Implementation of Lifecycle Validation Practices at CMOs [1]

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

Connecting a World of Pharmaceutical Knowledge

Working Team - Thanks

- Bob Beall (Leader) – ProPharma Group
- Lois Hintz – Cordon Pharma
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- Gretchen Allison - Pfizer

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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

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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?

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Agenda

Stage 0: Planning

Stage 1: Process Design - Knowledge Transfer

Stage 2a: Equipment & Facility Qualification

Stage 2b: Initial Process Validation Batches (PPQ)

Stage3: Ongoing Monitoring Strategy

Questions

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Stage 0: Planning

(CMO Selection)

1. Confidentiality Agreement
    A. Intellectual Property
    B. Commercial agreement
2. Audits / Due Diligence

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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

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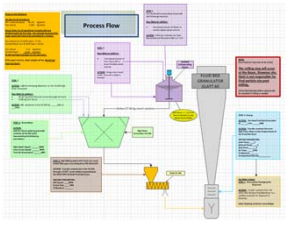
Stage 1, Step 1: Knowledge Transfer Plan

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



Contents:

1. Objective
2. Roles and Responsibilities
3. Raw Material details
4. Process Overview – Process Maps
5. Database Information – Scale, # of batches
6. Analytical Methods
7. Storage, transport, cleaning

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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

A. MAH presence at CMO (Person in Plant)
B. Deviations – notification, management, timelines
C. Contacts for each party
D. Changes to the agreement
E. 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.*

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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*

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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

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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:

Dev. status	Batch no.	Dose strength Hydro [mg]	Dose strength Placebo [mg]	Type of tablets	Control	Testing Parameter	Dosage form	Number IPC	based on	Start, End IPC	DS	No. Unit	unit	value	sdv
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	4	single	97.2	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	5	single	100.7	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	6	single	100.3	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	7	single	93.8	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	8	single	91.2	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	9	single	99.8	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	10	single	95.5	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	-	min	91.2	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	-	max	100.7	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	1	A	end	A	-	avge	97.3	3.0
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	1	single	95.2	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	2	single	99.1	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	3	single	95.9	-
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Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	5	single	96.3	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	6	single	101	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	7	single	97.2	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	8	single	95.1	-
Full scale	G78532	80	5	FDC	IPC	CU	tablet	3	A	start	T	9	single	96.6	-
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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

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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.

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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.*

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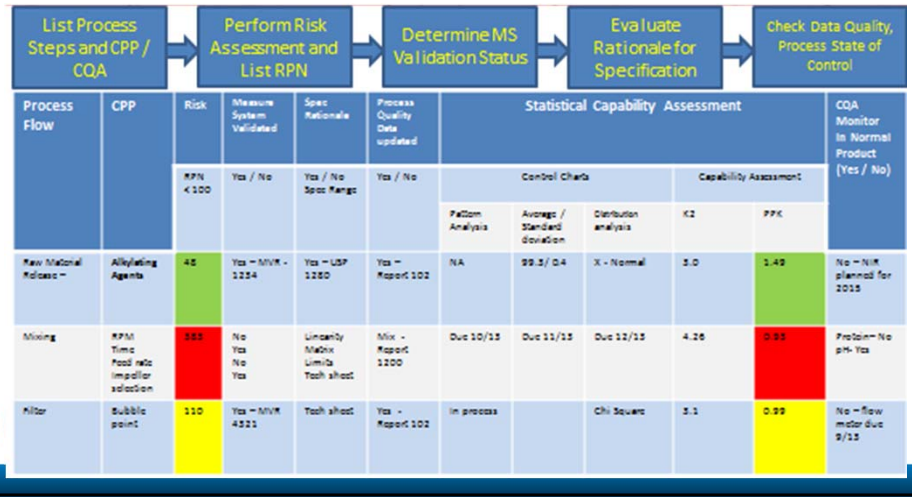
Stage 2a: Process Specific Risk Assessment

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

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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

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Activities	John Doe Owner/Champion	Jane Doe Sponsor	John Doe 2 Coach	Jane Doe 2 Capital Program	John Doe 3 Validation Lead	Jane Doe 2 QA Lead	John Doe 4, Engineering Director Steering Committee	Jane Doe 4, Validation Director Steering Committee	John Doe 5, PMO Director Steering Committee	Jane Doe 4, Focus Factory Director Steering Committee	Document Coordinator(s)
Provide PM Tools	I	C	R	C	I	I	I	I	A	I	I
Scheduling & Resources											
Project Organization Structure Development and Maintenance	R, C	A	R	C, I	I	I	C	C	I	I	I
Project Planning Activities	C, I	C, I	R	R, C	C, I	C, I	I	I	I	I	I
Create and Maintain Project Schedule	I	C, I	R	C, I	C, I	C, I	I		I	I	I
Schedule Updating/Communication	I	C, I	R	R, C, I	I	I	I		I	I	I
Project Resources Assessment and	R	A	R	R	I	C	R	I	C, I	I	I
Project Resources-Assignment and Coordination	A	C, I	I	C, I	R	R	R	I	I	I	I
Lead CORE Team Activities and Coordination	A	I	R	I	I	I	I	I	I	I	I
Lead Working Team Activities/Reporting: SOP's, Filling, etc.	A	I	C, I	C, I	C, I	C, I	I	I	I	I	I
Project Detail Task Management	A	I	I	R, C	R	R, C	R, C	I	I	I	I
Communication											
Issue Resolution (Drivers)	R	A	R	R, C	C, I	C, I	C, I	I	I	I	I
Communication Plan Continuous Development	C	C, I	R	C, I	I	I	I	I	C, I	I	I
Communication Enabling (eRooms, iPlan, etc.)	I	I	R	I	I		I	I	I	I	I
Project Scope Change Management	R	A	R	R, C	I		C, I	I	I	I	I
Budget											
Budget Management	R	A	I	R, C	I	I	R, C, I	I	I	C, I	I
Budget Management	A	I	I	R							
Reporting											
Project Reporting, Internal: Program Level	C, I	C, I	R	C	I	I	I	I	A	C, I	I
Project Reporting, External: BI	R, C	R	R, C	R, C	I	I	I	I	A	C, I	I
Project Reporting, External: Customers/Agencies	R, C	A	C, I	C, I	I	I	I	C, I	I	C, I	I
Document Coordination	I	I	A, R	C, I	C, I	C, I	I	I	I	I	R

R = Responsible = person who performs an activity or does the work
A = Accountable = person who is ultimately accountable and has Yes/No/Veto
C = Consulted = person that needs to provide feedback and contribute to the activity
I = Informed = person that needs to know of the decision or action (communication with this group is usually 1-way in nature, "Need to know")

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

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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

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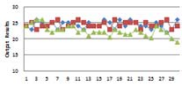
Stage 2b. Demonstrating Control

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

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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

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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

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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

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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.*

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Questions