



PMDA Perspectives

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Introduction of PMDA



- NAME: Pharmaceuticals and Medical Devices Agency
- Date of Establishment : April 2004
Established as an **Incorporated Administrative Agency** (IAA) in April, 2004.

<http://www.pmda.go.jp/english/index.html>

PMDA's 3 major work areas

Review and Audit for
Drugs/ Medical Devices
Efficacy and Safety

Consultation

Review of Efficacy and Safety

Conformity Audit for Application
Materials of GLP, GCP and GMP/QMS

Post- marketing **Safety**
Operations for Drugs /
Medical Devices

Reinforced Safety Information (Database)

Scientific Review and Research for Safety
Information

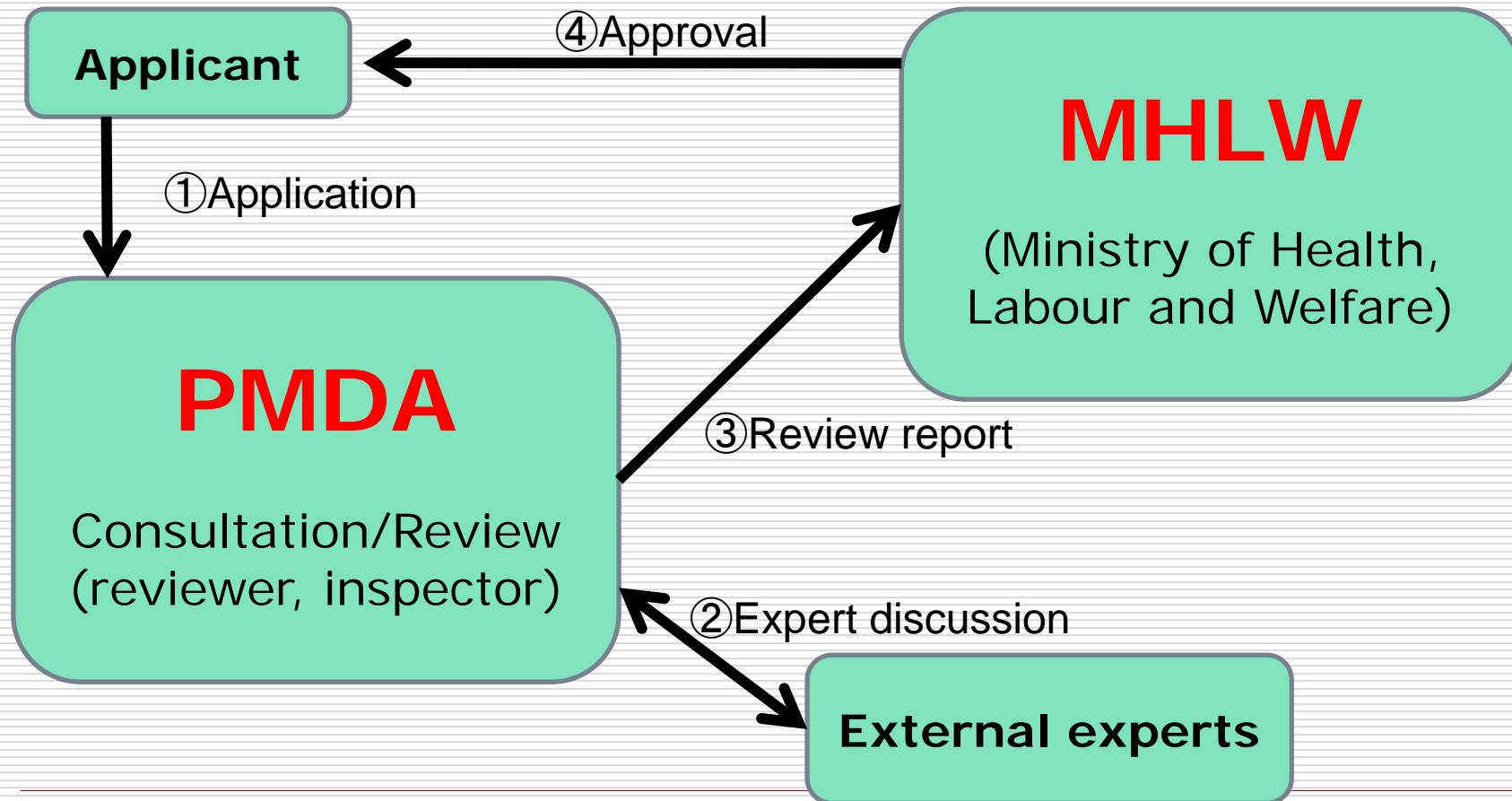
Information Provision (via the Internet),
Pharmaceutical Consultation for Consumers

Relief Service for ADR and
Other Infectious Disease

Provision of Medical Expenses,
Disability Pensions etc.

Relief Service for SMON, HIV-positive
and AIDS patients and HCV positive and
HC patients

Flow of the Review system



QbD Assessment Project

- In November 2011, PMDA launched a new project team to handle the participation in the EMA-FDA pilot program as an observer.
- The project team consists of reviewers, inspectors, etc..
 - Office of New drug I~V, GMP&QMS Inspection, International Programs, Standards and Guidelines Development

What PMDA learnt from our experience in the pilot program

- ❑ Our concerns about QbD are basically the same as FDA and EMA.
- ❑ There are no great differences in the evaluation approaches of QbD, FDA, EMA or PMDA.



But we have realized that ...

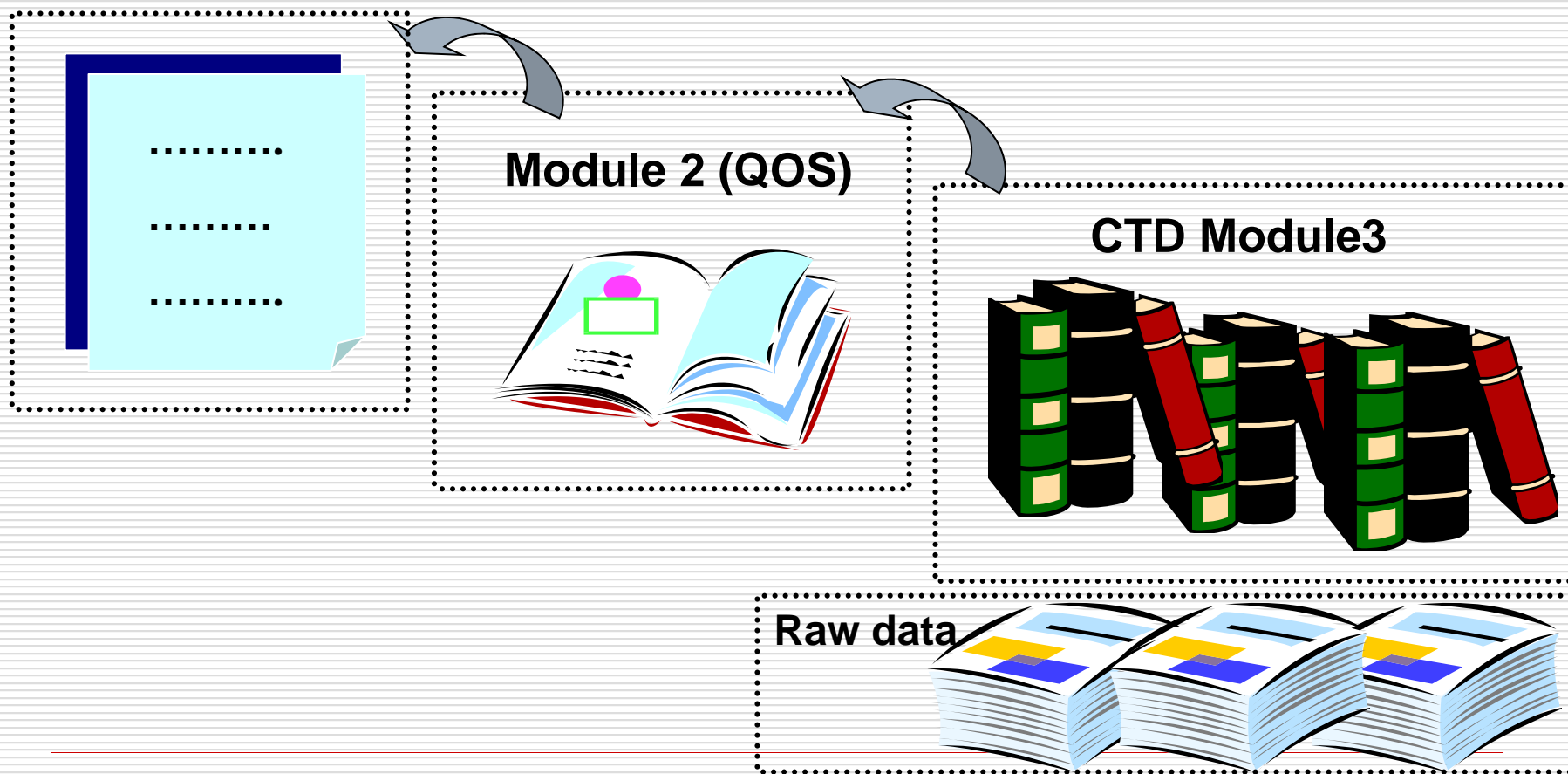
- ❑ Reviewers need a lot of time to assess the QbD approach even now and we tend to ask more questions than with traditional approach.
- ❑ Regulatory actions, especially post approval change actions, might be a little different because the regulatory framework of each regulatory agency is different.

Issues 1

- Module 2 (J-QOS) and Module 3
 - The content of J-QOS is getting larger. How can we take advantage of J-QOS?
- Managing application form
 - Is regulatory commitment (future change control system) written in the application form qualitatively and quantitatively adequate?
 - Distinguishing between review matter and GMP matter

Relationship between **Application Form** and CTD Documents in Japan

Application Form



Approval Matters

(Contents of Application Form)

- General name
- Brand name
- Composition
- Manufacturing process, including control of materials
- Specifications and analytical procedures
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Manufacturing sites information

Matters to be described in manufacturing field of Application Form

- All processes from raw material(s) to packaging process
 - A flow diagram of manufacturing process including:
 - Raw materials
 - Charge-in amount
 - Yield
 - Solvent
 - Intermediate materials
 - Process parameter (e.g. Target Value/Set Value)
 - A narrative description of manufacturing process
 - Acceptance criteria of starting material(s) and intermediate materials
 - In process control, Design Space and RTTR etc.

How to describe partial change matters and minor change matters

- Enter target/set values of process parameters and standard charge-in amounts in
 - 《 》 : partial change matter
 - 『 』 : minor change matter
- Enter items other than target/set values in
 - “ ” : minor change matter
 - No parentheses : partial change matter

Example of manufacturing description on AF

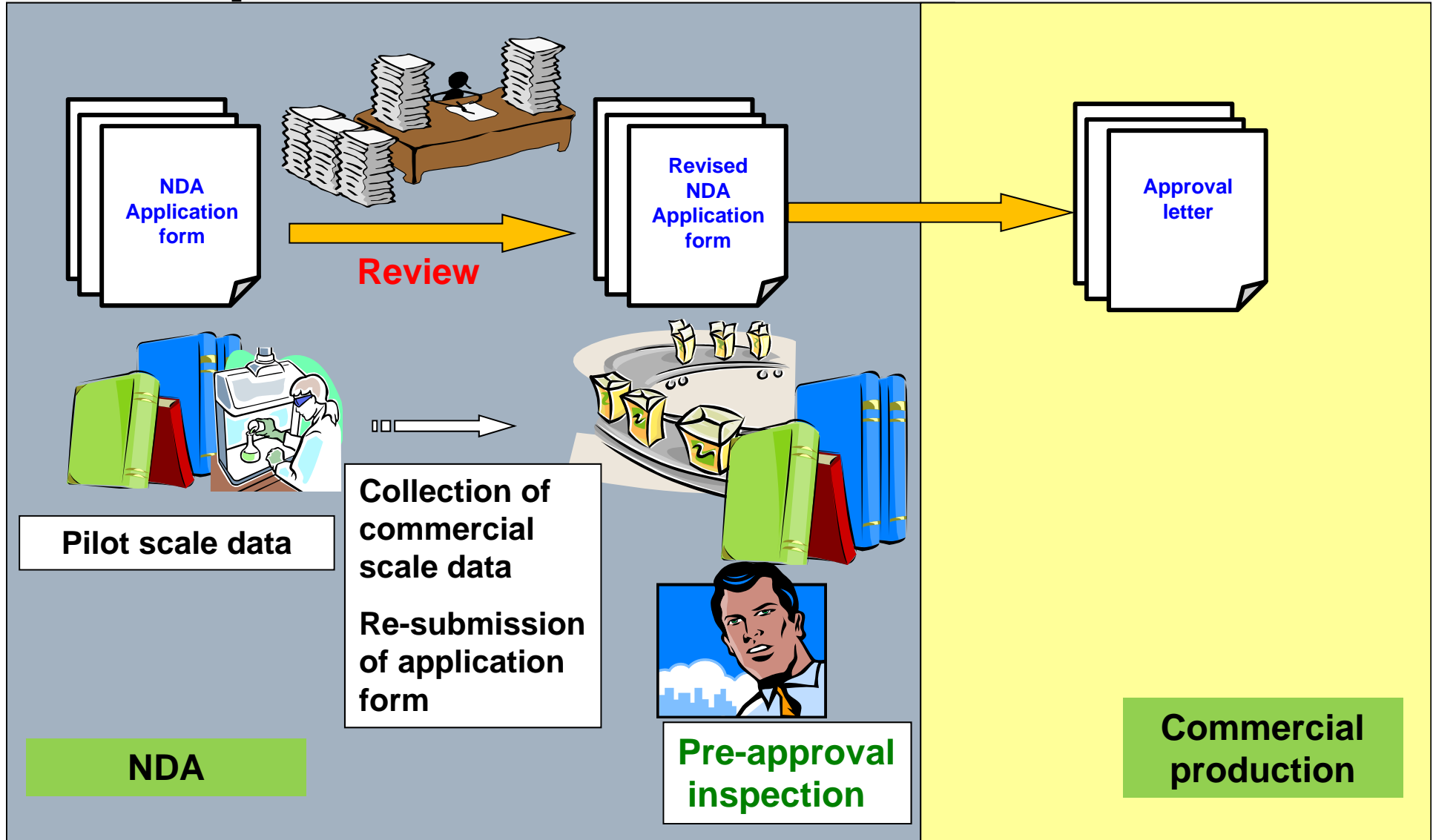
Step 1 (Critical Step)

CP-6〔(230kg)〕, tetrahydrofuran〔(1300L)〕, sodium carbonate〔(42.4kg)〕 are combined. Ethyl chloroformate “158 ~ 592kg” is added and the mixture is heated at temperature up to reflux.

Water (“25 to 35%” *weight per weight of ethanol) is added and the mixture is stirred at 〔20°C〕.

* Water quantity is relative to the ethanol quantity, ethanol volume and crystallization temperature are parameters establishing Design Space which controls the quantity of total impurities.

Framework for Review and GMP Inspection



Issues 2

- How to deal with Minor Changes in US and Type IA variation in EU
 - There are only two types of regulatory actions possibly taken in Japan
 - Partial change
 - Minor change (Notification)
 - Another choice
 - No statement of change in application form

Post-authorisation 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) |

Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of **critical process**: matter subject to approval
- Change in materials of **primary packaging component**
- Change in matters for **aseptic manufacturing**
- Change in specification of intermediate product in case that the test is **performed instead of release test of final drug product**.....etc.

But we can judge that on a case-by-case basis.



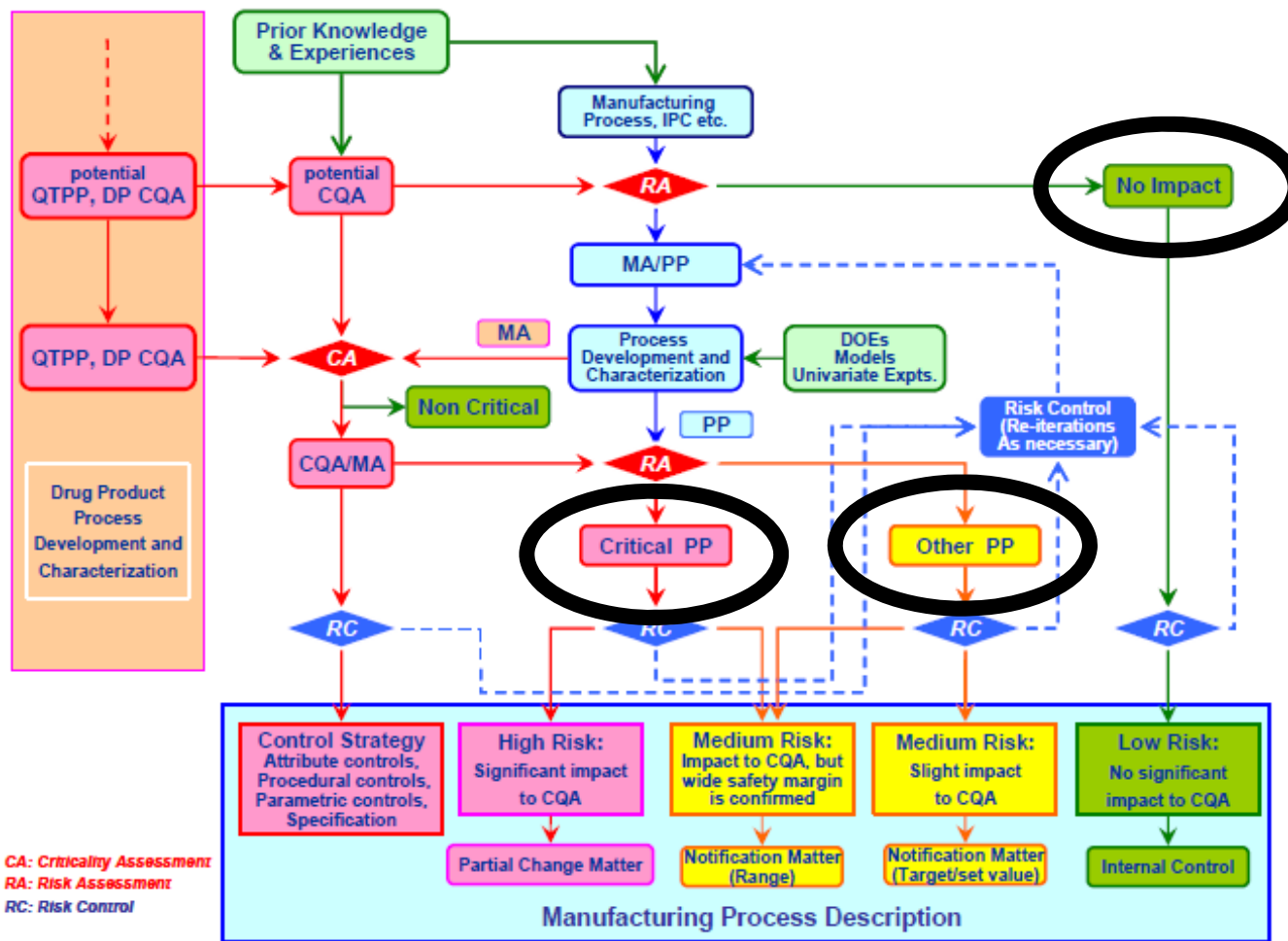
Flexibility for QbD applications

MHLW-sponsored Health Science studies

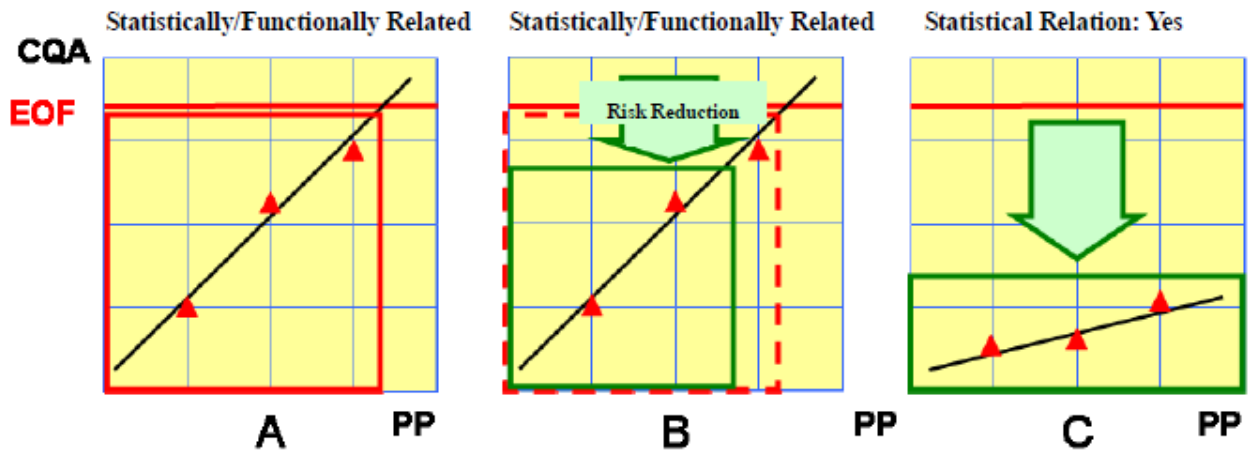
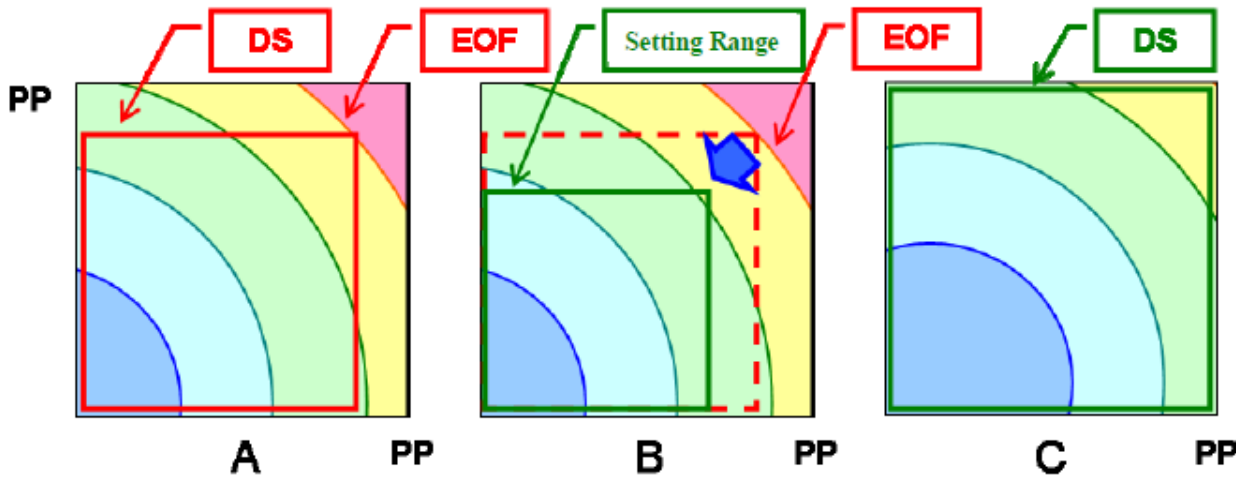
- Title : Research of Development and Manufacturing Information of Drug Substances
 - R&D of Drug Substances by the Methodology of Quality by Design -
- The group members are : researchers from National Institute of Health Sciences (NIHS); reviewers and inspectors from PMDA; industries (ex. Daiichi-Sankyo, Astellas, Pfizer, GSK, Shionogi, Otsuka, Takeda, Chugai, etc.)
- One of research results is the creation of the document sample of **Sakuramil (Sakuramil S2 mock)**.

[http://www.nihs.go.jp/drug/section3/H23SakuramilMock\(Eng\).pdf](http://www.nihs.go.jp/drug/section3/H23SakuramilMock(Eng).pdf)

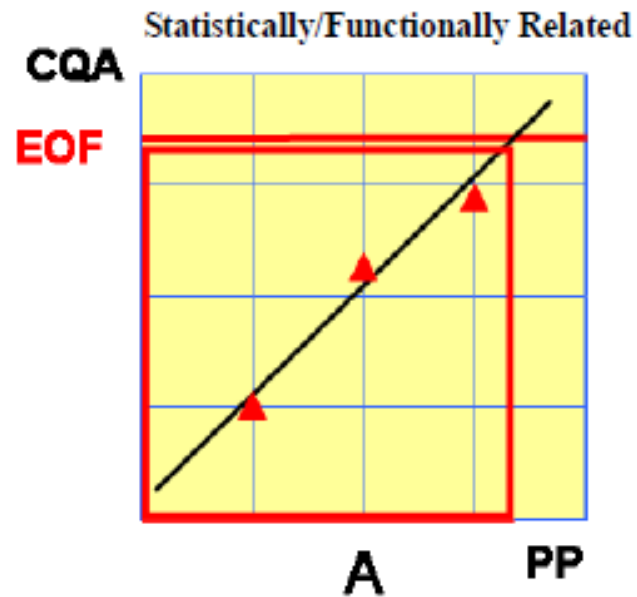
Flow diagram of the outline of manufacturing process development for drug substances



Concept of Risk of PPs When Setting DS from the Results of DoE



Case A



- Cases where Edge of Failure (EOF) exists within the range of planned Design Space (DS), and the end of DS (the range of Process Parameters (PPs)) is close to EOF



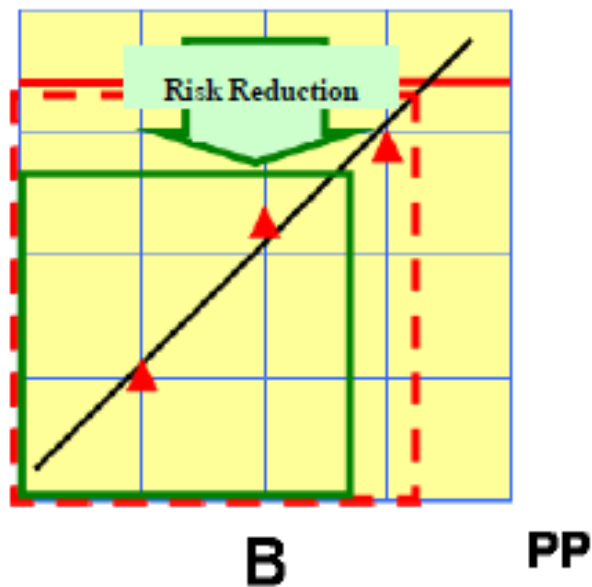
CPP



Partial change matter

Case B

Statistically/Functionally Related



- Cases where EOF exists within the range of planned DS but the end of DS is far from EOF by setting the range of PPs to be smaller than DS



CPP

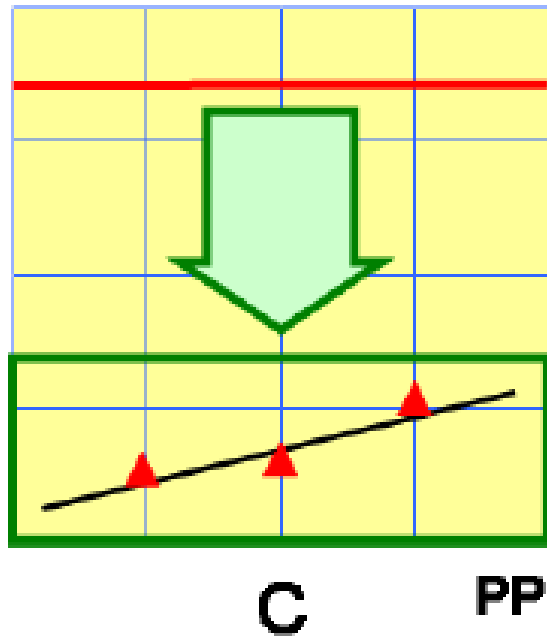


Risk Reduction

Minor change matter

Case C

Statistical Relation: Yes



- Cases where there is no EOF within the range of planned DS, and the realistically expected range of PPs is far from EOF

Other PP

Minor change matter

PMDA Experience with QbD

□ Applications with QbD in Japan

Number of approved products (until July in 2013)

| 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|------|------|------|------|------|------|
| 3 | 3 | 2 | 11 | 11 | 6 |

□ Consultations with PMDA on QbD

Number of Consultations (until July in 2013)

| 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|------|------|------|------|------|------|------|
| 1 | 0 | 2 | 2 | 4 | 3 | 2 |

Next Considerations

- Can industries open their experience?
 - I believe that we need to share our knowledge with real situation and/or document between regulators and industries.
- Do we need an annual reporting system in Japan?
 - I expect industries to manage low risk matters in their Pharmaceutical Quality System appropriately as GMP matters.
- Do we need a post approval change management protocol in Japan?
 - Our unique regulatory system, such as an application form, should be enough to maintain flexibility.

Thank you for your attention

