Implement Change Control into Your Process Validation Program

Presented By:

Institute of Validation Technology

QUALITY METRICS AND MANAGEMENT WEEK

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Areas covered today:

Part 1: Regulatory Expectation

Part 2: Change Control Process

Part 3: Case Studies 483s Requirements for Process Changes

Part 4: Process Validation Change Control Procedure
Regulatory Expectation

Part 1: Importance of a Change Control Program
Regulations

Guidance
Change Control is the Most Critical Element in a Pharmaceutical/Biotech Firm’s Quality Management System

Poor change control procedures create huge risk of non-compliance

FDA's Guidance Reinforces Importance of Implementing Effective Change Control Procedures as Critical Components in an Overall Quality System

See “Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations (cGMP)”

Regulated Firms Must Implement a Quality System Automating Change Management and Control Procedures Ensuring that they Comply with GxPs / Part 11
Change Control in the Quality System Environment

- Change Control is a Familiar cGMP Concept to Manage Change to **Prevent Unintended Consequences**
- Implementation of Change Control in cGMP is through the Assigned Responsibilities of the Quality Control Unit. Quality System also contains Change Control Activities, Including Quality Planning and Revision Control to Specifications, Process Parameters and Procedures
CC and the Quality System Model

• Change is in Terms of Creating Regulatory Environments that Encourage Continuous Improvement

• Manufacturer Empowered to Make Changes Based on Variability of Manufacturing Materials and Optimization of Process from Experience
Where is Change Control Mandated?

- FDA GMP – 21 CFR Part 211
- FDA GLP – 21 CFR Part 58
- FDA QSR – 21 CFR Part 820
- ICH Q7A for APIs
- EU GMP Annex 11
- OECD GLP Guidance
  - Interpretation of GLP by Regulators & Industry
Quality System Documents to meet Federal Guidelines

- Mission for computer system validation
- Policy or SOP for computer system validation
- List of all computer systems
- Written risk assessment from validation team
- Risk Management Validation Plan
- Project plan
- Vendor Audit

- Computer system validation plan
- SOP Configuration Management
- Protocol templates
- Review and approval of protocols
- Change Control Procedures
- Design specification - software intended to do and how is does it
- Test Plan and results based on design
Part 2:
Step by Step Process to Change Control
Change Control Procedure

Change required

Generate Change Request

GMP Implications?

Requalification? Revalidation?

Requalify Revalidate & Issue Reports

Implement Change & Insure GMP Requirements Done

Obtain Approvals

Issue GMP Report

Obtain Approval

Change is Permanent

End
Change Control Classification

- **Major changes** to process, materials, product or procedure require approval and documentation - common sense.
  - Changes having the greatest possible impact on compliance.
  - Potential of affecting or compromising product quality, safety or efficacy.
- **Improvements** to process, materials, product or procedure. Still need approval and documentation to substantiate this.
- **Minor changes** to process, materials, product or procedure - approval and documentation.
- **Emergency** Planned versus Unplanned Changes (Emergency vs. Non-Emergency)
Change Control Procedure

- **Initiate change** (simple form with justification, technical information and drawings)
- **Review and approval** (Quality unit, User group, Engineering, Validation professional, Safety and environmental)
- **Identify GMP implications**
• Define what is needed to make the change permanent
• Identify revalidation requirements and implement
• Change permanent
Emergency Changes

- Implement Change
- Fill out paper work and circulate for comments and approval (within 48 hours)
- Implement GMP required actions immediately
- Release is contingent on implementation of GMP requirements.
Initiating Change

• A short and concise form
• Should have space for comments and approvals
• Should have all information needed to render judgment
• Should have space to define requirements for implementing change
Change Request Form

Review, Requirements, and Approval

• Technical review and comments by engineering, technical services, operation, and QA-recommend approval/disapproval

• Review and approval by Change Control Committee (needed if disagreements occur above)

• Define requirements to be satisfied for change implementation; validation, document or drawing modification, procedure modification, etc.
Part 3:
Maintaining a Validated State
Don’t let Validation/Qualification look like this - Do You Have Control?
Revalidation and Change Control

• The Guidance for Industry Process Validation: General Principles and Practices mention change control 10 times

• There should be a quality assurance system in place which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes which could impact on product effectiveness or product characteristics, and whenever there are changes in product characteristics.

• After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.
• Case Study #1

  – When a change is made in raw material supplier, the manufacturer should consider subtle, potentially adverse differences in the raw material characteristics. A determination of adverse differences in raw material indicates a need to revalidate the process.
• Potential Solution:

  – One way of detecting the kind of changes that should initiate revalidation is the use of tests and methods of analysis which are capable of measuring characteristics which may vary.

  – Such tests and methods usually yield specific results which go beyond the mere pass/fail basis, thereby detecting variations within product and process specifications and allowing determination of whether a process is slipping out of control.
• Case Study #2

– The quality assurance procedures should establish the circumstances under which revalidation is required. These may be based upon equipment, process, and product performance observed during the initial validation challenge studies.

– It is desirable to designate individuals who have the responsibility to review product, process, equipment and personnel changes to determine if and when revalidation is warranted.
• Case Study #2, Cont.

– The extent of revalidation will depend upon the nature of the changes and how they impact upon different aspects of production that had previously been validated.

– It may not be necessary to revalidate a process from scratch merely because a given circumstance has changed. However, it is important to carefully assess the nature of the change to determine potential ripple effects and what needs to be considered as part of revalidation.
Case Study #2,

For example, in the production of a compressed tablet, a firm may switch from one type of granulation blender to another with the erroneous assumption that both types have similar performance characteristics, and, therefore, granulation mixing times and procedures need not be altered. However, if the blenders are substantially different, use of the new blender with procedures used for the previous blender may result in a granulation with poor content uniformity.
Revalidation and Change Control

• Solution
  – This, in turn, may lead to tablets having significantly differing potencies. This situation may be averted if the quality assurance system detects the equipment change' in the first place, challenges the blender performance, precipitates a revalidation of the process, and initiates appropriate changes. In this example, revalidation comprises installation/Operational qualification of the new equipment and performance qualification of the process intended for use in the new blender.

  – Typically, review of the original Risk Assessment to determine what the impact on the product quality and safety if process changes are made.
Case Study #3

- Failure to establish and maintain procedures for monitoring and control of process parameters for validated processes, as required by 21 CFR 820.75(b). Specifically, operating procedure OP 4.8.1 "Validation and Verification Procedures" made reference to installation and operational qualification. Furthermore, all procedures contained in this S.O.P. were not followed.
Case Study #3

- For example, review of documents presented for the validation of the vacuum bake process, excluding the temperature recording chart, had no recording, or any other method, to ensure that the various valve positions are in the proper position to draw a vacuum during the vacuum bake cycle. Failure investigation analysis for S#210218 concluded the device was hermetically sealed in room air.
Case Study # 3

- Your response states that the process validation procedure has been revised and that the vacuum bake process will be validated by Q1 2005. You also state that you will revise Document Action Request/Engineering Order Form (9196175) to record that a revalidation assessment has been performed and to identify if training is required. Please provide a copy of the revised validation procedure and form 9196175 for review. The adequacy and implementation will be verified during your next scheduled inspection.
• Case Study #4

  – Failure to review and evaluate the process and perform revalidation when changes or process deviations occur, as required by 21 CFR 820.75(c). Specifically, as early as May 2014 (S#200064, RGA Test Date 5120114) failure investigation of explanted devices established that cochlear implants were being returned without evidence of breach hermeticity and failing RGA (residual gas analysis for water/moisture).
Case Study #4

There was no documented evidence of revalidation after changes were made to vacuum system for two ovens vacuum bake oven process. Process revalidation is necessary to ensure that moisture is being removed from the implant prior to welding of the vent hole, which hermetically seals the device.
• Solution:

– During the change control process the conditions to bring the system back to a validated state should have been assessed. An addendum to the original protocol should have been issued and tested should have been performed to validate the process change.
Requirements for Process Changes

Part 4: Risk Base Approach
New Concepts/Emphasis

• Life-cycle concept
• Risk assessment
• Process design
• Process knowledge
• Process Monitoring
The Life Cycle Validation Approach

Validation Life Cycle

- Re-Validation
- Functional Specification
- Design Specification
- Design Qualification
- Impact Assessment
- Validation Master Plan
- Construction
- Protocols
- Performance Qualification
- Operation Qualification
- Installation Qualification
- Release
- Use
- Periodic Re-Evaluation
- Decommissioning
- Change Control
The Validation Lifecycle

<table>
<thead>
<tr>
<th>Validation Task</th>
<th>Functions</th>
<th>Phases</th>
<th>The Big Picture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of Process and Systems</td>
<td>Design → Install → Prepare → Start-up → Operate</td>
<td>Process R&amp;D → IQ/OQ Phase → PQ Phase → Monitor</td>
<td>Process Validation</td>
</tr>
<tr>
<td>Installation Qualification</td>
<td>Operational Qualification</td>
<td>Performance Qualification</td>
<td>Commercial Production</td>
</tr>
</tbody>
</table>
Impact Assessment The Categories

- **cGMP Direct Impact**
  - Direct impact on product quality
  - Validated
  - Contains critical components
  - May include enhanced documentation

- **cGMP Indirect Impact**
  - No direct impact on product quality
  - Often supports Direct Impact systems
  - Usually not validated

- **No Impact** – No impact on product quality
Relating Process Validation to Existing Processes

• **Approach**
  - Risk Assessment to select critical parameters and input and output parameters.
  - A statistically valid time frame or number of batches must be determined.
  - The data used to establish the parameters must be extracted from controlled documents.
  - The data extracted from the controlled documents will be analyzed to establish ranges.
Process Flow

Initiate Risk Management Process

Risk Assessment
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Mitigation (incl. elimination and avoidance) [Severity]
- Risk Reduction [Probability]
- Risk Acceptance

Risk Communication

Review (e.g. Inspections/Audits, Complaints)

Output / Results of the Risk Management Process

Risk Management tools & statistic toolbar (Resources, Interfaces & Link Functions)

No additional risk
## Step 1: Identify Risks Using Process Map

Convene participants from all relevant areas (Production, QA, QC, Packaging…)

Identify and rate failure modes for each process step by severity, probability, and detection

Assign Essential Control Points (ECP) based on ratings

### Risk Assessment Document

<table>
<thead>
<tr>
<th>Step</th>
<th>Process</th>
<th>Failure Mode</th>
<th>Hazard</th>
<th>Potential Cause</th>
<th>Existing controls</th>
<th>Detection Method</th>
<th>Sev</th>
<th>Prob</th>
<th>Det</th>
<th>ECP Y/N</th>
<th>ECP Where</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Pull released raw materials</td>
<td>Stability</td>
<td>Subpotency: delayed medical treatment</td>
<td>LIMS not referencing new #, ManMan only references old # causing incorrect CofA</td>
<td>Visual check of CofA with LIMS and ManMan(production)</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>NO</td>
<td>Issue: 23, 24, 26</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Collect Water @ 126 drop / WFI System (Processing tank #1,2,3)</td>
<td>High Count/ obj organism</td>
<td>Infection requiring medical intervention</td>
<td>WFI System failure</td>
<td>WFI System Validation, SOP (equipment, preventive maintenance, manual cleaning, manufacturing, training, environmental, procedures)</td>
<td>USP / EP water test,</td>
<td>10</td>
<td>8</td>
<td>3</td>
<td>YES</td>
<td>USP Test Procedure</td>
</tr>
<tr>
<td>4.2</td>
<td>Collect Water @ 126 drop / WFI System (Processing tank #1,2,3)</td>
<td>High Count/ obj organism</td>
<td>Infection requiring medical intervention</td>
<td>Container (tanks) contamination</td>
<td>Manual cleaning validation, equipment qualification</td>
<td>None</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>YES</td>
<td>CIP / SIP</td>
</tr>
<tr>
<td>4.3</td>
<td>Collect Water @ 126 drop / WFI System (Processing tank #1,2,3)</td>
<td>High Count/ obj organism</td>
<td>Infection requiring medical intervention</td>
<td>Improper sampling technique</td>
<td>Training, SOP</td>
<td>USP / EP water test,</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>YES</td>
<td>USP Test Procedure</td>
</tr>
</tbody>
</table>
• **Revalidation may be necessary under such conditions as:**
  • change(s) in the actual process that may affect quality or its validation status
  • negative trend(s) in quality indicators
  • change(s) in the product *design* which affects the process
  • transfer of processes from one facility to another
  • change of the application of the process
The need for revalidation should be evaluated and documented. This evaluation should include historical results from quality indicators, product changes, process changes, changes in external requirements (regulations or standards) and other such circumstances.
Revalidation and Change Control Assessment

• Revalidation may not be as extensive as the initial validation if the situation does not require that all aspects of the original validation be repeated. If a new piece of equipment is purchased for a validated process, obviously the IQ portion of the validation needs to be repeated. However, most of the OQ aspects are already established but some testing may be required to confirm. Some elements of PQ may need to be repeated, depending on the impact of the new equipment.
Another example might be if a raw material supplier is changed, the impact of that change on the process and resultant product should be considered. Parts of OQ and PQ might need to be redone, as the interaction between the new raw material and the process may not be fully understood.
• Monitor and Control (Track and Trend)

• Trends in the process should be monitored to ensure the process remains within the established parameters. When monitoring data on quality characteristics demonstrates a negative trend, the cause should be investigated, corrective action may be taken and revalidation considered.
Process Monitor: Change Control

• Routine Commercial Manufacturing
  – Monitor critical operating and performance parameters
    • Utilize appropriate tools, e.g., Statistical Process Control
  – Monitor product characteristics (e.g., stability, product specifications)
  – Monitor state of personnel training and material, facility/equipment and SOP changes
  – Investigate OOS for root cause and implement corrective action.
Revalidation Considerations

- When monitoring data on quality characteristics demonstrates a negative trend, the cause should be investigated, corrective action may be taken and revalidation considered.

- Any changes in the process and/or product including changes in procedures, equipment, personnel, etc., should be evaluated to determine the affects of those changes and the extent of revalidation if required.

- Verification versus Validation
Revalidation - Criteria for Consideration?

- Change in the process from manual to automated manufacturing and vice versa
- Change in the personnel or training of the personnel
- Data received from a complaint file
- A significant change in the manufacturing facility and/or environmental controls under which components or devices are manufactured
- A significant change in the composition (formulation) of manufacturing materials or components used in manufacturing
- New or changes in sterile pkg. materials, suppliers, process parameters, etc.
Understanding the Interactions

RESOURCES

- Systems & Equipment

CONTROLS

- Change Management
- Training
- Procedures

Personnel
Any Questions???