Implementation of Lifecycle Validation Practices at CMOs

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1 Based on the ISPE Discussion Paper “Implementation of Lifecycle Validation Practices at Contract Manufacturing Organizations”, November 2015

Working Team - Thanks

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Overview

- This presentation provides an overview of the ISPE Discussion Paper “Implementation of Lifecycle Validation Practices at Contract Manufacturing Organizations”.
- Divided into sections based upon the FDA January 2011 Guidance for Industry “Process Validation: General Principles and Practices”

Terminology:
MAH – Market Authorization Holder (Contract Giver)
CMO – Contact Manufacturing Organization (Contract Receiver)

http://ispe.org/publications-guidance-documents/series#discussion-papers

Why did we write the article?

Process Validation is challenging.
Use of CMOs adds more complexity.

- Complex Contracts – Co-licensing, In-licensing, Co-Promotion, etc.
- Responsibilities
- Less control / Indirect oversight
- Competing / Coordinated Production Schedules
- What happens when things go wrong?
Agenda

Stage 0: Planning

Stage 1: Process Design - Knowledge Transfer

Stage 2a: Equipment & Facility Qualification

Stage 2b: Initial Process Validation Batches (PPQ)

Stage 3: Ongoing Monitoring Strategy

Questions

Stage 0: Planning

(CMO Selection)

1. Confidentiality Agreement
   A. Intellectual Property
   B. Commercial agreement

2. Audits / Due Diligence
Stage 1. Process Design - Knowledge Transfer

1. Knowledge Transfer Plan
2. Quality Agreement
3. Process Design Plan
4. Process Database Transfer
5. Development Summary Report from MAH
6. CMO Skill Set Assessment

Stage 1, Step 1: Knowledge Transfer Plan

**Purpose:** Details how development knowledge will be transferred from MAH to CMO.

**Contents:**
1. Objective
2. Roles and Responsibilities
3. Raw Material details
5. Database Information – Scale, # of batches
6. Analytical Methods
7. Storage, transport, cleaning
Stage 1, Step 2: Quality Agreements

**Purpose:** Defines what the GMP manufacturing and filing requirements are and who will be responsible for completing each required activity.

**Contains:**
1. Scope of work to be performed
2. Roles & Responsibilities, including Quality Unit
3. Facilities & Equipment; MAH review and acceptance
4. Materials Management
5. Product Specific Terms
6. Laboratory Controls (Analytical methods)
7. Documentation

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**Stage 1, Step 2: Quality Agreements**

**Contains:**
8. Change Control (including subcontractors)

**Other Typical Elements**
- MAH presence at CMO (Person in Plant)
- Deviations – notification, management, timelines
- Contacts for each party
- Changes to the agreement
- Batch Disposition

**Note:** *EudraLex Volume 4 Chapter 7 defines outsourced activities in the European Union and in May 2013 FDA provided a draft guidance for industry for Contract Manufacturing Arrangements for Drugs: Quality Agreements.*
Stage 1, Step 2: Quality Agreements

Special Considerations / Best Practices
1. Understand the risks related to PPQ and identify personnel who have applicable skills and training for implementation
2. Roles will change depending on CMO business partner
3. Ensure quality oversight, do not bind CMO best practices with red tape
4. Ensure change management system on both sides supports understanding and development through risk reduction

Note - May of 2013 the FDA provided draft Guidance for Industry - Contract Manufacturing Arrangements for Drugs: Quality Agreements

Stage 1, Step 3: Process Design Plan

Purpose: Provides details of the QbD process design to convey preliminary critical quality attributes derived from MAH developmental data.

Contents
1. List of studies conducted, goals, parameter adjustments
2. Risk evaluation of proposed changes including scale up, process changes, raw material changes
3. Definition of RPN numbers and acceptance criteria
4. Preliminary list of CPP’s
5. List of required studies to fill gaps
Stage 1, Step 4: Process Database Transfer

**Purpose:** Provides detail on raw material lots, in process parameters and finished product results

Enables multi-variant analysis.

Sharing with CMO

Example:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1, Step 4</td>
<td></td>
<td>Process Database Transfer</td>
</tr>
</tbody>
</table>

Stage 1, Step 5: Development Summary Report

**Purpose:** Provided by MAH to CMO to define the process and justify control strategy based upon developmental studies.

**Contains**
1. Risk Reduction Plan
2. Completed CPP/CQA Matrix
3. Control Strategy
4. Test Method Variability
5. Statistical evaluation of study data
6. Statement about development status
Stage 1, Step 6: CMO Skill Set Assessment

Purpose: Baseline gap assessment of CMO team’s skills related to technical transfer. Defines resources needed for product transfer success.

Contents
1. Base skill sets required for individual processes
2. Gap Assessment of CMO SME skills vs. required skill sets
3. Training plan to close the gap

Note: This is a joint assessment from both MAH and CMO.

Stage 2a. Equipment and Facility Qualification (MAH Assessment / Acceptance)

Purpose: Verify that the CMO’s qualification of facility and equipment is fit for the intended use.

Contains
1. Review of utilities, equipment and facility qualification status
2. Computer Validation / Data Integrity
3. Assess Cross Contamination & Cleaning Validation
4. Gap assessment, high risk areas and agreed remediation plan
5. Transportation Validation – Moving Product

Note: Various CMO qualification approaches are acceptable, it is not necessary to be the same as the MAH’s, but the qualification must demonstrate suitability.
Stage 2a: Process Specific Risk Assessment

1. Process Specific Risk Assessment - Example

Stage 2a. Cleaning Validation

**Purpose:** Ensure CMO products and processes will not contaminate MAH products. Ensure MAH products and processes will not contaminate CMO’s other products.

**Contains**

1. Listing of types of products produced at CMO or audit assessment practices
2. List of shared equipment, materials processed or contained
3. Assessment of cleaning methods and cleaning results
   A. Analytical Methods Validation and Transfer
Stage 2b. Working with CMO - PPQ batches

1. Roles and Responsibilities
2. Validation Plan and Protocols
   A. Number of PPQ batches
3. Use of Developmental, Clinical and Engineering data
4. Existing Validated Processes at the CMO
5. Demonstrating Control
6. Validation Summary Report

Stage 2b. Roles and Responsibilities

**Purpose:** Defines roles and responsibilities (aligned with Quality Agreement) related to PPQ process.

**Contains:**
1. RACI – Responsible, Accountable, Consulted, Informed
Stage 2b. Validation Plan and Protocol(s)

**Purpose:** Defines how process control will be demonstrated including rationale for number of batches and samples to show control.

**Contains:**
1. Purpose and Scope of process validation
2. Validation Approach
3. Required Documentation
4. What data will be included in validation and why
5. Deliverables and Acceptance Criteria
6. Deviations
Stage 2b. Use of Developmental / Engineering Data

**Purpose:** Defines how and when to use developmental, clinical and engineering data to support validation.

**When To Use**
- When adequate controls were in place
- When data represents process utilized

**When Not To Use**
- After process changed
- When not representative
  - Process at CMO different than development at MHA
- Ongoing investigation

Stage 2b. Demonstrating Control

**Purpose:** Agree on definition of what process control is (confidence) and system used to demonstrate process is in a state of control, illustrating that the control strategy is effective.

**Methods Utilized:**
- Statistical rationale – Use of significant number of process samples
- Demonstration of both inter and intra batch control
- Continuous verification – PAT
- Control Charts

>Note: ISPE has published articles identifying development of a statistical rationale for the number of batches required
Stage 2b. Validation Summary Report

**Purpose:** Documented evidence that process was in a state of control at the end of validation. Protects both MAH and CMO.

**Contains:**
- Summary of studies
- Conclusion – Was the validation end point achieved? Is distribution justified?
- Signatures from both CMO and MAH QA units

Stage 3. Ongoing Process Verification

1. Continued Process Validation Strategy
2. Written into the Commercial Agreement and Quality Agreement
3. Defining Quality Metrics and Annual Reporting
Stage 3. Continued Process Validation Strategy

**Purpose:** It is critical that both MAH and CMO agree on commercial expectations, what the sampling strategy will be, how trends will be identified, addressed and reported.

**Contains:**
- Listing of acceptance criteria
- Identification of trends
- Notifications & notification thresholds
  - Out of trend vs. out of specification
- Corrective action and preventative action process
- Risk reduction strategy

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Stage 3. Commercial Agreement & CPV

**Purpose:** Additional commercial terms are required for batch disposition related to ongoing verification.

**Additions to commercial agreement:**
1. Disposition of out of trend batches
2. Value of risk reduction
3. Financial implications related to batch disposition
Stage 3. Quality Metrics and Annual Reporting

**Purpose:** Define what quality metrics will be utilized and data related to annual report.

**Contains:**
1. Who is responsible for assessing quality metrics
2. What data will be collected / reported
3. When data will be reported
4. What information is utilized in MAH and CMO reports
5. Annual Product Reviews

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Conclusion

- *MAH and CMO need to work together on lifecycle validation activities*
- *Guidelines provide an overview of requirements, but the individual product and process needs are the cornerstone of successful tech transfer & lifecycle validation*
- *Successful implementation requires cooperation and sharing.*
Questions