Role of QOS in PMDA Review Process

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Take-home massage

Role of QOS in Japan review system is... an important interface of QbD-driven product for risk communication between industry and regulatory.
Disclaimer

- The information in this presentation...

- Is not intended to create any new expectations beyond current regulatory requirements.

- Is not official views of PMDA.

- Contains my personal point of view.
Outline

- Relationship between Application Form (AF) and CTD Documents in Japan
- Description of Partial & Minor Change Matters in AF
- Sakuramil S2 mock
- Role of QOS: case of crystallization process in STEP 1 in Sakuramil drug substance
- Summary
- References
Relationship between Application Form and CTD Documents in Japan

Module 1 (AF)

Module 2 (QOS)

Module 3

Approval Matters

Extracted

Major review document

Summarized

FDA/PQRI Conference on Evolving Product Quality on Sep 17, 2014
Approval Matters
(Contents of AF)

- 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 AF

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 RTRT etc.
## Post-authorization procedure

<table>
<thead>
<tr>
<th>Risk of Changes</th>
<th>Japan</th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td><strong>Partial change</strong> (Application for approval of variation)</td>
<td>Major change (Prior approval supplement)</td>
<td>Type II variation (Application for approval of variation)</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td><strong>Minor change</strong> (Notification within 30 days after implementation or shipping)</td>
<td>Moderate change 1)Supplement-changes being effected (CBE) in 30 days 2)Supplement-changes being effected (CBE)</td>
<td>Type IB variation (Notification before implementation and MAHs must wait a period of 30 days) Type IA variation (Immediate notification)</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td><strong>SOP</strong> (Under GMP change control)</td>
<td>Minor change (Annual report)</td>
<td>Type IA variation (Notification within 12 months after implementation)</td>
</tr>
</tbody>
</table>
Description of Partial & Minor Change Matters in AF

☐ Enter items other than target/set values in
  - Nothing: Partial Change Matter
  - “ ”: Minor Change Matter

☐ Enter target/set values of process parameters and standard charge-in amounts in
  - 《 》: Partial Change Matter
  - 『 』: Minor Change Matter

→ AF system in Japan provides clear description of post approval change controls.
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℃』.

Acknowledgement : Sakuramil S2 mock
Questions arise

- CPP = Partial Change matter? (one-to-one correspondence?)

- CPP as Minor Change matter
  → Does it mean “Regulatory Flexibility” by QbD?

- What’s expected QOS for QbD-driven product?
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).
Sakuramil S2 mock is

- To illustrate the contents to be included in 2.3.S.2.6 “Manufacturing Process Development” regarding chemically synthesized drug substance.

- To take into consideration the description into QOS using QbD.

- Prepared without taking account of a rule of maximum 40 pages.
Synthetic flows of Sakuramil drug substance

**STEP 1**

1) **Reaction:** Ethyl chloroformate
2) **Crystallization:** Ethanol/water

**Starting Material**

**CP-6**

**CP-7**

Starting Material

**1) Reaction:** *CP-8*
2) **Crystallization:** Ethanol/water

**STEP 2**

**CP-9**

Sakuramil drug substance

Acknowledgement: Figure 2.3.S.2.2-1 Sakuramil S2 mock

FDA/PQRI Conference on Evolving Product Quality on Sep 17, 2014
Potential Review Points of Sakuramil drug substance

1) Reaction: Ethyl chloroformate
2) Crystallization: Ethanol/water

1) Reaction: CP-8
2) Crystallization: Ethanol/water

Genotoxic
Specification?
Synthetic routes?
Justification?

4 design spaces
Risk assessment?
Multivariate studies?
Description in AF?

Poorly soluble
QTPP?, CQA?
Control Strategy?

FDA/PQRI Conference on Evolving Product Quality on Sep 17, 2014
QOS is a practical tool to capture the whole picture.

Module 1 (AF)

Module 2 (QOS)

Module 3

poor background info.

suitable as an entrance

huge!
Contents of Sakuramil S2 mock

- 2.3.S.2.2 Description of Manufacturing Process and Process Controls
  - Synthetic routes
- 2.3.S.2.3 Control of Materials
  - Control of Starting Materials & Raw materials
- 2.3.S.2.4 Control of Critical Steps and Intermediates
  - Control of Critical Steps & Intermediates
- 2.3.S.2.6 Manufacturing Process Development (total 51 pages)
  - Potential CQA, SM Justification, Risk Assessment, Control Strategy Development, Multivariate Studies, Final Design Space and Control Strategy
- 2.3.S.4.1 Specifications and test methods
  - RTRt and Skip testing are included
- 2.3.S.4.5 Justification of Specifications and test methods
  - Summary of Control strategy for Sakuramil
Role of QOS: case of crystallization process in STEP 1

**CP-6**
- **STEP 1**
  - 1) Reaction: Ethyl chloroformate
  - 2) Crystallization: Ethanol/water

**CP-7**
- **STEP 1**
  - Design spaces

**CP-9**
- **STEP 2**
  - 1) Reaction: CP-8
  - 2) Crystallization: Ethanol/water

Genotoxic
- Specification?
- Synthetic routes?
- Justification?

Risk assessment?
- Multivariate studies?
- Description in AF?

Poorly soluble
- QTPP?, CQA?
- Control Strategy?
Role of QOS: case of crystallization process in STEP 1 (part 1)

- 2.3.S.2.2 Description of Manufacturing Process and Process Controls
  - Synthetic routes

- 2.3.S.2.3 Control of Materials
  - Control of Starting Materials & Raw materials

- 2.3.S.2.4 Control of Critical Steps and Intermediates
  - Control of Critical Steps & Intermediates

- 2.3.S.2.6 Manufacturing Process Development
  - Potential CQA, SM Justification, Risk Assessment, Control Strategy Development, Multivariate Studies, Final Design Space and Control Strategy

- 2.3.S.4.1 Specifications and test methods
  - RTRt and Skip testing are included

- 2.3.S.4.5 Justification of Specifications and test methods
  - Summary of Control strategy for Sakuramil
Role of QOS: case of crystallization process in STEP 1 (part 2)

For development of design space, as a initial risk assessment, each step of the manufacturing process was divided into focus areas (FA) and evaluated individually.

<table>
<thead>
<tr>
<th>Sakuramil CQA</th>
<th>Focus Areas (FA) in Step 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FA1</td>
</tr>
<tr>
<td>Chirality</td>
<td></td>
</tr>
<tr>
<td>CP-6</td>
<td>Low</td>
</tr>
<tr>
<td>CP-7-1</td>
<td>High</td>
</tr>
<tr>
<td>CP-8</td>
<td>N/A</td>
</tr>
<tr>
<td>CP-3</td>
<td>Low</td>
</tr>
<tr>
<td>CP-4</td>
<td>Low</td>
</tr>
<tr>
<td>CP-5</td>
<td>Low</td>
</tr>
<tr>
<td>Total</td>
<td>High</td>
</tr>
</tbody>
</table>

Acknowledgement : Table 2.3.S.2.6-7 Sakuramil S2 mock
Role of QOS: case of crystallization process in STEP 1 (part 3)

QOS provides multivariate studies of Step 1 crystallization.

**Design of DoE**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>Standard</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling Rate (° C/min)</td>
<td>0.15</td>
<td>0.36</td>
<td>0.5</td>
</tr>
<tr>
<td>Final Temperature</td>
<td>14</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Final Concentration (L/kg, volume of ethanol relative to CP-6)</td>
<td>4</td>
<td>7.22</td>
<td>10</td>
</tr>
<tr>
<td>Addition Time (min)</td>
<td>15</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Volume of Water (% w/w, volume of water relative to ethanol)</td>
<td>10</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Agitation Rate (rpm)</td>
<td>150</td>
<td>test</td>
<td>350</td>
</tr>
<tr>
<td>Hold Time prior to Water Addition (hr)</td>
<td>2</td>
<td>test</td>
<td>4</td>
</tr>
<tr>
<td>THF (%v/v)</td>
<td>1</td>
<td>test</td>
<td>6</td>
</tr>
</tbody>
</table>

**Ethyl Homolog Levels in Step 1 Crystallization**

**Total Impurities (%)**

Acknowledgement: Table 2.3.S.2.6-10, Figure 2.3.S.2.6-20 & 21 Sakuramil S2 mock
Role of QOS: case of crystallization process in STEP 1 (part 4)

QOS provides Summary of Control Strategy & DS.

<table>
<thead>
<tr>
<th>CQA</th>
<th>Control Strategy</th>
<th>Design Space</th>
</tr>
</thead>
</table>
| Ethyl Homolog ≤1.0% in drug substance  | • Design Space for Step 1 (parametric control)  
  • Specification in CP-7 of ≤ 1% to be used when appropriate.  
  ○ Test for ethyl homolog CP-7-1 in CP-7 for 25 batches at commercial launch. If demonstrates control via design space, eliminate this test and use RTRt in a parametric sense. | The design space for Step 1 demonstrated the highest possible amount (even under stressing conditions) of ethyl homolog to be 0.3%. This is well below the 1% specification/qualified level in drug substance.  
No edges of failure were identified in the Step 1 design space. This is a very robust process. |
| Total impurities NMT 5% (Step 1, intermediate MA) | • Specification for total impurities in Step 1 of ≤ 5%                                                                                                                                                           | It is well recognized that water (the “poor” solvent) can increase the level of impurities. The NOR for this parameter is 28-32% for Step 1  
• The % water for the crystallizations in Step 1 at the high level are CPP’s.  
  ○ 50% water Step 1 CPP                                                                 |
Role of QOS: case of crystallization process in STEP 1 (part 5)

Description in AF

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].

* This quantity is one of parameters establishing Design Space. This parameter is critical, however, risk affecting on DS CQA is low through control strategy established to operate process parameter good enough within the specified range. In consequence, this parameter is defined as medium risk and described as range of notification.

Acknowledgement : Sakuramil S2 mock
Role of QOS: Summary

- Risk communication between industry and regulator provides an opportunity to accept CPP as Minor Change matter.

- QOS facilitates risk communication.
Relationship between Application Form and CTD Documents in Japan

Module 1 (AF)

Module 2 (QOS)

Module 3

Approval Matters

Extracted

Major review document

Summarized
Module 3 as a foundation of AF

- Drilling down into data and information for deep understanding of risk assessment & control strategy

Module 1 (AF)
Module 2 (QOS)
Module 3
Essence of QOS is extracted for AF

Module 1 (AF)

Module 2 (QOS)

Risk assessment
Control strategy

Module 3
Take-home massage

Role of QOS in Japan review system is... an important interface of QbD-driven product for risk communication between industry and regulatory.
References

- Sakuramil S2 mock
Thank you for your attention

QbD Assessment Project at PMDA
http://www.pmda.go.jp/english/service/qbd_e.html