Japanese Application Form: PMDA’s Perspective on Manufacturing Process Description

Reiko YANAGIHARA, Ph.D.
Principal Reviewer
Division of Pharmacopoeia and Standards for Drugs
Office of Standards and Guideline Development / PMDA
Projects Across Multi-Offices in PMDA

Needs for discussion among offices in PMDA

- Review experience
- Increase in opportunity for international cooperation
- Transparency
- Development of guidelines
- state-of-the-art technology
- ICH

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Projects Across Multi-Offices in PMDA

- Post-approval Manufacturing Changes Project
- QbD Assessment Project
- Companion Diagnostic and Omics Project
- Pediatric and Orphan Drugs Project
- Nanomedicine Initiative Project
- Global Clinical Study Project
- Cardiovascular Risk Evaluation Project
- Innovative Statistical Strategies for New Drug Development
- Microdose Trials Project
Outline

- Application Form in Japan
- Description of manufacturing process in AF
- Review on the description of manufacturing process
- Comments on proposed mock-up from JPMA
  - Production Culture step
  - Affinity Chromatography step
- Summary
Application Form in Japan

- Contents of Application Form are the approved matters in Japan.
- CTD M2 and M3 are review documents.

Application Form
(included in Module 1.2)

CTD M2.3 (QOS)

extracted

CTD M3

summarized
Contents of Application Form

◆ Japanese accepted name (non-proprietary name)
◆ Brand name
◆ Composition
◆ Manufacturing process
◆ Specifications and analytical procedures
◆ Dosage and administration
◆ Indications
◆ Storage condition and shelf-life
◆ Manufacturing sites information
Advantages of Japanese Approved Form

◆ Transparency:
  • It clearly indicates the reporting categories (e.g. partial change approval and minor change notification) for each item.
  • Thus it is a good tool to share the regulatory process required for post approval change of each item between the sponsor and regulator.

◆ Flexibility: Classification of the reporting categories varies depending on the control strategy of the product being registered.
1. Manufacturing Facility

• Manufacturing process
• Manufacturing process section has subsection entitled with the name of manufacturer

<Example>
【No】:001  
【Name】: XXX.Inc.  
【Manufacturing process】:  
Responsibility: Cell culture step, Purification step, Testing of DS
  1.Cell Culture
    ......  
【Next step】: 002

Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law
PFSB/ELD Notification No. 0210001/ February 10, 2005
2. **Preparation and Control of Expression System**
   - Construction of expression vector
   - Preparations of MCB and WCB
   - Control of MCB and WCB (characterization, stability testing, preparation of new WCB etc.)
3. Manufacturing Process

Manufacturing Process from cell culture and purification steps to storage which include:

- Crucial steps for the quality assurance of the product
- Materials, reagents, equipment and process parameter which have potential impact on the product quality
- Detailed description for the equipment with specific function (e.g. function and volume)
- Critical steps including test method and acceptance criteria for in-process test
- Critical intermediate including storage condition and hold time, test method and acceptance criteria if in-process test is set
3. Manufacturing Process

◆ Materials

• Raw materials used in cell culture process such as component of cell culture media
• Raw materials of biological origin used in the manufacturing process of drug substance (e.g., monoclonal antibody or enzymes used in purification step)
• Country in origin, body part and processing method for materials derived from ruminant
• For human or animal-derived materials, elements that are considered crucial to ensure the product safety (e.g., donor screening method, inactivation/removal steps for adventitious agents)
Description of Mfg Process: How it should be described

In appendix for chemical entities, it is stated that manufacturing process should be described so that one can understand the flow of manufacturing step and it is not appropriate to describe PCA elements separately from MCN elements.

For biopharmaceuticals, it is also considered that manufacturing process should be described so that one can understand the flow of manufacturing steps.
Tools to describe PCA matters and MCN matters

For the manufacturing process

◆ target/set values of process parameters
◆ charge-in amounts

《 》: PCA matter
『 』: MCN matter

◆ items other than target/set values

“  ”: MCN matter
No parentheses : PCA matter
Purpose of the process
- to inactivate adventitious viruses at low pH

CPP
- pH
- Hold time
- Temperature

<Description in Application Form>
Protein A eluate is adjusted to pH 3.5-3.7. The pH adjusted solution is held at 15-30°C for 30–120min, neutralized to pH 6.5 and clarified via depth filtration.
What CMC reviewers focus on

- Whether it is possible to supply the product of the desired quality to the market consistently, based on the review documents.

- Elements essential for quality assurance of the product are appropriately described in application form.
Prior knowledge & Pharmaceutical development studies

Identification of CQA (Critical Quality Attribute)
- Structure
- Physicochemical properties
- Bioactivity
- Impurities

Acceptable ranges for CQA

Identification of Critical Process Parameters

Establishment of control strategy
- Material control
- Process parameter
- Process evaluation
- In-process control
- Product testing

Analytical data of the batch used in non-clinical and clinical studies

Application Form
Rational should be provided based on:
- Critical Quality Attributes
- Prior Knowledge
- Process/product development data
- Process characterization data
- Critical process parameters which may affect CQAs
- Process evaluation results
- Overall control strategy
Flexibility in Mfg. process description

- Process/product understanding
- Demonstrated ability to consistently manufacture the product of the desired quality
Comments on proposed description on
1. Production Culture Step
2. Affinity Chromatography Step
Production Culture

The expansion culture fluid is used to inoculate a culture vessel (with a capacity of 15000 L) containing ≪7000 L≫ of Medium 3 to a viable cell density of ≪1 × 10^5 cells/mL≫ and cultured at ≪37°C≫ and ≪pH○≫. After ◊ days of culture, the culture is fed with ≪3000 L≫ of Medium 3 and further cultured at ≪37°C≫ and ≪pH○≫. After ♦ days of culture, the culture is fed with glucose solution to a final concentration of ≪□ g/L≫ and production culture is continued for a total of ≪X days≫.

In-process test:
• Bioburden: < ○○ CFU/mL
• Adventitious virus: negative
• Mycoplasma: negative

Among other things, we think the proposed PCA items should be described in most cases.
Items which are claimed not to be described in AF

- Dissolved CO₂ level
- Dissolved oxygen concentration
- Osmotic pressure
- Agitation speed
- Vessel internal pressure
- Aeration rate
- Monitoring items: residual nutrient component level, metabolite level

There are cases where some parameters above are identified as CPPs.
The harvested culture fluid is loaded onto an affinity column packed with \( X \text{ L} \) of resin (PRODUCT NAME or equivalent) to allow adsorption of desired antibody. The column is washed with Buffer A, followed by elution with Buffer B at a flow rate of \( \bigcirc \bigcirc \text{ cm/h} \). With the absorbance monitored at 280 nm, the fraction containing desired antibody is pooled (start of pooling at OD\(_{280} \bigcirc \bigcirc \); end of pooling \( \times \times \) ) to obtain the eluate pool.

### Buffer Composition

<table>
<thead>
<tr>
<th>Buffer</th>
<th>Composition</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer A</td>
<td>Tris ( \times \times \text{ mol/L} ), ---</td>
<td>-</td>
</tr>
<tr>
<td>Buffer B</td>
<td>Sodium acetate ( \ll \times \times \text{ mol/L} ), ---</td>
<td>6.5</td>
</tr>
</tbody>
</table>
There may be a case where the following parameters are considered CPPs

- Column loading
- Bed height
- Flow rate
- Buffer composition, pH
- Buffer volume
- Temperature ...etc.

Possible impacts:
- Leached Protein A
- Increase in half antibody
- Removal of process-related impurities
- Removal of adventitious viruses ...etc.
In the case where the contribution of affinity chromatography step to viral clearance is expected, acceptable ranges for critical parameters for virus clearance should be described in AF.

- The description would be different in the case where affinity chromatography has some viral clearance ability but has minor contribution on viral clearance.
Demonstrated ability in process control

- As for the description of target value or range, demonstrated ability to control parameters well within acceptable range is considered.

- For chemical entities, it is required to submit the tabulated information in CTD M1.13 on rational for MCN matters and non-described matters to help reviewers to evaluate the AF description.

**PFSB/ELD Administrative Notice / January 1, 2010**

<table>
<thead>
<tr>
<th>No</th>
<th>Mfg.process</th>
<th>AF</th>
<th>MBR</th>
<th>Justification for parameter classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MCN</td>
<td>Target/operating range</td>
<td>acceptable range</td>
</tr>
<tr>
<td>001</td>
<td>step1</td>
<td>『20℃』</td>
<td>○〜○℃</td>
<td>○〜○℃</td>
</tr>
</tbody>
</table>

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The classification of process parameters may vary based on a sponsor’s product/process understanding and the demonstrated ability in process control.

Thus it is difficult to use the mock-up as a general format for monoclonal antibody product.

However,

We think it is important to discuss and share how to describe AF based on accumulated knowledge and experiences both in industries and regulators since the Guideline publication in 2005.

For further discussion, the case study using hypothetical mAb product may be useful.
Summary

- **Advantage of Japanese Application Form**
  - Flexibility
  - Transparency: Good tool to share the necessary regulatory process for post approval changes.

- **What to be described on manufacturing process**
  - Description level: the principle and flow of the manufacturing step should be understandable.
  - Elements which may have impact on the product quality should be described.

- **Consideration on the description of manufacturing process**
  - Product and process understanding.
  - Demonstrated ability in process control
  - Contribution of the process to the overall control strategy
Thank you for your attention!

Special thanks to colleagues in Office of Cellular and Tissue-based Products