New Drug Application of Biotechnology products in Japan

Approval Contents (i.e. Legal binding) related to CMC part

JPMA Biopharmaceutical Committee Technology Working Committee
Takao Kojima

CASSS CMC Strategy Forum Japan 2015
Outline

1. Overview of relationship between Application Form and J-CTD
   - J-NDA / Application Form and J-CTD
   - Approval Contents

2. Change Control for Approval Contents
   - Variation Applications
   - Application format for PCA and MCN

3. Issues Regarding the current Application Form (J-M1.2) "legal Binding" for Biotechnology Products
   - Description of Application Form (J-M1.2) for Biotechnology products

4. Approaches taken at JPMA Biopharmaceutical Committee
1. OVERVIEW OF RELATIONSHIP BETWEEN APPLICATION FORM AND J-CTD AS ITS ATTACHMENT
J-NDA / Application Form and J-CTD
Application Form

- Product Name
- Ingredient and Contents
- Manufacturing Process
- Dosage and Administration
- Indications
- Storage and Shelf life
- Specification and Testing Method
- Manufacturing Sites

Evidence
Module 1 is region specific and written in Japanese

Module 2 is the primary review unit for PMDA (written in Japanese)

M 3, 4 and 5 can be written in English.

Lengthier, more contents than US or EU version

including Application form

Module 2
J-NDA / Application form and J-CTD

**Approval Letter**
- Approval #
- NDA Date
- Reexamination Period
- International Birth Date
- Approval Date

Contents described in **Approval Letter** are "legal binding" approval matters.

**Evidence**
- Product Name
- Ingredient and Contents
- Manufacturing Process
- Dosage and Administration
- Indications
- Storage and Shelf life
- Specification and Testing Method
- Manufacturing Sites

**Approval Contents**
- Approval #
- NDA Date
- Reexamination Period
- International Birth Date
- Approval Date

Contents described in **Approval Letter** are "legal binding" approval matters.
Approval Contents
Module 1.2 : Application Form
Approval contents

- Product Name
- Ingredient and Contents
- Manufacturing Process
- Dosage and Administration
- Indications
- Storage and Shelf life
- Specification and Testing Method
- Manufacturing Sites

Any changes in the matters entered in the Application Form shall be addressed in administrative regulatory procedures (PCA or MCN).
2. CHANGE CONTROL FOR APPROVAL CONTENTS
Variation Applications
LCM regulatory system in Japan

- **New Drug Application (NDA)**
  - Required for change in the brand name, active ingredients or their content or dosage form

- **Partial Change Application (PCA; sNDA)**
  - Acceptable for change in ingredients other than the active ingredient, their contents, dosage and administration, indication, manufacturing method, specification and test method, etc

- **Minor Change Notification (MCN)**
  - Acceptable if proposed change is minor (no effect to the quality, efficacy or safety of the product)
## Difference between PCA and MCN

<table>
<thead>
<tr>
<th>PCA (partial change application)</th>
<th>Major</th>
<th>MCN (minor change notification)</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prior to the change</td>
<td></td>
<td>1. 30 days after the change</td>
<td></td>
</tr>
<tr>
<td>2. Regulatory review</td>
<td></td>
<td>2. Reviewed at next PCA</td>
<td></td>
</tr>
<tr>
<td>3. Data required (basically)</td>
<td></td>
<td>3. No data submitted</td>
<td></td>
</tr>
<tr>
<td>(US : PAS, EU : Type II)</td>
<td></td>
<td>(US : CBE, EU : Type IA)</td>
<td></td>
</tr>
</tbody>
</table>

**Prior** to the change  
12M  
**30 days after**  
Change occurs
### Biotechnology products

<table>
<thead>
<tr>
<th>PCA (partial change application)</th>
<th>MCN (Minor Change notification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Package form change/addition</td>
<td>1. Site change/addition (test)</td>
</tr>
<tr>
<td>2. Site change/addition (DS, DP, storage, package)</td>
<td>2. Manufacturing Process change (allowed part*: marked “ ”『 』)</td>
</tr>
<tr>
<td>3. Ingredients’ prescription change</td>
<td></td>
</tr>
<tr>
<td>4. Manufacturing Process change</td>
<td></td>
</tr>
<tr>
<td>5. Testing method change</td>
<td></td>
</tr>
</tbody>
</table>

* Identified in the application form Justification provided in the CTD

### Synthetic products

<table>
<thead>
<tr>
<th>PCA (partial change application)</th>
<th>MCN (Minor Change notification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Package form change/addition</td>
<td>1. Site elimination (one of several sites)</td>
</tr>
<tr>
<td>2. Site change/addition (DS, DP)</td>
<td>2. Site addition (storage/package/test)</td>
</tr>
<tr>
<td>3. Ingredients’ prescription change</td>
<td>3. Manufacturing Process change (allowed part*: marked “ ”『 』)</td>
</tr>
<tr>
<td>4. Manufacturing Process change</td>
<td></td>
</tr>
<tr>
<td>5. Testing method change</td>
<td>4. Tightening of specs</td>
</tr>
</tbody>
</table>
Application format and Approval contents for Partial Change Application and Minor Change Notification
Application format of PCA and MCN is different from one of NDA.

➢ The sections in relation to the change are only required to submit.

In the case of PCA or MCN with changing of manufacturing procedures....

1. General information (eg. name, address, product name....)
4. Manufacturing procedures
   - Category of formulation
   - Name of manufacturing site
   - Manufacturing procedures; Consists of scope, animal derived materials, procedures, process controls
9. Manufacturing sites information with license numbers

Above sections would be described in M1.2, and the approval contents in this variation would be limited to part of M1.2.
Application format of M1.2 for PCA/MCN

Partial Change Application Form
- General information
- Manufacturing Process

Submission
Only the changed section is described.

Review (PCA)

Minor Change Notification Form
- General information
- Manufacturing Process

Attached Data (PCA)
- Process validation data, comparability data (characteristics, specifications, stability etc.), etc.

Depends upon degree or substance of the change.
Approval contents of M1.2 for PCA/MCN

Approval Letter
- PCA Date
- Approval Date

Approval (PCA)

Only the changed section is described.

Not exist one M1.2 which is reflected the latest approval content of all sections.
Approval contents of M1.2 for PCA

Approval Letter
- PCA Date
- Approval Date

Approval Letter
- Approval #
- NDA Date
- Reexamination Period
- International Birth Date
- Approval Date
Approval contents of M1.2 for PCA

- Product Name
- Ingredient and Contents
- **Manufacturing Process**
- Dosage and Administration
- Indications
- Storage and Shelf life
- Specification and Testing Method
- Manufacturing Sites

Approval Letter

- PCA Date
- Approval Date

Approval contents of M1.2 for PCA
Approval contents of M1.2 for MCN

- Minor Change Notification Form
  - General information
  - Manufacturing Process

- Approval Letter
  - Approval #
  - NDA Date
  - Reexamination Period
  - International Birth Date
  - Approval Date
Approval contents of M1.2 for MCN

- Product Name
- Ingredient and Contents
- Manufacturing Process
- Dosage and Administration
- Indications
- Storage and Shelf life
- Specification and Testing Method
- Manufacturing Sites

Minor Change Notification Form

- General information
- Manufacturing Process

Approval contents of M1.2 for MCN
3. ISSUES REGARDING THE CURRENT APPLICATION FORM (J-M1.2) "LEGAL BINDING" FOR BIOTECHNOLOGY PRODUCTS
Description of Application Form (J-M1.2) for Biotechnology products
Description of Application Form (J-M1.2)

NDA Documents - CMC part -

Module 1.2

Application form
- Product Name
- Ingredient and Contents
- Manufacturing Process
- Dosage and Administration
- Indications
- Storage and Shelf life
- Specification and Testing Method

Pick out Module 2.3
Summarize

Module 2.3

Module 3
Module 3

Raw data
The matters entered in the application form (J-M1.2)

- After approval, any changes in the matters shall be addressed in administrative regulatory procedures (PCA or MCN).
- MCN items are evaluated during the review as to whether it can be accepted.
- Critical target or set values cannot be set as MCN items.

However, in the case of biotechnology products ...

- Almost all of the changes in the matters shall be required PCA.
The matters entered in the Application Form (J-M1.2) of NDA should be described with consideration for future life-cycle management.

To ensure quality required for assuring efficacy and safety of drugs
Current Description of Application Form (J-M1.2) for Biotechnology products

Aren't the items, which should be controlled under GMP, included for biotechnology products? Isn't there overlap in description?

GMP Documents
- product master formula, production instructions, SOPs...

Module 1.2
- Application Form

Module 2.3
- Manufacturing Process
- Specification and Testing Method

M 1.2 Application Form

M 2.3 QOS

M 3 Quality Reports
Current Description of Manufacturing Process

- Manufacturing sites
- Manufacturing procedures

It is described the detailed procedure for the operation.

- Describe process up to starting materials, cell culture, purification and storage.
- Raw materials, animal derived materials and reagents that are likely to affect the quality.
- Major equipment, important process parameters (temperature, pH, time) and in-process control tests.
- Each process parameter should be defined as major/minor by brackets.
- Test items, analytical methods and criteria if in-process test are required for critical processes.
- Storage condition and period for critical intermediates.

For Biotechnology products, too much details are to be described from the previous time, and different contents are described from the company or requested by PMDA etc.
Description of Specification and Testing Method

- Test name
- Specifications and testing methods

Usually it is described which shows the whole procedure.

- In principle, use the test listed in JP.
- When a test is not listed as general testing methods in JP, detailed testing method including criteria needs to be described.
- Description needs to be compliant with JP.
- Reagents name including supplier name, and whole kinds of test solution needs to be described.
- Unlike description in the column for manufacturing process, specification and testing method including reagents and test solution are subject to PCA in principle.
4. APPROACHES TAKEN AT JPMA BIOPHARMACEUTICAL COMMITTEE TECHNOLOGY WORKING COMMITTEE
Conducted research and discussion for the description of each manufacturing process, parameter, control tests etc.

what should be the approval content as a legal binding in the manufacturing process in order to ensure quality required for assuring efficacy and safety of antibody drugs?

Based on risk evaluation information, experience and knowledge ....

Preparation of mock-up draft of Manufacturing Process for drug substance of antibody drugs.
In the near future, we intend to exchange views with PMDA regarding the specific description examples of the column for manufacturing process for drug substance of antibody drugs in Application Form.