine reference/representative batch/lot for PV or Stability Test?
  - Handling deviations
    - How to restart manufacturing?
  - Cleaning Strategies
    - How to set a timing of Cleaning

Strongly Recommend to have PMDA consultations prior to submission!

Thank you for your attention