OVERCOMING CHALLENGES IN PROCESS VALIDATION 2015

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OVERVIEW AND OBJECTIVES

• Discuss frequent process validation problems
  Global input from multiple pharma / device meetings
  *JVT* series “PQ Forum”
  Application to all PV and qualification

• Propose solutions and recommendations
  Multiple global companies
  New problems – Evolving solutions
  Participants identify new problems
OUTLINE

1. FDA PV Guidance recommendations
   - Validation approach and PQ enhancements
2. Technical basis for validation
   - Stage 1 support and specifics
3. Documentation – General and specific
4. Support functions – PM, calibration, training
5. Infrastructure – Managing validation function/QS
6. Validation Approval Committee
   - Roles and responsibilities

Interactive Discussion. Attendees discuss identified and new PV problems and solutions throughout presentation.

PLEASE PARTICIPATE – ADD NEW PROBLEMS
PROCESS VALIDATION AND QUALIFICATION

Process Validation – Process Qualification
PV – PQ -- PPQ

Qualification

Equipment #1
Equipment #2
Equipment #3

Analytical methods validation

Process is validated

Qualification

HVAC
Utilities
Facilities
Computers
1. FDA PV GUIDANCE RECOMMENDATIONS

Problem: Implement the new (2011) guidance
Why the problem?

Organizations implementing lifecycle approach -- Reasons
- US FDA guidance, Health Canada guidance, EMA draft guidance
- Global communication
- ICH Q8, Q11
- Logical approach – development, performance, and maintenance
- Application to other processes, equipment, facilities, etc.

Organizations not implementing lifecycle approach -- Reasons
- "Its only a guidance."
- "Let’s see what happens."
- "It’s only for USA."
- "We will consider it if we get observations."
- Too costly, no headcount
FDA PV GUIDANCE (2011)

Lifecycle approach expectations –

Stages and enhancements
  – Strategy and approach
  – Stage expectations
  – PPQ enhancements

GUIDANCE CONTENT IS NOT NEW
LIFECYCLE APPROACH TO PROCESS VALIDATION
FDA, 2011

Definition: Collection and evaluation of data, from the process design stage throughout commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation involves a series of activities over the lifecycle of the product and process.

Three stages of activities:
• Stage 1 – Process Design – Development and scale-up activities
• Stage 2 – Process Qualification – Reproducible manufacturing
• Stage 3 – Continued Process Verification – Routine manufacturing

STAGE 1 AND STAGE 3 EMPHASIS – NEW PARADIGM
ABOVE CONCEPTS APPLICABLE TO ALL PROCESSES, EFU, ETC.
LIFECYCLE APPROACH RESPONSIBILITIES

Stage 1. R&D, Technical Support, Engineering, other technical functions.
Stage 2. Validation
Stage 3. QA with function support

NEW PARADIGM
INTEGRATED ORGANIZATIONAL APPROACH
STAGE 1: QUALITY BY DESIGN (QbD)

Quality target product profile (QTTP)
Critical quality attributes (CQA)
Critical material attributes (CMA)
Critical process parameters (CPP)
Design space
Scale-up and technology transfer
Identify input variables
Input variable control strategy
Continuous improvement
Other considerations: PAT, risk analysis

DEVELOPMENT PROCESS DEFINED
GLOBAL GUIDANCES
VALIDATION PHILOSOPHY

• Validation is confirmation.
• Acceptable (passing) results are expected.

• Validation is not
  – R&D
  – Final stage of development process
  – Optimization
  – Fine-tuning
  – Debugging
LIFECYCLE APPROACH

• Three stages of validation
  1. Design and development – Understanding
  2. PQ – Demonstration (traditional validation)
  3. Continued process verification – Monitor and maintain

• Emphasis on process understanding – CQA, CPP, CMA, sources of variation, variation control

• Emphasis on maintaining validated state
  – Ongoing improvements expected

• Lifecycle approach integrates original PV, ICH, QbD, and device concepts into unified approach

• Risk level determined that dictates amount of work.

• Rational decisions and judgments.
VALIDATION HISTORY

1978
GMP includes Validation.

1987
Development → VALIDATION → Control

2008-2011
Lifecycle approach
UNDERSTANDING → PQ → MONITORING
LIFECYCLE APPROACH STATUS 2015

- Full commitment
- Partial (high) commitment
- Partial (low) commitment
- No commitment

WHERE IS YOUR ORGANIZATION?
APPLICATION AREAS

- Processes: Manufacturing, cleaning, analytical, all processes
- Equipment “processes:” HVAC, water
- Equipment, facilities utilities, computers,
- Quality systems

APPROACH

- Design and understanding
- Demonstrate
- Monitor and maintain

USE SAME APPROACH FOR ALL VALIDATION / QUALIFICATION
IMPLEMENTATION

How do you change an organization?
1. Crisis approach
2. Other
3. Organization focus
4. Personal focus
IMPLEMENTATION

1. Identify high risk areas
2. Senior management discussion
   - Risk to operation
   - Personal risk
3. Function management discussion – risks to operation
   - Technical areas
   - QA
4. Identify receptive individuals in high risk area
5. Training of appropriate individuals
6. Start slowly
7. Communication. Modify strategy as needed to insure success
8. Success is essential
9. Expand effort based on success
10. Expect resistance
2. TECHNICAL BASIS FOR VALIDATION

What is the problem?

• Technical errors – General approach and specific situations

Why the problem?

• Inexperience
• Historical precedence
• Workload
• Lack of technical understanding
CLEANING VALIDATION
PRODUCT RESIDUE PROBLEMS

Physical and chemical properties of residue as a basis for cleaning

• Residue chemistry, cleaning agent chemistry, and process must be consistent. Would you clean an acid with a base or with another acid?

Residue solubility in most-difficult-to-clean matrix

• Determination of the true worst-case residue is critical for the cleaning matrix. The consequences of incorrect identification of worst-case products are disastrous.

“Cleanability” in determining the most-difficult-to-clean residue

• Solubility and toxicity not only considerations for determination of worst-case compounds
PHYSICAL AND CHEMICAL PROPERTIES OF RESIDUE AS BASIS FOR CLEANING

PROBLEM: No basis for cleaning procedure

- Arbitrarily chosen
- “Best” method at site
- Methods used for years for all products
- Bought soap at local store – sale price
Case study #1: Antibiotic suspension containing insoluble API (base)

Original cleaning method: Water, PurW, dry
- No documented cleaning validation for many years
- Unknown peaks on original cleaning validation attempts
- API insoluble

Second method: Alkaline soap wash, water, PurW, dry
- Unknown peaks again
- API insoluble

Final method: Acid wash, alkaline soap wash, water, PurW, dry – Significant improvement
- No residues. Unknown peaks determined to be flavors.
- API dissolves (acid-base neutralization)

Consider active drug and other residue chemistry in development of cleaning process
Case study #2: Small molecule API oral liquid product. API insoluble

Original cleaning method

- Alkaline cleaning agent with manual intervention
- Acid cleaning agent (full strength) when white residue noted.
- Small parts soaked in acid cleaning agent (full strength)
- Cleaning method difficult, ineffective, and unsafe

Liquid product – alcohol / glycol solvent system

- Change cleaning method to alcohol initial rinse. API soluble

Final method: Alcohol rinse/soak, alkaline wash, water, PurW, dry – Significant improvement

- No residues
- Easy and safe method

Consider active drug and other residue chemistry in development of cleaning process
CLEANING PROCEDURE DEVELOPMENT PROCESS
Stage 1 R&D

1. API technical analysis.
2. pH solubility profile pH 1-12.
3. Solubility in proposed cleaning liquid.
4. pH-stability profile pH 1-12.
5. Laboratory cleaning studies confirmation.
6. Analytical method development based on stability data.
7. Testing of all excipients with analytical method.
   - Source of unknown peaks

CLEANING PROCEDURE TECHNICAL BASIS
pH-SOLUBILITY AND pH-STABILITY IS BASIC R&D WORK
ANALYTICAL METHOD MEASURES ACTUAL RESIDUE
ANALYTICAL METHOD DETECT OTHER EXCIPIENTS
RESIDUE SOLUBILITY IN MOST DIFFICULT TO CLEAN MATRIX BASIS FOR CLEANING PROGRAM

PROBLEM: Wrong basis for worst-case residue

Water solubility – USP Tables

• Is this adequate? Depends on cleaning procedure

pH effect – API with ionizable groups?
Solubility in cleaning agent?

• Determine solubility at range pH 1-12
• Understand solubility at pH of cleaning liquid
• Understand solubility in cleaning agent liquid
pH SOLUBILITY PROFILE, pH 1-12

Solubility
mg/ml

Drug A

Drug B

pH 1

7

12
## CLEANING MATRIX
Determine Worst-Case Soil

<table>
<thead>
<tr>
<th></th>
<th>SOLUBILITY (mg / ml)</th>
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<tr>
<td></td>
<td>pH 1</td>
<td>Water</td>
<td>pH 12</td>
<td>Alkaline Cleaning Agent</td>
</tr>
<tr>
<td>Drug A</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Drug B</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Drug C</td>
<td>5</td>
<td>5</td>
<td>150</td>
<td>250</td>
</tr>
<tr>
<td>Drug D</td>
<td>150</td>
<td>10</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Drug E</td>
<td>125</td>
<td>10</td>
<td>100</td>
<td>250</td>
</tr>
</tbody>
</table>

Consider acid cleaning agent for drugs D and E
"CLEANABILITY" IN DETERMINING MOST DIFFICULT-TO-CLEAN RESIDUE IN MATRIX

PROBLEM: Incomplete evaluation of worst-case residue

What factors should be considered to determine worst case residue?
Most companies use
• Solubility (pH?)
• Toxicity

OK for site with simple dosage forms
All aqueous solution products (LVP, SVP)
“CLEANABILITY” IN DETERMINATING MOST DIFFICULT-TO-CLEAN RESIDUE IN MATRIX

Matrix = Products cleaned by same cleaning procedure

Other considerations
• Solubility in cleaning liquid
• Toxicity
• Concentration in dosage form
• Cleanability
  – Formulation components major effect
  – Cleaning personnel input
  – Dirty hold time
  – Soil-surface interactions (e.g., air-liquid interface)
OTHER CONSIDERATIONS

- Consider flavor and color oils
- Dyes/lakes may be more difficult to clean than active drug
- Consider solubility of all components
- Alcohol explosivity
- Solvent toxicity
EQUIPMENT PROBLEMS

Non-uniform contamination transfer
• Non-uniform contamination is a worst-case situation and should be addressed. Calculations are demonstrated.

Most difficult-to-clean locations in equipment
• Sites should have an SOP with a defined procedure for identification of most-difficult to clean locations in equipment. These locations are then used in sampling for cleaning validation.
MOST-DIFFICULT-TO-CLEAN EQUIPMENT LOCATIONS

PROBLEM: No rationale for sampling of cleaned equipment.

• Sampling locations chosen arbitrarily.
• Easiest-to-clean locations chosen
PROCEDURE TO DETERMINE SAMPLING LOCATIONS

Specific documented procedure recommended
• Equipment technical evaluation
• Observation of equipment after processing
• Equipment disassembly review
• Cleaning procedure review
• Equipment evaluation review
• Operator interviews

SOP describing above
Documentation of above for equipment sampling
# EQUIPMENT SAMPLING INSTRUCTIONS FOR CLEANING VALIDATION

## EQUIPMENT: IMPACT MILL

<table>
<thead>
<tr>
<th>EQUIPMENT SAMPLING LOCATION</th>
<th>PRODUCT CONTACT MATERIAL</th>
<th>SAMPLE TYPE</th>
<th>RATIONALE</th>
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</thead>
<tbody>
<tr>
<td>1. Rotor</td>
<td>Stainless Steel</td>
<td>Swab</td>
<td>Maximum residue accumulation. Maximum product contact</td>
</tr>
<tr>
<td>2. Screen</td>
<td>Stainless Steel</td>
<td>Swab</td>
<td>Maximum residue accumulation. Maximum product contact</td>
</tr>
<tr>
<td>3. Discharge Chute</td>
<td>Stainless Steel</td>
<td>Swab</td>
<td>Maximum residue accumulation. Maximum product contact</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X SAMPLED EQUIPMENT</th>
<th>ASSET#</th>
<th>EQUIPMENT NAME</th>
<th>LOCATION</th>
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</thead>
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<tr>
<td>Equipment #XXX</td>
<td></td>
<td>Impact Mill</td>
<td>Room XXX</td>
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<tr>
<td>Equipment #XXX</td>
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<td>Impact Mill</td>
<td>Room XXX</td>
</tr>
<tr>
<td>Equipment #XXX</td>
<td></td>
<td>Impact Mill</td>
<td>Room XXX</td>
</tr>
</tbody>
</table>

Pictures are representative of all impact mills.

**SAMPLED BY:**

**VERIFIED BY:**
CLEANING PROCESS PROBLEMS

• Manual cleaning qualification
Manual cleaning is an inherently high risk activity.

• Cleaning procedure documentation
Cleaning procedure documentation should be equivalent to manufacturing process documentation -- Exact requirements with personnel accountability.

• Dirty hold time (time to initiate cleaning)
At lease one run at worst-case DHT
Worst-case DHT is not always longest DHT

• Campaign length
Max number of lots must be controlled
“Between lot procedure.”
CLEANING PROCEDURE

PROBLEM: Exact documentation for process reproducibility

• Fill volume
• Amount of cleaning agent = concentration
• Time
• Temperature
• Flow rate (impact)
• Verification of key steps
CLEANING PROCEDURE
(Cleaning Batch Record)

SOP
• Fill tank half full
• Add half scoop of soap
• Scrub as needed
• Rinse until clean
• Re-scrub and re-rinse if needed

CLEANING PROCEDURE RECORD
• Fill tank with 500 L water. Sign/date __________
• Add 20.0 kg cleaning agent. Sign/date __________
• Disassemble Part A. Steps 1, 2, 3, 4, 5
• Scrub for 20 minutes. Sign/date __________
• Disassemble Part B. Steps 1, 2, 3, 4, 5
• Soak Part B in cleaning liquid for 10 minutes. Sign/date __________
• Rinse Part A and Part B with 50 L water. Sign/date __________
• Rinse with 50 L Purified Water. Sign/date __________
• Dry with compressed air
RESIDUE RECOVERY STUDIES

PROBLEM: Is residue able to be quantitatively recovered from surfaces?

- Product contact materials
- High % of total surface area – identify all areas to be sampled
- Obtain representative coupons from equipment fabricators
  - Order coupons with new equipment
- Recovery should be consistent and high (e.g., >50%)
- Recovery factor used in calculations
  - Multiple approaches
- Done in lab by lab personnel – consideration for future training

ANALYSIS IS MEANINGLESS WITHOUT RECOVERY STUDIES
Protocol requires BME samples for potency.
Acceptance criteria: 95-105%

B = 95%
M = 100%
E = 105%

All results pass

Conclusion?

POST PQ MONITORING?
Protocol requires BME testing
Acceptance Criteria: Not More Than 6.0%

Results:
B = 2.0%
M = 2.1%
E = 6.0%

All data pass acceptance conclusions.
Conclusions?

POST PQ MONITORING?
3. DOCUMENTATION PROBLEMS

- Problem lists
- Technical writing rules
- Good documentation practices
  - Raw data availability
IMPORTANCE OF VALIDATION PQ DOCUMENTS

• Validation documents always requested in regulatory audits
• Documentation is retained forever
• Documents reviewed long after people are gone
  – Documents must “stand alone”
• Early documents (Request, Plan, Protocol) reviewed when project is in-progress or not completed
• FDA auditors often focus on documentation – validation documents often requested in advance of audit

Above sometimes difficult for technical people
FDA Process Validation Guidance has greatly expanded the scope of validation

- Lifecycle approach – documents from development through commercialization
- Traditional validation documents (protocol and results) less important

Validation organizations should lead sites in transition to lifecycle approach

- Multiple groups at site must now contribute to process validation lifecycle approach documents

Lifecycle approach being applied to all validation and qualification (equipment, facilities, cleaning, etc.)
VALIDATION DOCUMENTS -- BASICS

- Written for the reader – US vs. Europe
- Objective: Understanding
- Clarity much more important than brevity
- Stand-alone document
- Potential for review in 10+ years
- Author / Management not available for explanation
- Spelling and grammar correct
  - Need good writers
  - Simple sentences
  - Simple words
VALIDATION PQ DOCUMENTS

• Comments on validation PQ documents apply to all validation qualification
• Design and development for cleaning, EFU, computer systems, etc.
• Scientific and technical basis for all validation / qualification
• Validation initiation, Validation Plan, protocol, and results for all validation / qualification
• Outlines presented applicable to all validation / qualification
PROCESS VALIDATION PQ DOCUMENTS

Stage 1 documents – Process Design
- Specific documents from R&D / technical area

Stage 2 documents – Process Qualification (traditional validation)
- Validation Request / Plan
- Validation Protocol(s)
- Engineering Studies
- Others
- Validation Results / Report

Stage 3 documents – Continued Process Verification
- PQ requirements – additional testing based on PPQ results
- Routine monitoring
- Associated validation and qualification – Equipment and analytical
- Other associated documents – Related to PPQ
VALIDATION PQ DOCUMENTS

Validation PQ (Stage 2) documents are:

• Validation initiation and plan
• Protocol(s)
• Results

Stage 1 documents are referenced in PQ.
Some Stage 3 documents based on Stage 2 results.
EFU and analytical documents support PQ.
Associated documents (training, etc.) connected to PQ.
STAGE 1 DOCUMENTS -- PROCESS DESIGN

Technical areas must be aware that their documents are critical to validation throughout the product lifecycle.

• Direct support of Stage 2 PQ – their work is basis of validation
• R&D technical reports consistent with raw data
• Rapidly retrieved (within 30 minutes)
• Accessed throughout product lifecycle
• Personal support of regulatory audits
• Stand-alone documents
• **Documents = Specific QbD requirements – CQA, CPP, Variation control, others.**
• Applies to processes, cleaning, analytical, equipment, facilities, utilities, control systems, others.

R&D / TECHNICAL AREAS NOT ACCUSTOMED TO THESE REQUIREMENTS AND EXPECTATIONS
STAGE 1 DOCUMENTS – POTENTIAL PROBLEMS

• Reports not available – Specific requirements
• Reports not retrievable
• Reports incomplete
• Reports poorly written
• Reports not approved
• Personnel not available
• **Original data not available**
• **Substandard documentation practices – original data**
• No signature / date
• Data transpositions
• Data transfer problems
• Data transfer not verified
• Inconsistent data
• Multiple sources of same data inconsistent
STAGE 1 DOCUMENTS – SPECIFIC REQUIREMENTS

- Quality target product profile (QTTP)
- Critical quality attributes (CQA)
- Critical material attributes (CMA)
- Critical process parameters (CPP)
- Design space
- Identify input variables
- Input variable control strategy

ABOVE INFORMATION NEEDED FOR PQ
STAGE 1 DOCUMENTATION SUMMARY

Technical people not accustomed to GMP documentation requirements

• Original data records
• Documentation practices
  – Cross-outs and explanations
  – “Whiteouts”
  – Postdating
  – Sign and date
  – Others

TRAINING ON GMP DOCUMENTATION PRACTICES HIGHLY RECOMMENDED
VALIDATION STAGE 2 DOCUMENTS

- Validation initiation
- Validation plan
- Protocol(s)
- Results
- Summary for complex validation
Validation initiation: Template
Validation Plan: Outline
Protocol: Template or outline
  PV: Depends on site product complexity
  EFU: Outline
Results: Same as protocol

MODEL DOCUMENTS RECOMMENDED
Initiation: Statement of recommended validation
- What?
- Why needed?
- Why acceptable?
- Impact of validation – risk analysis
- Approach to accomplish – Validation Plan
- Approvals

Plan: Details of work to accomplish validation
- Description of strategy and approach
- References from Stage 1 work supporting validation
- Approvals

MAY BE SINGLE DOCUMENT OR TWO SEPARATE DOCUMENTS
• Objective of validation
• Why needed?
• Impact of validation
  – Risk analysis
• Why acceptable?
  – Compliance to internal requirements, policies, engineering standards, etc.
  – Regulatory impact (Prior approval, CBE, CBE30, etc.)
  – Other systems or product impacted
  – Procedure changes or other document changes
  – Notifications to affected groups (internal, external, labs)
• Validation plan -- Approach to accomplish validation

Above applicable to equipment and other qualification
HAVE MODEL DOCUMENTS AVAILABLE
VALIDATION INITIATION -- PROBLEMS

• Inconsistent content
  – Form with standardized information needed – outline sections

• Poorly written
  – Inadequate information

• Prematurely written
  – Written to meet business goals
  – Written to demonstrate future intent

• Amendments necessary -- changes usually required

Validation initiations should be submitted for approval only after objective and scope of validation is determined and work details (risk/testing/sampling) determined. Amendments are a planning failure regardless of justification.

HAVE MODEL DOCUMENTS AVAILABLE
VALIDATION INITIATION SUMMARY

• Establish template for all validation / qualification
• Minimize writing
• Simple words, simple sentences
• Clear and concise.
• Provide details in Validation Plan
VALIDATION PLAN
MOST IMPORTANT DOCUMENT

OUTLINE

• Introduction
• Technical information
• Validation strategy and testing
• Validation documentation
  – List of required protocols, reports, procedures, etc.
  – Administrative benefit
• References
  – List of reports and scientific references (including Stage 1 reports)

HAVE MODEL DOCUMENTS AVAILABLE
Validation Plan -- Comprehensive explanation

Validation Protocol -- Execute Validation Plan with details

Results -- Execute protocol – Pass / Fail / Discussion

Conclusion: Process / equipment is validated
VALIDATION PLAN

INTRODUCTION

• Overview describing validation / product / process / equipment / etc. (consistent with request)
• Requirements to complete validation
  – Conformance to regulations and internal policy
  – Impact of change to maintain the validated state
  – Impact on regulatory submission
  – Impact of change on procedures, drawings, other documents
  – Notifications to other areas internal and external (e.g., environmental agency, internal test labs) impacted by validation
VALIDATION PLAN

TECHNICAL INFORMATION

• Basic product / process / equipment description
  – Formula
  – Process
  – Specifications
  – Include non-technical description information

• Technical aspects of validation / qualification

• Reference to technical reports from Stage 1

• Total validation approach
  – Experimental studies
  – Past data (retrospective data)
  – Validation protocols
  – Other work
  – New procedures

• Number of lots – related to impact of change and risk

WRITTEN FOR THE READER
VALIDATION PLAN

VALIDATION STRATEGY AND TESTING

• Prospective validation only

• Types of testing -- general
  – Regulatory specifications
  – Internal controls
  – Process tests

• Tests and rationale – general
  – Address changes – based on risk analysis

• Sampling and rationale – general
  – Exceed routine QA testing – based on impact and risk analysis

• Data treatment – general
  – Statistical data treatment and confidence limits

• Acceptance criteria – general

• Post-validation testing (Stage 3)

DETAILS OF ABOVE PROVIDED IN PROTOCOLS
SAMPLING AND RATIONALE

• Sampling templates recommended
• Specified sampling for each unit operation
• Sampling pages approved by Validation Approval Committee
• Consistent sampling for all processes – minimize judgments by document writers.
• Risk-based
• Cleaning validation example.
## VALIDATION PLAN

### VALIDATION DOCUMENTATION

<table>
<thead>
<tr>
<th>Doc #</th>
<th>Title</th>
<th>Date complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>XXX Validation Initiation</td>
<td></td>
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<tr>
<td>02</td>
<td>XXX Dryer Engineering Study</td>
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<tr>
<td>03</td>
<td>XXX Dryer Qualification</td>
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<td>04</td>
<td>XXX Process Scale-up Engineering Study</td>
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<tr>
<td>05</td>
<td>XXX Process Validation</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Update Validation Master Plan – Product and Equipment sections</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>XXX Project Summary Report</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>XXX Reference document</td>
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<tr>
<td>09</td>
<td>XXX Reference document</td>
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</tr>
</tbody>
</table>
VALIDATION PLAN

REFERENCES

• R&D Reports
  – R&D reports
  – QbD required documents

• Development and analytical reports

• Published literature

Scientific and technical support to validation plan

Report copies should be stored in validation area or readily accessible (within 30 minutes)
TECHNICAL REPORTS

• Readily available
• Consistent across large technical groups
• Approved by management
• Linked to original data
  – Observe / store original data
  – Original documentation practices?

VALIDATION MUST REVIEW ORIGINAL DATA

• Rapidly retrievable
• Consistent with technical report
• Documentation practices
VALIDATION PROTOCOLS

Validation is CONFIRMATION.

• Validation must pass.
• There must be no question about expected success in validation.
• There must be no anxiety about validation performance and testing.
• Validation should be boring.

If above not possible: Engineering study.
VALIDATION PROTOCOLS

• Execution of the Validation Plan
• Testing details
• Sampling details
• Sampling sheets
• Data sheets
• Data treatment
• Acceptance criteria
• Minimal text repetition from Validation Plan

PROTOCOL EASILY WRITTEN IF VALIDATION PLAN IS THOROUGH
VALIDATION PROTOCOL OUTLINE

• Objective of validation – specific protocol
• Validation description – specific
• Validation approach
• Testing and rationale -- specific
• Sampling and rationale -- specific
• Data sheets (summary)
• Data treatment -- specific
• Acceptance criteria – specific
  – All testing must have acceptance criteria
  – No FYI testing in validation

VALIDATION IS CONFIRMATION
SAMPLING PAGES

Designed sheet with space for expected data
Data treatment specified
Signature and data of person supplying data
Highly recommended for Operators or persons not familiar with sampling
Data pages consistent with sampling pages
Sampling pages approved by Validation Approval Committee and are part of protocol.

• Prevents missing data in complex protocols
• Record sampling and / or testing
UNIT OPERATION: Tablet compressing, lot # ________________

TEST: Content Uniformity (SOP # XX-XXX).

SAMPLE: 10 Tables each from beginning, middle, and end of batch on each day of manufacturing. Acceptance criteria: ________________

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Sample #1 by</th>
<th>Date</th>
<th>Sample #2 by</th>
<th>Date</th>
<th>Sample #3 by</th>
<th>Date</th>
<th>Sample #4 by</th>
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<th>Sample #5 by</th>
<th>Date</th>
<th>Sample #6 by</th>
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<td>1</td>
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VERIFIED BY (signature/date):
Day 1__________  Day 2__________  Day 3__________  Day 4__________  Day 5__________
RESULTS PAGES

• Results pages (blank) may be added to protocol.
• Standardize presentation of data and facilitate results review.
• Results pages are approved by Validation Approval Committee
## RESULTS PAGE EXAMPLE

Product ____________  Lot # _______________
Validation # __________

### TEST RESULTS (Circle P -- Pass or F -- Fail)

<table>
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<tr>
<th>Sample #1</th>
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VALIDATION PROTOCOL OUTLINE

Introduction
Unit operations
Testing with justification
Sampling with justification
Sampling pages
Data pages and treatment
Acceptance criteria with justification

HAVE MODEL DOCUMENTS AVAILABLE
VALIDATION PROTOCOL -- PROBLEMS

No plan
No basic explanation of validation
No statement of strategy and approach
No test rationale
No sampling rationale
Missing samples – missing data
How to treat data
No discussion of results
No acceptance criteria rationale
No validation statement
Poorly written

WRITTEN FOR THE READER
VALIDATION RESULTS

- Execution of the protocol
- Compilation of testing required in protocol
- Deviations or problems
- Discussion
- Conclusion

WRITE GOOD PLAN
PROTOCOL CONSISTENT WITH PLAN
RESULTS CONSISTENT WITH PROTOCOL

WRITE RESULTS DISCUSSION FIRST – MOST IMPORTANT
VALIDATION RESULTS OUTLINE

Introduction
Data sheets compiled
Data treatment
Results
Deviations, Non-conformances, etc.
Discussion
  • “Results pass” is not sufficient.

Validation statement:
  “Results indicate that ___ is validated.”
Post-validation monitoring plan

WRITE DISCUSSION SECTION FIRST – MOST IMPORTANT SECTION

HAVE MODEL DOCUMENTS AVAILABLE
## RESULTS PAGE

Product ____________ Lot # _______________
Validation # __________

### TEST RESULTS (Circle P -- Pass or F -- Fail)

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VALIDATION RESULTS PROBLEMS

• Missing data
• Documentation practices on raw data
• Raw data and results inconsistent
• Inadequate or no discussion of results
• Inadequate or no discussion of amendments or deviations
• No conclusion statement
• Poor grammar and composition
DOCUMENT OUTLINES or TEMPLATES?

Document templates very difficult

- Labor intensive
- Do not fit every situation
- Templates OK for limited-product plant

Suggested approach

- Document outline of major sections
- Document outline evolves
- Model approved documents available
- Model approved documents improved and are replaced
RECOMMENDATIONS TO MINIMIZE PQ DOCUMENTATION PROBLEMS

• Validation training for all involved
• Validation writer training
• Templates or outlines for documents
• Model documents
• Technical writing principles
• Validation Approval Committee responsibilities and training
• Write key sections first
4. SUPPORT FUNCTIONS

What is the problem?
• Systems problems

Why the problem?
• Inexperience
• Workload
• Lack of understanding
SUPPORT FUNCTIONS

VALIDATION SUPPORT FUNCTIONS

- Preventive Maintenance
- Calibration
- Training
SUPPORT FUNCTIONS PROBLEMS

- PM overdue
- PM differs from manufacturer’s recommendation
- Calibration overdue
- Calibration differs from Manufacturer’s recommendation
- Operator training overdue
- Supervisor training overdue
- Quality Control / Assurance training overdue
SWAB SAMPLING TECHNIQUE, RELIABILITY, AND TRAINING

PROBLEM:

- Swab sampling must recover product residue.
- Sampling personnel must be trained and qualified.
- Periodic retraining should be considered.
SAMPLING PERSONNEL TRAINING

Representative sampling sites
  • Use of auxiliary equipment

Representative of most difficult analytical methods
  • Volatile solvents – time constraints
  • Extension poles?

Re-training considerations
  • Who does sampling?
  • Personnel skills
SUPPORT FUNCTIONS PROBLEMS

• Check PM, calibration, training before initiating validation

• Correct deficiencies
  – Training system problems – is training appropriate
  – Compliance issues

• Electronic monitoring systems
5. INFRASTRUCTURE

What is the problem?
System problem
  – Validation business process
  – Validation variation
  – What is your approach to validation?
  – How do you manage the validation function?
RESPONSIBILITY OF THE VALIDATION FUNCTION

If products fail specifications, does validation have responsibility?

If re-cleaning is needed, does validation have responsibility?

If equipment fails, does validation have responsibility?

If QA receives an FDA-483 observation, does validation have responsibility (depending on topic)?

Is validation primarily a documentation library?

THE PV GUIDANCE HAS CHANGED THE SCOPE, CONTENT, AND RESPONSIBILITY OF VALIDATION
DEFINITIONS AND OBJECTIVES

Quality by Design (QbD)
Validated processes and equipment
Process of validation -- Lifecycle approach to process validation
QbD consistency with process validation

FDA Quality Systems
Validation Quality System
QbD / Lifecycle approach to the validation quality system
Risk management applications
QUALITY BY DESIGN (QbD)

Development Focus

• Target product profile (TPP) and critical quality attributes (CQA)
• Drug substance and excipient properties
• Formulation design and development
• Manufacturing process design and development
• Identification of critical process parameters (CPP) and critical material attributes (CMA)
• Risk assessment and design space
• Scale up, identification of variables, and control strategy

Red = Original QbD
QbD and PROCESS VALIDATION

QbD provides focus on design and development. Integration of manufacturing experience throughout lifecycle will results in product and process continuing improvements.

QbD consistent with ICH Q8 and Q11.

Lifecycle approach to process validation integrates QbD principles.

Lifecycle: Design/development → Performance → Monitoring/maintenance

Lifecycle approach being applied to other processes, equipment, utilities, quality systems, etc.
FDA QUALITY SYSTEMS

FDA Definition: Formalized business practices that define management responsibilities for organizational structure processes, procedures, and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement.
  • Management responsibilities
  • Resources
  • Manufacturing
  • Evaluation
VALIDATION QUALITY SYSTEM

Two components:

1. Validated products, processes (manufacturing, cleaning, packaging, etc.), equipment, utilities, facilities, control systems, computer systems, analytical instruments – the “product” of the validation system.

2. The process of accomplishing validation – the infrastructure of the validation function. Protocol strategies, testing approaches, documentation packages, approval committee responsibilities, document library, improvement projects, etc.
## QbD and VALIDATION QUALITY SYSTEM (QS)

### Manufacturing
- Target product profile
- Critical quality attributes
- Critical process parameters
- Variation and controls
- Risk assessment
- Monitoring attributes and process
- Improvement projects

### Validation QS
- System objective
- System attributes
- System parameters
- Variation and controls
- Risk assessment
- Monitoring metrics
- Improvement projects
QbD PROCESS VALIDATION
QSbD VALIDATION QUALITYSYSTEM -- LIFECYCLE APPROACH

PRODUCT and PROCESS

- Target profile
- Critical quality attributes – product specifications
- Critical process parameters
- Variables and control
- Risk assessment
- Continuous improvement

LIFECYCLE APPROACH:  Design/development, PQ, Monitoring → Improvements
(Stage 1 → Stage 2 → Stage 3)

VALIDATION QUALITY SYSTEM

- Objectives – system and individual process steps
- Attributes
- Parameters
- Variables and control
- Risk assessment
- Improvement projects

LIFECYCLE APPROACH:  Design, Demonstration, Monitoring → Improvements

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Quality System Design
Is the quality system properly designed to conduct the validation business process? What about outsourced products, outsourced processes, outsourced validation/qualification?

Quality System Performance
Does the quality system perform as designed?

Quality System Monitoring and Maintenance
What is done to maintain quality system performance?
QUALITY SYSTEM QUESTIONS

Procedures for all validation quality system activities -- Manufacturing processes, cleaning processes, analytical processes, equipment qualifications, other qualifications, computer systems, and other categories of validation/qualification?

Model documents for above categories of activities regarding validation initiation, validation plans, protocols, results, and reports?

Validation documents templates?

Validation training for validation personnel

Validation training for associated functions?

Validation document writer training?

Adequate number of validation personnel?

Expertise of validation personnel?

Expertise of Validation Approval Committee?

Responsibilities consistent with expertise?

Technical writers?

Personnel development and training?

Validation facilities?

Facility security?

Document library?

Electronic systems?

Electronic systems to monitor throughout, open documents, errors, etc.?

Monitoring on validated processes?

Monitoring on qualified EFU?
VALIDATION QUALITY SYSTEM BUSINESS PROCESS

PROJECT INITIATION, DESIGN, AND DEVELOPMENT BY SITE FUNCTION
1. Validation provides information on future needs in support of PQ
2. Validation receives / accesses recommended documents

PROCESS QUALIFICATION (PQ)
3. Validation initiation
4. VAC approval
5. Protocol written
6. VAC approval
7. Test results and post-validation recommendations
8. VAC approval
9. Validation administrative closure
10. Document storage

POST VALIDATION
11. Post-validation protocol initiation
12. VAC approval
13. Test results
14. VAC approval
15. Validation administrative closure
16. Document storage
17. Monitor validated process, EFU, etc. performance
18. Validation reviews

IMPROVEMENT PROJECTS
19. Initiate validation improvement projects
20. Complete validation improvement project including implementation
21. Complete validation change proejcts
VALIDATION QUALITY SYSTEM -- PROBLEM EXAMPLES

MANUFACTURING EQUIPMENT AND PROCESSES
• Operators did not perceive changes to be changes – inadequate change control
• Everything was “like-for-like” or not significant.

CLEANING VALIDATION
• No technical basis for cleaning
• Operators did whatever needed “to get the job done.”

CLEANING VALIDATION SAMPLING
• Sampling personnel not adequately trained – false negative data

DOCUMENTATION
• Numerous documentation problems such as data recording, original data, back dating, etc.

DOCUMENTATION COMPLIANCE
• Documentation not compliant with corporate requirements or regulatory expectations

DOCUMENTATION GRAMMATICAL
• Documentation poorly written

SAMPLING PROBLEMS
• Sampling personnel not adequately trained

NON-STERILE “CLEAN” PROCESSES
• Sampling personnel not adequately trained in microbiology

LIKE-FOR-LIKE CHANGES
• No testing of correct installation
VALIDATION QUALITY SYSTEM – CORRECTIVE ACTION PROJECTS

Validation Training Module
Validation Protocol Writer Training
Cleaning Validation Training
Cleaning Visual Inspection Training
Documentation Practices Training
Validation Approval Committee Training
Validation Approval Committee Procedure and Responsibilities
Validation Model Documents
Like-for-Like Approval (non-protocol) Process
Microbiology Training
Validation Policy Changes

RECORD CORRECTIVE ACTION PROJECTS IN VMP
WHY THE PROBLEM? -- VALIDATION CATEGORIES

Process validations
• Manufacturing
• Cleaning
• Packaging
• Analytical
• Others

Qualifications – IQ, OQ, PQ; ASTM E2500
• Equipment
• Facilities
• Utilities
• Computer systems
• Others

EACH VALIDATION UNIQUE
WHY THE PROBLEM? – ORIGINATORS OF VALIDATION / QUALIFICATION PROJECTS

R&D
Technical Support
Process Engineering
Facilities Engineering
Maintenance
Analytical R&D
QA/QC
Other

EACH GROUP UNIQUE. EACH WITH SPECIFIC EXPERTISE. EACH WITH SPECIFIC LANGUAGE AND TERMINOLOGY. ALL ABOVE GROUPS MUST UNDERSTAND VALIDATION OBJECTIVES.
VALIDATION QUALITY SYSTEM LIFECYCLE
QUANTITATIVE MONITORING -- EVALUATION

Performance of validated products, processes, equipment, etc. Do validated processes, EFU, etc. have problems due to validation deficiency, amount of testing, risk evaluation?

External audit observations
Documentation quality
Document throughput. “Open” validation projects – time open
Amendments to validation plan
Amendments and deviations to protocols
Rejected documents
Validation failures
Other document problems
6. VALIDATION APPROVAL COMMITTEE (VAC)

What is the problem?
• Undefined responsibility of VAC

Why the problem?
• Inexperience
• Workload
• Lack of understanding
Validation Approval Committee function and responsibilities must be clearly defined.

VAC IS INTERNAL REGULATORY AUDITOR
VALIDATION DOCUMENT APPROVAL
VALIDATION APPROVAL COMMITTEE (VAC)

VAC must review documents with perspective of a regulatory auditor

• Assure acceptability of technical validation and product quality
• Assure compliance with regulations, policies, and industry expectations
• Assure acceptability of documentation.
  – Spelling and grammar

VAC IMPORTANT PARTNER WITH VALIDATION
Technical validation

• Scientific and technical principles
• Consistent approach
• Supports objective of validation
• Supports routine manufacturing in type of testing and sampling
• Support routine manufacturing in duration of sampling and testing
• Results and discussion support data
• Correct technical conclusions
• Equipment testing support entire operating range used in manufacturing
VALIDATION APPROVAL COMMITTEE

• Training consistent with area of expertise
• Specialized training on validation function
• Emphasize role of internal auditor

VALIDATION APPROVAL COMMITTEE IS NOT

Training for new personnel
Expeditor for engineering documents
VAC RESPONSIBILITIES

Compliance with:

• Corporate policies and requirements
• Site policies and requirements
• Government agency laws (guidelines?)
  – Domestic
  – International
• Local laws
• Industry standards and expectations
• Customer requirements
TECHNICAL WRITING

- Impersonal – factual – no creativity
- Grammatically correct
- Clear and concise
- Outlines, sections, lists, and bullets
- Concluding statements following discussions
Three simple rules for validation documentation:

• Clear, complete, concise, and consistent
• “Stand-alone” documents written for the reader
• Short sentences and simple words.
SUMMARY – PV CHALLENGES 2015

1. FDA PV Guidance Problems
2. Technical Problems
3. Documentation Problems
4. Support Functions Problems
5. Infrastructure Problems
6. Validation Approval Committee
CHALLENGE – PV GUIDANCE IMPLEMENTATION

Problem: Implement the FDA PV Guidance
   – Stage approach
   – PQ enhancements

Implementation Plan
   – Identify high risk areas
   – Senior management and function management discussion
   – Identify receptive individuals in high risk area
   – Training of appropriate individuals
   – Start slowly – Success is essential
   – Expand effort based on success
   – Expect resistance

PV GUIDANCE IS NOT NEW -- GLOBAL CONSISTENCY
CHALLENGE -- TECHNICAL PROBLEMS

Problem: Technical approaches and specific judgments

General: SME expertise to recommend approach
Specific: Scientific judgment

GET APPROPRIATE PEOPLE INVOLVED
STAGE 1 SME
Problem: Inadequate documentation

- System problems
- Technical writing
- Good documentation practices

- Unified approach to validation / qualification
- Validation training
- Validation protocol writer training
- Templates and outlines
- Model documents
Problem: Overdue functions supporting validation

Check PM, calibration, training before initiating validation

Are systems appropriate?

Electronic monitoring systems
Problem: Variable validation function

Validation Quality System function

• “Product” – validated processes, equipment, utilities, computer systems, etc.
• Infrastructure – Process of conducting validation

Infrastructure lifecycle approach:
1. Design and develop
2. Demonstrate performance
3. Monitor
4. Initiate improvement projects as indicated

Determine business process

QSbD for business process: Objectives, attributes, parameters, variation, control of variation, risk, evaluation, review performance
Problem: VAC responsibility undefined

VAC: Internal regulatory auditor

- Technical validation and product quality
- Compliance with regulations, policies, and industry expectations
- Assure acceptability of documentation.
  - Spelling and grammar
NEW CHALLENGES

Please your help with new challenges!

Thank you.
PAUL L. PLUTA, PhD

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