Managing Change in Manufacturing

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King Henry VIII – Flagship ‘Mary Rose’

- Launched 1509
- Numerous ‘improvements’
  - More guns (and ports)
  - Heavier guns
- Sunk 1545
  - Fighting the French!
Managing Change in Manufacturing

- Link to ICH Q10
- Types of Product and Process change
- Importance of knowledge to effective change management
- Consider another high tech industry
- Key Messages
Product Lifecycle (ICH Q10)

ICH Q10 Pharmaceutical Quality System

Pharmaceutical Development ➔ Technology Transfer ➔ Commercial Manufacturing ➔ Discontinuation

Investigational products

GMP

Management Responsibilities

Process Performance & Product Quality Monitoring System
Corrective Action / Preventive Action (CAPA) System
Change Management System
Management Review

PQS elements

Knowledge Management
Quality Risk Management

Enablers
Change Management

Changes *WILL* happen throughout the product lifecycle

- **Proactively** *due to business or technical reasons*
  - Part of continual improvement initiatives
- **Reactively** *driven as part of CAPA*
  - Due to deviations, OOS, batch rejections

The Pharmaceutical Quality System must include a *robust* change management system

- Use of knowledge and Quality Risk Management
Changes - Forced or Voluntary?

Some things **must be** changed – where we have no option
- Supplier stops trading
- Customer complaints

Other things **can be** changed – where we do have an option
- Equipment modernisation / Software upgrade
- QC test method improvement
- Continual improvement initiatives

We always need to consider the risk versus benefit of each change
- But the biggest risk by far is an uncontrolled change
- Small changes do not always equal low risk
## Types of Product and Process Change

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<th>Managed through formal change control system</th>
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Continual Improvement and Change Management

1. Continual Improvement
   - Change verified as successful

2. Process Change
   - Controlled via robust change management system

3. Process Control
   - Part of the company culture

Controlled via robust change management system
Typical Change Management Process Map

1. Change Identification & Characterisation
   - What data needs to be developed?
   - What is the potential impact?
   - How it will be measured?

2. Change Impact assessment
   - Estimate risk (e.g. severity, probability, detectability) posed by a proposed change

3. Execution of technical steps

4. Change Approval (With or without regulatory approval as necessary)
   - Documents the change, the results, and QU approval

5. Action Plan

6. Review of effectiveness
   - No change to perform

Described in the company PQS
Increased knowledge increases chances of successful change

Increased knowledge comes from:
- Experience!
- Increased Product Understanding
- Increased Process Understanding

But how do we systematically capture such product and process understanding?
Change Management: Importance of Knowledge

- Development Report
- Tech Transfer Report
- Initial Validation Report
- Continuous Verification
- Annual Product Reviews
- Internal and external events (deviations, complaints)

Effective Change vs. Knowledge Diagram
But these key pieces of data

- Need to be available to the manufacturing site
- Used as reference data when assessing changes

The people need to be trained and educated as appropriate for their daily work

- On the most recently available knowledge
- ...and the background/reasons for changes
Change Management: Traditional Process Validation

Knowledge/ Process Performance

...Development Transfer Manufacturing.....

validation batches

Process drift?
• Materials?
• Equipment?
• People?
• Procedures
• Systems?
• Lack of interest?
Change Management: Continuous Verification

- More batch data
- Trend monitoring
- More knowledge
Continuous Verification: Process Monitoring

**Process Tracking and Trending**
- Address trends before they become problems
- Verify changes are successful

**Product Quality Monitoring**
- Analyze critical process parameters & critical quality attributes in the control strategy
- Reduce sources of variation
  - If it brings quality improvement

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**Control Limits: Derived from Historical Release Data**

![Updated Control Chart of Assay; 3 new batches]

**Trend Limits: Derived from Historical Stability Data**

![Trend Limits]
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Raw Material variability is one major of pharmaceutical process variation

Can give rise to process variation – even if raw material is within the agreed specification limits

This ‘natural variability’ needs to be understood and controlled
Example of Uncontrolled Change – Fraud/Malpractice

- Fraudulent change of raw material (glycerin, heparin, etc)
  - Improved fingerprinting of high risk susceptible raw materials
  - Supplier audits and controls

- Operator decides to wash machine parts at higher temperature 80°C instead of 50°C for a shorter time period without change control
  - Thought he was doing continual improvement!
  - His heart was in the right place!

Always ask: Technical, System, or Management issue

Sanoﬁ Aventis
Because health matters
Example of Uncontrolled Change – Accident or Error

Accident/Errors Examples

Operator accidentally drops scissors into the product during processing
- First time using a new isolator
- Process design had not been thought through

Operator accidentally selects wrong cleaning cycle
- Master batch record updated as part of change
- New cycle entered into CIP as part of change
- …but old cycle was not deleted
Nailing Down the Processes

- Need to ‘nail down’ process to avoid changes via accident or error

- Remove possibility for process parameters to be changed by malpractice, accident or error
  - e.g. machine parts washer

- Use of FMEA when considering process design, process changes
  - e.g. scissors in product,

- Need to train everyone on change control procedure
  - Good change control will be as good as the training and education
  - Include training on serious consequences of uncontrolled change
  - Build it into the culture of the company/site
Standard 1: Detect and eliminate process variability and uncoordinated changes.

- Implement methods for early detection of changes in materials, parts, or assemblies

Standard 3: Understand and reduce process risks

- Understand potential risk when a change is implemented

- Document process for reporting changes to processes, materials, methods, etc. to the appropriate individuals for analysis and potential impacts.

Standard 7: Identify and evaluate changes to equipment and environment.

- Identify the baseline and manage and control any changes to that baseline.
- Analyze changes for potential impacts to risk, safety, etc.
- Ensure changes are coordinated, reviewed, and approved by authorized individuals.
- Maintain documentation of changes.
Summary: Management culture is key to effective change control

Managers must lead by example

- Create and maintain strong change control system and culture
  - Management support for problem identification, reporting, and continual improvement

- People must be trained and educated on the change control system

- Ensure QRM tools used as part of the change control when appropriate

- Nail down process to avoid change by accident or error
  - Are issues technical, system, or management related
Summary: **Knowledge is key to effective change control**

People must systematically obtain and utilise the knowledge available to them as part of change control

- To make the best judgements of risk (QRM)
  - Small changes do not always equal low risk!

- To be able to demonstrate scientific and logical justification

- And to continually add to the product and process knowledge
Thank you for your attention