Revised Pharmaceutical Affair Law and Pharmaceutical Development

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Contents

- Revised Pharmaceutical Affairs Law
  - 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

Analytical procedures (JP style), acceptance criteria

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

From Development to Use

Research & Development

MHLW

Evaluation of quality, effect & safety (manufacturing approval for each product)

Prefecture

Manufacturing (manufacturing license)

Sale

Use

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)

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

Current

Product

- Manufacturing Application (MHLW)
- Quality, Safety & Efficacy
- Manufacturing Approval

Establishment

- License application (Prefecture)
- inspection (5 yearly renewal)
- Establishment License
- Start manufacturing

Partial subcontracting

Partial License

REVISED

Product

- Marketing Application (MHLW)
- Quality, Safety & Efficacy
- Marketing Approval

Establishment

- Licensed Marketing Approval Holder
- Self production OR Subcontracting
- Licensed Establishment

Start production

- MHLW inspection: New drug & biologics
- Prefectural inspection: Others

- Recurred for each product
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

OLD APPLICATION
Manufacturing Application

CTD-BASED APPLICATION
Marketing Application

Approval Matter (Specification)

GAIYO

Batch Data etc

Possibility that changes affect drug quality

Quality Information

Partial Change (application)

Minor change (notification)

Module 2

Batch Data etc

Module 3

Application form

Specification + Manufacturing (Process control)

Large

Quality Information
Proposed Framework for Review And Inspection

- Application form
- Partial Change
  - Minor Change
- Review
  - Collection of production scale data
  - Re-submission of application form
  - Pre-approval inspection
  - Validation Data etc
- Application of partial change
- Approval letter
- Notification of minor partial change
- GMP inspection
- Commercial Production

New Drug Application

Pilot scale data
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.

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**Diagram:**

- **Case 2**
  - Observed Value B

- **Case 1**
  - Observed Value A

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**Permissible range**

**Temp**
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

<table>
<thead>
<tr>
<th>Partial Change Approval Application</th>
<th>Minor Partial Change Notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in the principle of unit operation of critical process</td>
<td>Process parameter to control the quality endpoint criteria</td>
</tr>
<tr>
<td>Change in process control criteria as quality endpoint criteria</td>
<td></td>
</tr>
</tbody>
</table>
Flow Diagram of Manufacturing process (Tablet)

<table>
<thead>
<tr>
<th>Step</th>
<th>Operation</th>
<th>Raw Material</th>
<th>In-process Test</th>
<th>Quality endpoint criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Step</td>
<td>Blending</td>
<td>Kakikukekon</td>
<td></td>
<td>Content Uniformity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium Carmellose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Granulation</td>
<td>Hydroxypropylcellulose</td>
<td>Process Control 1</td>
<td>Dissolubility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stability of dissolution</td>
</tr>
<tr>
<td></td>
<td>Drying</td>
<td></td>
<td>Process Control 2</td>
<td>Water act.</td>
</tr>
<tr>
<td>2nd Step</td>
<td>Size Granulation</td>
<td>Screen &lt; 1mm</td>
<td>Quality endpoint criteria</td>
<td></td>
</tr>
</tbody>
</table>

- **Process Control 1**: Particle size
- **Process Control 2**: Temp. of exhaust air
- Quality endpoint criteria
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

<table>
<thead>
<tr>
<th>OLD PAL</th>
<th>Revised PAL</th>
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<tbody>
<tr>
<td>- Criteria for pass-fail decision</td>
<td></td>
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<tr>
<td></td>
<td>- Criteria for pass-fail decision</td>
</tr>
<tr>
<td></td>
<td>- Specification of final drug product</td>
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<tr>
<td></td>
<td>- Specification of final drug product</td>
</tr>
<tr>
<td></td>
<td>- Process control</td>
</tr>
<tr>
<td></td>
<td>- Basic document for SOP</td>
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</tbody>
</table>
Role of P2 document in reviewing NDA under revised PAL

Issues described in Module 3

Matters subject to approval

Minor partial change notification

Partial change approval application