Revised Pharmaceutical Affair Law and Pharmaceutical Development

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  - What will change and what will not change?
- Role of P2 Document in reviewing NDA under revised PAL

Revised Pharmaceutical Affairs Law

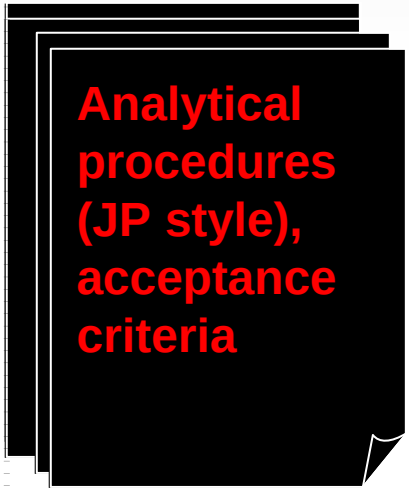
-What will change and what will not change?-

- **Issue not to be changed:**
  - **Approval letter**
- **Issues to be changed:**
  - **From manufacturing approval to marketing approval**
  - **Requirement of detailed description in application form about manufacturing and manufacturing control**
  - **Introduction of notification system pertaining to minor change**

Japanese Approval System

-Relationship between Application Form and CTD Documents-

Application form
(in Japanese)

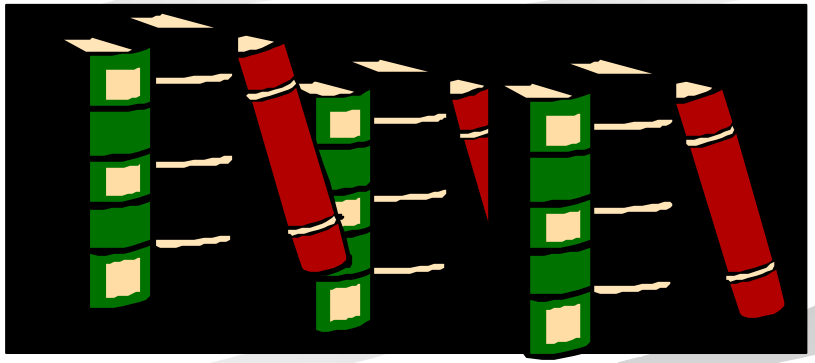


Module 2 (in Japanese)

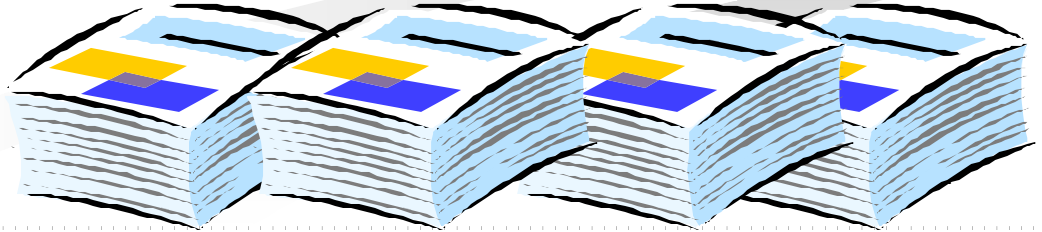
1.Tabulated summary of specifications
2.Analytical procedures (JP style)
3.- - - - - 4.- - - - 5.- - - -

Module 3 (in English or Japanese)

S4.1 Specification
S4.2 Analytical Procedures
S4.3 Validation of Analytical Procedures
S4.4 Batch Analyses
S4.5 Justification of Specification



Raw data



Application Form and Approval Matter

- Contents provided in NDA application form are dealt with as “matters subject to approval
- Contents described in approval letter are ’legal binding’ approval matters
- Used for pass-fail decision

Approval Matter

- General name (for drug substance)
- Brand name
- Composition
- Dosage and administration
- Manufacturing process including control of materials
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures

Partial Change

- **Applicants are required to file an application form for partial change in case that they intend to alter a content of current approval.**
  - **Unnecessary to file an application for the partial change in so far as there is no change in the current application form.**

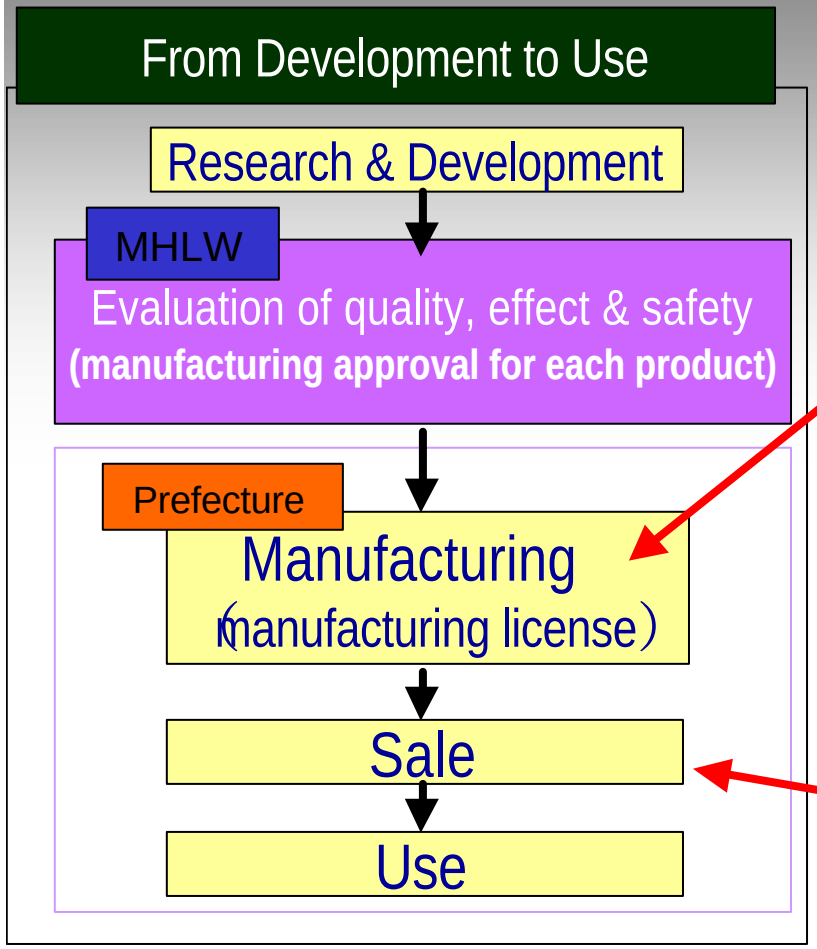
Revision of Pharmaceutical Affairs Law : Three Major Items of Perspectives

- **Revision of Medical Device Regulation**
- **Consolidation of Safety Measures for "Bio-Genomic Century"**

  → **Urgent need to provide comprehensive legal statutes for safety of biological products**
- **Approval System Revision and Post-marketing Safety Measure Reinforcement**

  → **Harmonised approval system with US/EU for better adaptations to CTD guidance**

Revision of approval/license system for Pharmaceuticals and medical devices



Attention to manufacturing

Current system

1. Companies are supposed to have their own manufacturing establishment
2. "Approval" is for "manufacturing", not for "marketing" (**Minister manufacturing approval**)
3. Final manufacturing "license" is issued, based on approval. (Mainly **prefectural manufacturing licensing**)

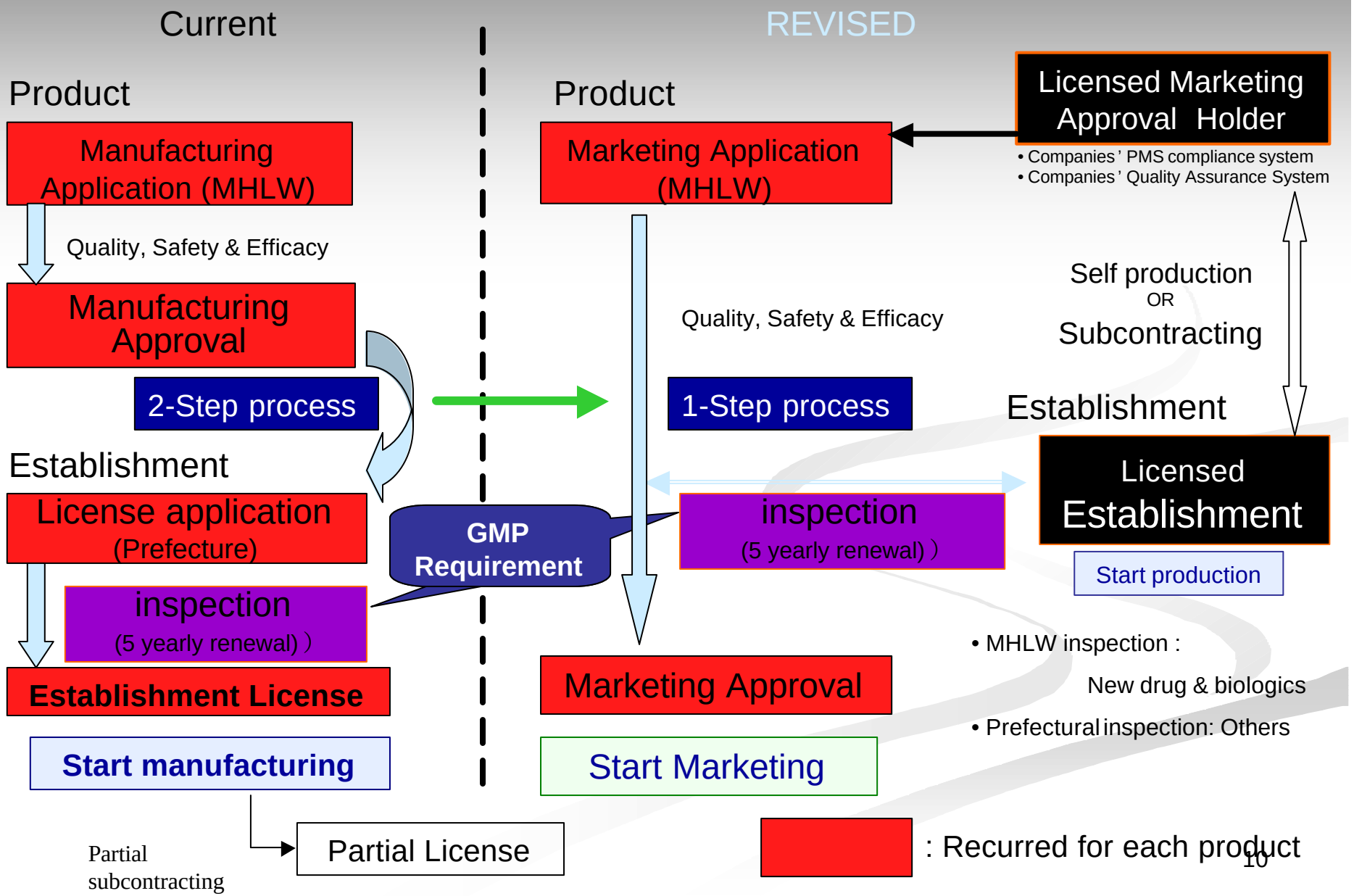
Attention to whole process
(from manufacturing to PMS)

Changed System

1. Introduction of **"Marketing Approval"** for overall evaluating quality, safety & efficacy and manufacturing for marketing
2. Manufacturing establishment license is separated from product authorisation process, which allows companies to subcontract whole manufacturing process
3. Instead, company's ability of pharmacovigilance is subject to review for Marketing Approval Holder (MAH)

Comparison Flowcharts of Approval and License (Current/Revised)

Points: (1) MAH's requirements for PMS system, (2) Allow complete subcontract manufacturing, (3) Introduce marketing approval system



Matter Subject to Approval under Revised Pharmaceutical Affairs Law

(Chemical drug substance and drug product)

- Manufacturing cite
- Manufacturing method
  - Detailed information about
    - Manufacturing process and process control
    - Control of material
    - Container-closure system

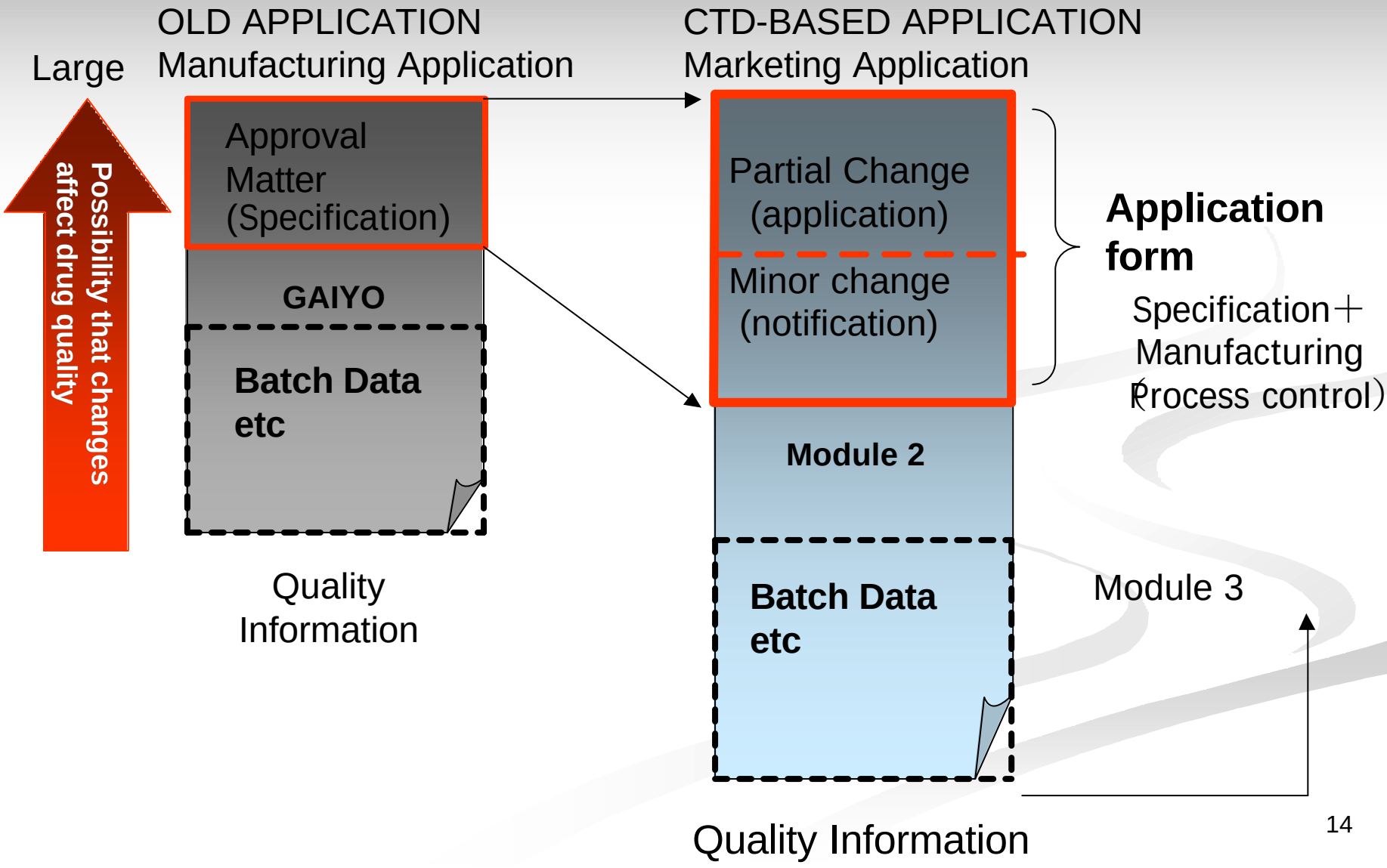
Minor Partial change-1:

- Change having a moderate and /or minimal potential to have an adverse effect in quality
  - Notified by manufactures within 30 days after change is carried out.
  - In case of these changes, manufacturers confirm that the change does not affect quality and file data in their facilities
  - Manufactures need not take procedures for approval of partial change.
  - During GMP inspection, GMP inspectors confirm that the procedure of change is appropriate.

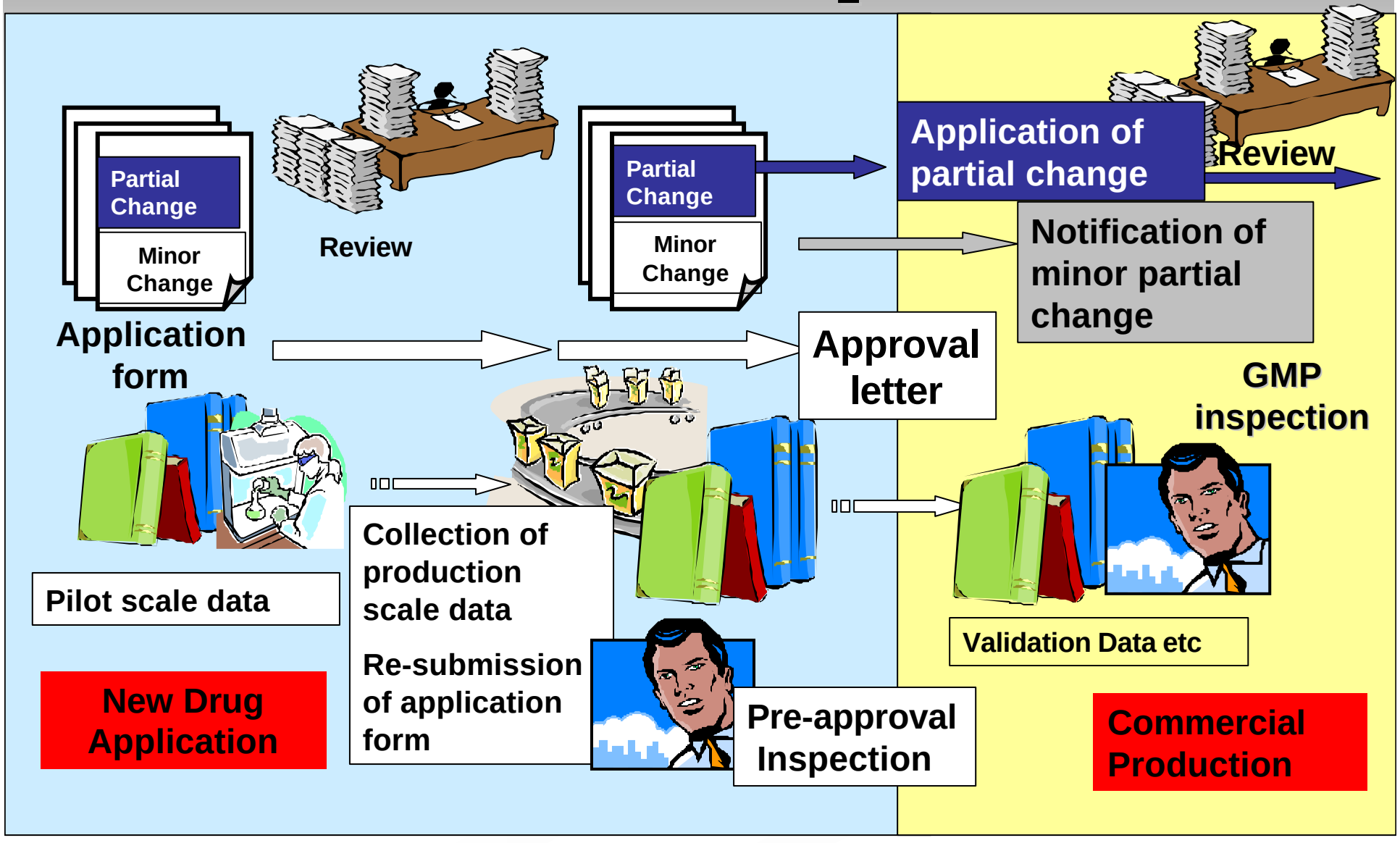
Minor Partial change-2

- Applicant should previously discriminate and establish the matters to be subject for partial change approval application at the change application hereafter, or those to be subject for minor change notification.
- Regulator should approve matters described in application format, considering the matter is subject for partial change application or for minor change notification.

Application Form after Enforcement of Revised Pharmaceutical Law



Proposed Framework for Review And Inspection



Matter to Be Described in Application Form -Drug Products-

- All process from the raw material(s) to the primary packaging process
  - A flow diagram of manufacturing process including:
    - Raw materials
    - Charge-in amount
    - Yield
    - Solvent
    - Intermediate materials
    - Process parameter (Target Value/Set Value)
  - A narrative description of manufacturing process

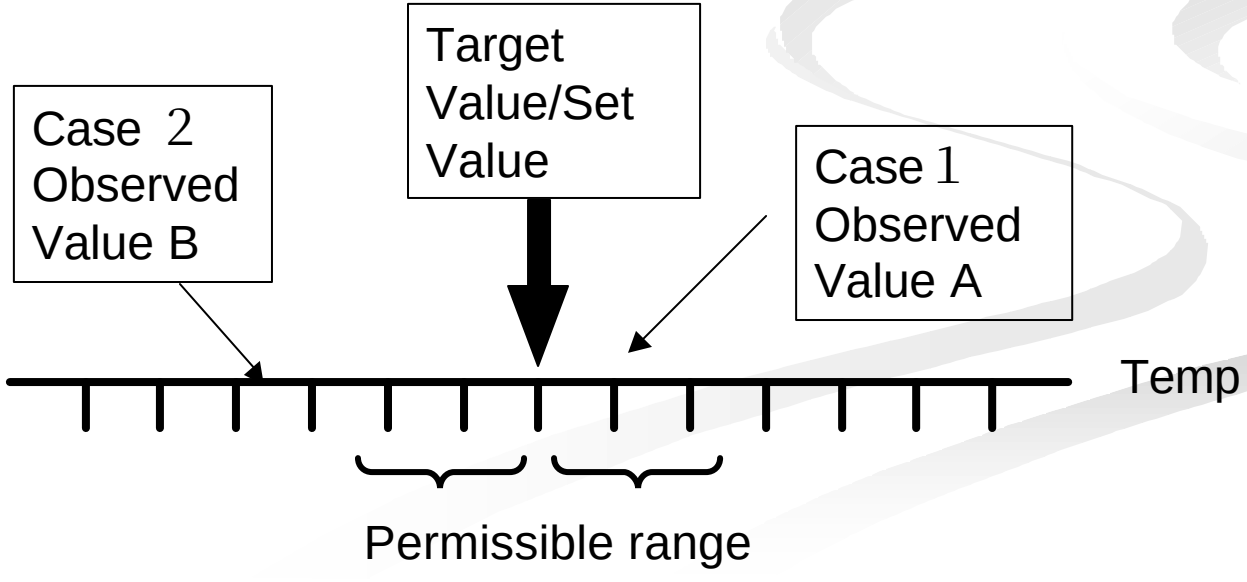
Narrative Description of Manufacturing Process

- Matters needed for assuring the quality consistency should be selected

- Quantities of raw materials, critical processes, process control, equipment, process parameter (speed, time, temp., pressure, pH, etc)
- Test and acceptance criteria of critical step and intermediate
- Identity and specification of primary packaging material (or manufacturer and type number of the packaging material)

Target Value/Set Value- 1

- **In case that target value/set value are set:**
  - **Permissible range of target value/set value must be described on the master production documents or SOPs.**
- **Case B:**
  - **The suitability of product should be judged based on GMP.**



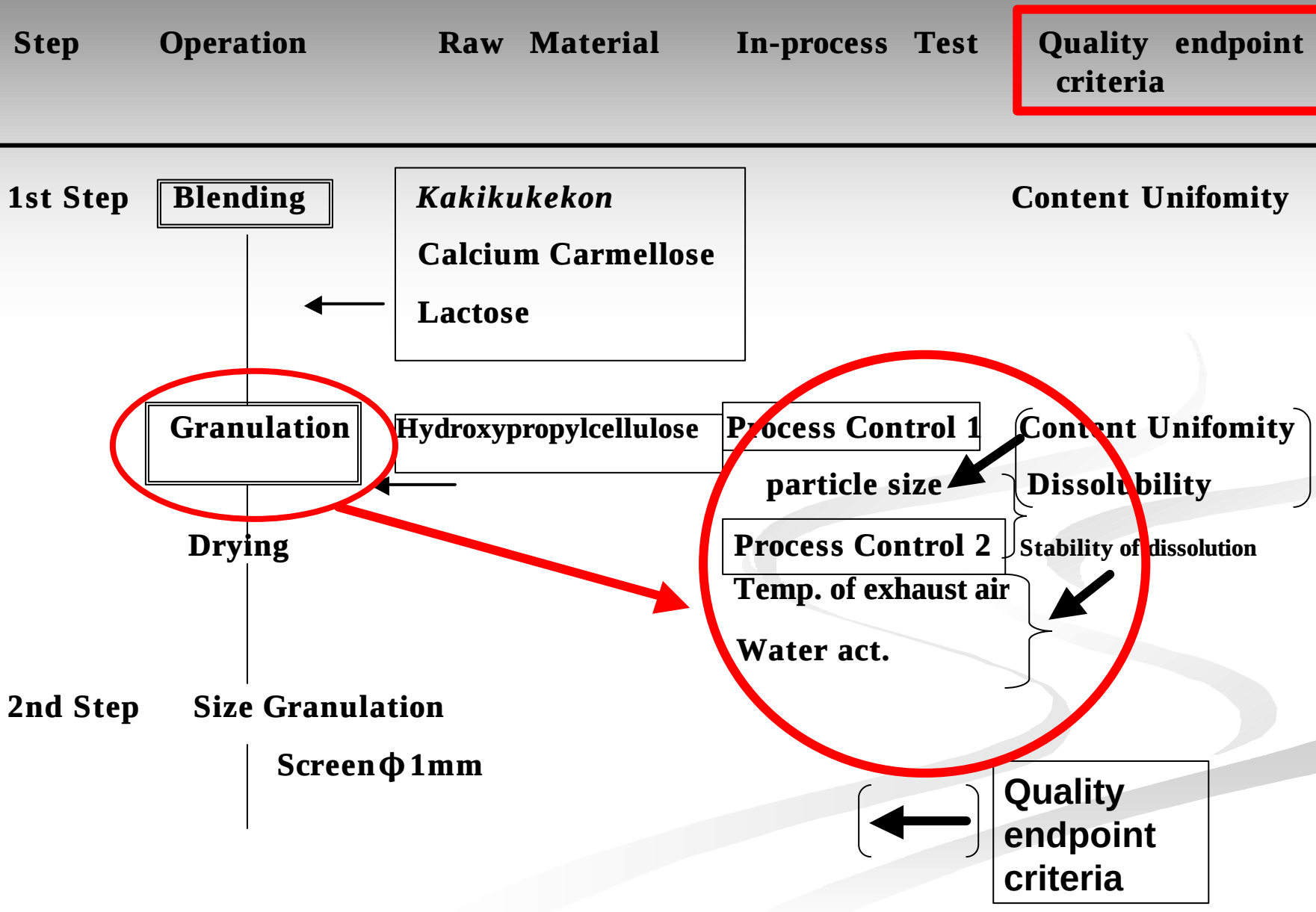
Target Value / Set Value-2

- In case that the parameter is set in order to utilize as a parametric release:
- In case that parameter can affect the quality significantly:
  - A permissible range should be specified in the format for approval.
  - The value is used for conformance evaluation on the relevant batch with the manufacturing method written on the approval letter.

Distinction between Partial Change Approval Application And Minor Change Notification

Partial Change Approval Application	Minor Partial Change Notification
Change in the principle of unit operation of critical process	Process parameter to control the quality endpoint criteria
Change in process control criteria as quality endpoint criteria	

Flow Diagram of Manufacturing process (Tablet)



Example of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - In that case, the evaluation methods which was approved at the time of previous submission might be invalidated.
- 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

Role of P2 Document in Reviewing New Drug Application (NDA) under Revised Pharmaceutical Affair Law (PAL)

- **Information described in P2 might make a decision whether some matters are subject to application of partial change or not.**

Role of Approval Matter

OLD PAL

- Criteria for pass-fail decision
  - Specification of final drug product

Revised PAL

- Criteria for pass-fail decision
  - Specification of final drug product
  - Process control
- Basic document for SOP

Role of P2 document in reviewing NDA under revised PAL